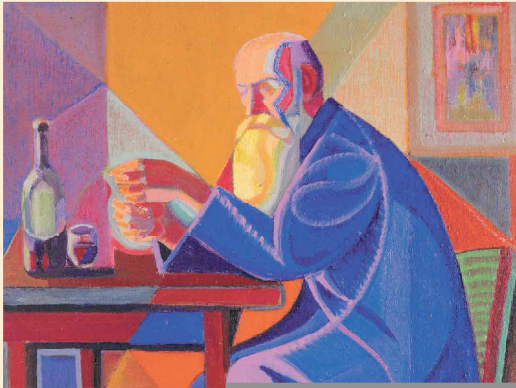




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## Project Synopses

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Co-ordinator of QLK6-2001-00108 (“Woldage”)

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European Commission

# **Project Synopses**

## **Key Action 6 The Ageing population and disabilities 1999-2002**

**Prepared by Christel Jaubert and Alexandra Resch**

Directorate-General for Research  
5<sup>th</sup> Framework Programme  
Quality of Life and Management of Living Resources



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# Introduction

The ageing of Europe's population will be a crucial challenge for the 21<sup>st</sup> century. Society will be facing three major changes: first, increasing numbers of active older people demanding new social structures and opportunities; second, increasing numbers of disabled older people requiring new interventions and improved health and social care with resulting economic consequences; and third, complex economic, technological, organisational and social challenges involved in the ageing of society.

If society wants to benefit from these changes, innovative social, organisational and technological responses are needed.

Under the Fifth Framework-Programme for Research and Technological Development in the Quality of Life Programme, Key Action 6 on the "Ageing population and their Disabilities" was established to respond to these challenges. Community wide cross-sectoral multidisciplinary research, combining and integrating efforts in the biological, biomedical, psychological, economic and social fields are supported to promote the global objective: healthy ageing.

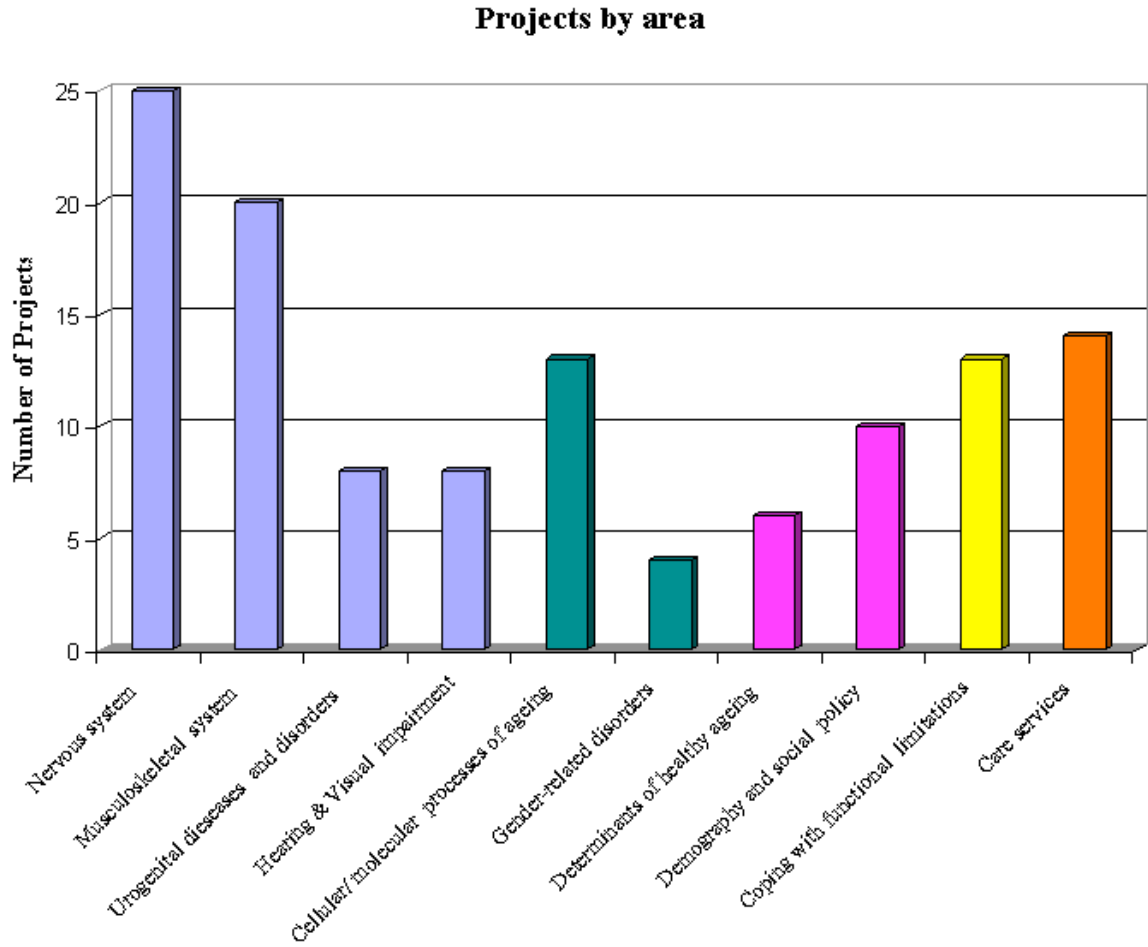
In the period from 1998 to 2002 over 170 million Euro have been committed to support research in ageing relevant areas, with a total of 121 research and co-ordination projects being supported. The number of projects and the budget allocated to the different research areas covered by Key Action 6 can be found in Figures 1 and 2.

The present booklet is a compendium of all research and co-ordination activities supported by Key Action 6 from 1998 to 2002. It summarises the main features of the projects and it provides the Research Community, industries and all interest groups with information on each funded project.

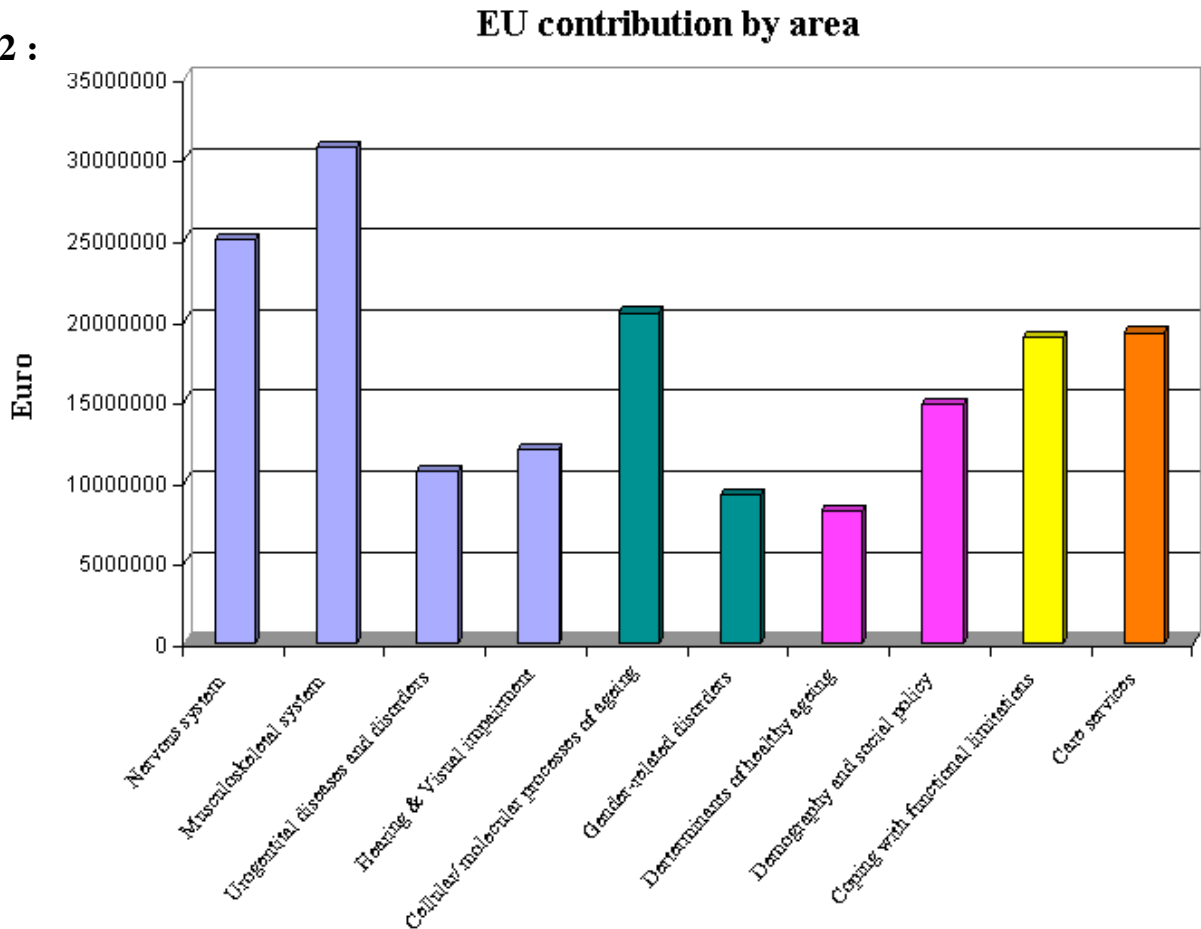
Key Action 6 adopted a problem-solving approach, in which it aimed "to put research to work" in order to meet the challenges posed by both the ageing of individuals and the ageing of society. It aimed to do so by taking a well-balanced holistic approach towards the challenges of an ageing population. Impressive scientific results have been already achieved by some of the projects using this "holistic approach". However, the impact and the "spin-off" of these research activities can only be measured in the medium or long term.

A. Hoeveler  
Head of Unit  
"Ageing population" and "Poverty related diseases"  
DG Research, Health Directorate  
November 2002

**Figure 1:**



**Figure 2 :**



# Quality of Life and Management of Living Resources (1998-2002)

## Key Action 6: “The Ageing Population and Disabilities”

### Introduction

Key Action 6 “The Ageing Population and Disabilities” aimed to put research to work to address the major challenges of an ageing population. Therefore Community wide cross sectoral multidisciplinary research has been carried out, combining and integrating efforts in the biological, biomedical, psychological, technological, economic and social fields. More specific objectives and deliverables were: To promote healthy ageing, by improving the understanding of the basic processes of physiological and molecular ageing, as well as the management of age-related illnesses and to cope better with disability and improving the basis for the policy and planning of social welfare systems.

The key action was organised into five action lines, which in turn contained different sub-areas:

### Action line 6.1: Age-related illnesses and health problems

This action line focused on creating European added value in research of clinical significance for the early detection of, prevention or delay in onset of, treatment of and rehabilitation from age-related diseases and disorders of high morbidity among older people. In particular, it sponsored the co-ordination of research projects already funded at the national and international levels and the networking of research teams with the stakeholders in the research. Priorities identified were:

- Nervous system: stroke, Alzheimer’s disease and other forms of cognitive impairment, depression, Parkinson’s disease and peripheral neuropathies;
- Musculo-skeletal system: muscular atrophy, osteoporosis and degenerative joint diseases;
- Urogenital system: incontinence and prostate disorders;
- Other gender-specific health problems;
- Sensory systems: visual and auditory impairments;
- Pain.

### Action line 6.2: Basic Processes of Physiological Ageing

This action line aimed at improving understanding of the basic biological processes of (normal) physiological ageing. It addressed in particular the question of why the human body becomes generally less proficient and more fragile as it ages and also more susceptible to disease, taking account of gender-related effects. The long-term goals are to strengthen the evidence base for public health strategies to promote healthy ageing and possibly to identify new routes for positive interventions in the ageing process. Priorities identified were:

- The basic cellular and molecular processes underlying the physiological process of ageing, but excluding the pathogenesis of specific diseases;
- Functional genomics as applied to human ageing, including interactions between genetic factors and environmental and behavioural factors;
- The genetic epidemiology of ageing, including cohort studies, in particular of the oldest old.

### **Action line 6.3: Demographic and social policy aspects of population ageing**

As a basis for socio-economic policy and planning in the light of the expected demographic changes, this action line concentrated on predicting the evolution of pertinent characteristics of the ageing population and on examining the impact of population ageing on society. It also addressed the social determinants of healthy ageing and well-being in old age. Priorities identified were:

- Population studies aimed at predicting policy-relevant characteristics of an ageing population (including functional status, health and care status, dependency, housing and household status, economic status);
- Policy-relevant socio-economic studies on the impact of population ageing: (a) on the sustainability of social welfare systems, in particular health care and pensions; (b) on social cohesion and intergenerational relationships; (c) on social exclusion and inclusion; (d) on the participation of older workers in the labour market; and (e) on the development of the voluntary and community sectors;
- Studies of the social, economic, cultural and behavioural determinants of healthy ageing and of well-being in old age, including studies of the factors motivating older people to adopt healthy life styles.

### **Action line 6.4: Coping with functional limitations in old age**

This action line supported the development and evaluation of technologies and systems designed to reduce the impact of disabilities on older people, to restore their functions and to mitigate the challenge to them of their social and physical environments. Priorities identified were:

- Technological products and systems contributing to greater mobility and less dependency, both inside and outside the home, including in the work-place;
- Caring and nursing products designed to support older people in their own homes;
- Improving postural stability and preventing falls;
- Technical aids to rehabilitation;
- Optimum forms of physical and/or cognitive exercise.

### **Action line 6.5: Health and social care services to older people**

This action line aimed at contributing to the evolution of effective, efficient and user-friendly care services for older people, by supporting comparative evaluation and research into the organisation, delivery and planning of care. Priorities identified were:

- The efficiency, quality and user-acceptability of different modes of health and social care organisation and delivery (with particular emphasis on their interfaces);
- The role and needs of informal carers and of the voluntary sector, and their relation to the formal care sector;
- Health inequalities, including ethical issues associated with setting priorities for care provision to older people;
- Consequences of the vulnerability of older people: elderly abuse, violence and neglect;
- Arrangements to enable older people to stay in their own homes, particularly by extending domiciliary care, by integrating services at the local level, or by promoting different housing structures and living environments;
- Stimulating the capacity for self-care by older people;
- End-of-life and palliative care, including their ethical aspects.



## **Index of Projects by action line and area:**

### **Action line 6.1: Age-related illnesses and health problems**

#### **Nervous system**

<b>Project Number</b> QLK6-CT	<b>Acronym</b>	<b>Project Title</b>	<b>Page</b>
1999-02004	MANAD	Microglial activation in neurodegeneration in Alzheimer's disease: a therapeutical target	16
1999-02038	GHS AND AGEING	Growth hormone secretagogues for improving body composition and quality of life in the aged	18
1999-02111	GENERALE	Genetic and behavioural risk factors for ageing-related coronary and cerebrovascular disease in Europe	20
1999-02112	Oxidant stress in AD	Interactions between oxidative stress and the activation of mitogenic signalling in Alzheimer's disease	22
1999-02140	LSDE	Connectivity in language rehabilitation in stroke and dementia	24
1999-02173	STN and Parkinsonism	High frequency stimulation of the subthalamic nucleus: a therapeutic approach to Parkinson's disease	26
1999-02178	NEST-DD	Network for efficiency and standardization of dementia diagnosis	28
1999-02189	APP-PS	Validation of single and multiple transgenic mice models for Alzheimer's disease	30
1999-02203	TARGET ASTROCYTES IN AD	Targeting astrocytes to disrupt inflammation-neurodegeneration coupling	32
1999-02238	Grasping Alzheimer	Fe65-APP-XII protein-protein interaction network: new tools for Alzheimer's disease diagnosis and therapy	34
2000-00179	NEUROSTEROIDS & AGEING	The role of neurosteroids in healthy ageing: therapeutical perspectives	36
2000-00318	NICOTINE & AGEING	Nicotine, nicotinic receptors and ageing	38
2000-00384	EPSND	Early pathogenic markers of slow neurodegenerative diseases	40
2000-00446	LADIS	Impact of age-related brain white matter changes on transition to disability in the elderly	42
2000-00502	NCI-MCI	Neuroreceptor changes in mild cognitive impairment	44
2000-00661	EMSA-SG	European multiple system atrophy study group	46
2001-00120	RESCUE	Rehabilitation in Parkinson's disease: strategies for cueing	50
2001-00170	CERISE	Collaborative evaluation of rehabilitation in stroke across Europe	52
2002-02332	ESPRIT	European Stroke Prevention in Reversible Ischaemia Trial	54
2002-02435	Zinc	The role of zinc metabolism in Alzheimer's disease. Elaboration of a new strategy for prevention and therapy of Alzheimer's disease.	56
2002-02455	DESCRIPA	Development of screening guidelines and diagnostic criteria for predementia Alzheimer's disease	58
2002-02514	ECSN	European Carotid Stenting Network	60
2002-02583	SMILE	Rapid Stroke Marker Detection via Immunosensors utilising Labelless Electrochemical and Resonant Mass Detection, Step 2 of EXAW-1999-01799	62
2002-02645	ICTUS	The Impact of Treatment with Acetylcholinesterase Inhibitors (AChE I) on Europeans with Alzheimers Disease (AD)	64
2002-00296	DIADEM	Obstacles and facilitators in diagnosing and managing early dementia in EU member status	68

## Musculoskeletal system

<b>Project Number</b>	<b>Acronym</b>	<b>Project Title</b>	<b>Page</b>
QLK6-CT-			
1999-02024	MIAB	Mechanical integrity and architecture of bone relative to osteoporosis, ageing and drug treatment	72
1999-02034	Ageing Muscle	Investigation of mechanisms for maintenance and regeneration in the ageing muscle	74
1999-02072	Cytokines destr OA	Role of cytokines and growth factors in cartilage destruction in osteoarthritis (OA)	76
1999-02108	GENOSPORA	New genes and targets for osteoporosis	78
1999-02234	EPILA	Opioid treatment of chronic pain and inflammation in the locomotor system	80
2000-00139	NEW	Neuromuscular assessment in the elderly worker	82
2000-00417	PENAM	Pan-european network for ageing muscle	84
2000-00487	SPARE PARTS	Chondral and osseous tissue engineering	86
2000-00530	AGEING MUSCLE	Ageing-related muscle wasting: causes, prevention and reversal	88
2001-00323	BETTER-AGEING	Physical frailty and loss of functional independence in old age: the role of physical activity	90
2002-00491	NEMO	Network in Europe on male osteoporosis	92
2002-02243	OSTEODENT	The diagnostic validity of dental radiography techniques for identifying osteoporotic patients	94
2002-02288	OB-AGE	Obesity and disease in ageing	96
2002-02363	ADOQ	Advanced Detection of Bone Quality	98
2002-02440	3D-QCT of Osteoporotic Hip	Improvement of Hip Fracture Prediction in Osteoporotic Subjects by Low-Dose Volumetric QCT Assessment and Finite Element Analysis of the Proximal Femur	100
2002-2582	Eurodisc	Interverbal disc degeneration : interplay of age, environmental and genetic factors	102
2002-02629	GENEMOS	Genetic markers for Osteoporosis	104
2002-02700	JOINT SCAFFOLD	Development and clinical evaluation of bioreplaceable small joint prosthesis for the correction of destructed small joints in rheumatoid arthritis and osteoarthritis	106
2002-02710	FEMUS	Femur Ultrasound Scanner	108
2002-02285	ENIGMA	European Network for Investigating the Global mechanisms of Muscle Abnormalities In COPD	110

## Urogenital diseases and disorders

<b>Project Number</b>	<b>Acronym</b>	<b>Project Title</b>	<b>Page</b>
QLK6-CT			
2000-00064	HRI	Hypoxic renal injury	114
2000-00159	ProCure BioPharm	Prostate disorders: procurement of biomarkers and pharmaceuticals	116
2000-00271	Prostate Gene Therapy	Specific cytotoxic agents to treat prostate disorders in elderly males: targeted gene therapy	118

2000-00280	Polyvirus	Polymer-virus hybrid vectors for safe and efficient gene therapy of prostate cancer	120
2000-00565	(E)UROESTROGEN(E)S	Oestrogens and age-related urogenital diseases: basic and clinical approaches	122
2000-00602	ARPC	Molecular mechanisms of androgen resistance in prostate cancer	124
2001-00218	OASIS	The role of functional asymmetry of sphincter innervation in incontinence	126
2002-02174	CONTRAST	Contrast enhanced ultrasound imaging in the diagnosis and treatment of prostate cancer.	128

## Hearing and Visual impairment

Project Number QLK6-CT-	Acronym	Project Title	
1999-02094	EUREYE	A multi-centre study of risk factors for macular degeneration	132
2000-00569	PRORET	Neuroprotection in the retina	134
2002-00151	EUROKINESIS	Oculomotor function and self-motion perception in the elderly	136
2002-00214	AMDREAD	Age-related macular degeneration	138
2001-00385	PRO-AGE-RET	Protection against ageing in the retina	140
2001-00279	CORTIVIS	Cortical visual neuroprosthesis for the blind	142
2002-00331	ARHI	Identification of environmental and genetic risk factors for Age Related Hearing Impairment	144
2002-02494	PHOTAGE	Photoreceptor Dynamics in Age-Related Macular Degeneration. Consequences for early diagnosis.	146

## Action line 6.2: Basic Processes of Physiological Ageing

### Cellular and molecular processes of ageing

Project Number QLK6-CT-	Acronym	Project Title	Page
1999-02237	PISDAP	Prevention of iron storage disease in the ageing population	150
1999-02002	DNAGE	Role of oxidative DNA damage and repair in ageing	152
1999-02031	IMAGINE	Immunology and ageing in Europe	154
1999-02071	AGEGEN	Identification and characterisation of genes controlling longevity and ageing in an animal model	158
1999-02187	ROLE OF CAMS IN AGEING	Age-related changes in learning and memory	160
1999-02193	SHARE	The role of proteasome in human ageing: implications for anti-ageing strategies	162
2000-00054	MITAGE	Testing the mitochondrial theory of ageing	164
2000-00616	CELLAGE	Molecular mechanisms of senescence and ageing	166
2001-00175	AGEING ECM	Mechanisms of ageing in extra-cellular matrices	168
2001-00310	FUNCTIONAGE	Functional genomics and proteomics in human molecular gerontology and geriatrics	170
2001-00332	TELASTAR	Towards the maintenance of tissue elasticity for healthy ageing	172
2002-02258	OLDCLOCK	Ageing and the biological clock in the brain	174
2002-02283	T-CIA	T cell immunity and ageing	176

## Gender-related disorders

Project Number QLK6-CT-	Acronym	Project Title	Page
2000-00736	BURDIS	Burden of disease in old people	180
2000-00338	OVAGE	Early development of ovarian follicles - determination of the timing of menopause	182
2000-00499	SLEEP IN AGEING WOMEN	Sleep disorders in menopausal and postmenopausal ageing women	184
2001-00258	EMAS	European male ageing study: symptoms of ageing in men, and their endocrine, genetic and psychosocial correlates	186

## Action line 6.3: Demographic and social policy aspects of population ageing

### Determinants of Healthy Ageing

Project Number QLK6-CT-	Acronym	Project Title	Page
2000-00211	HALE	A multi-disciplinary approach to healthy ageing and its determinants in 11 European countries	190
2000-00320	WHOQOL-OLD	The measurement of quality of life in older adults and its relationship to healthy ageing	192
2001-00128	ECHA	European challenge for healthy ageing	194
2001-00241	EPIC-elderly	The role of diet on the longevity of elderly Europeans	196
2001-00280	ESAW	Ageing well: European study of adult well being	198
2001-00334	ENABLE-AGE	The home environment as a determinant for healthy ageing	200

### Socio-economic impact

Project Number QLK6-CT	Acronym	Project Title	Page
1999-02161	SEDHA	Socioeconomic determinants of healthy ageing: from description to explanation	204
2000-00038	RESPECT	Research action for improving elderly workers safety, productivity, efficiency and competence	206
2001-00360	SHARE	Survey on health, ageing and retirement in Europe	208
2001-00475	NURSE'S EXIT STUDY	Sustaining working ability in the nursing profession – investigation of premature departure from work	210
2001-00517	AGIR	Ageing, health and retirement in Europe	212
2002-02292	SOCIOLD	Socio-economic and occupational effects on the health inequality of the older workforce	214
2002-02297	ECUITY III	The dynamics of income, health and inequality over the life cycle	216
2002-02310	FELICIE	Future elderly living conditions in Europe	218
2002-02426	AMANDA	Advanced Multidisciplinary Analysis of New Data on Aging	220
2002-02500	DEMWEL	Demographic uncertainty and the sustainability of social welfare systems	222

## Action line 6.4: Coping with functional limitations in old age

### Coping with functional limitations/ Technologies

Project Number QLK6-CT-	Acronym	Project Title	Page
1999-02236	MOBILATE	Enhancing outdoor mobility in later life: personal coping, environmental resources, and technical support	226
1999-02282	GENTLE/S	Robotic assistance in neuro and motor rehabilitation	228
2000-00375	HRV	The role of home respiratory ventilators in the management of chronic respiratory failure	230
2000-00405	ELDERATHOME	The prerequisites of the elderly for living at home: criteria for dwellings, surroundings, facilities	232
2000-00653	ENABLE	Enabling technologies for persons with dementia	234
2001-00458	FRR	Friendly rest room for elderly people	236
2001-00536	DRIFTS	Dynamically responsive intervention for tremor suppression	238
2001-00118	AGILE	Aged people integration, mobility, safety and quality of life enhancement through driving	240
2002-02399	SIZE	Life quality of senior citizens in relation to mobility conditions	242
2002-02442	IMLOAD	Improving Implant Fixation by Immediate Loading	244
2002-02576	NICMS	Research, development and demonstration of a novel non-invasive continence management system	246
2002-02674	EduPark	Patient education in Parkinson's Disease	250
2002-02705	PROFANE	Prevention of Falls Network Europe	252

## Action line 6.5: Health and social care services to older people

### Care services

Project Number QLK6-CT	Acronym	Project Title	Page
1999-02035	IMPROVE	Implementation of patient involvement instruments to improve general practice care for older people	256
1999-02070	ACMEPLUS	A hospital admission case-mix system for elderly patients	258
1999-02182	OASIS	Old age and autonomy: the role of service systems and intergenerational family solidarity	260
1999-02205	DISABILITY PREVENTION	Disability prevention in the older population	262
2000-00002	AD HOC	The aged in home care project	264
2000-00303	INFOPARK	Information, health & social needs of older, disabled people and their carers.	266
2000-00584	CARMEN	The care and management of services for older people in Europe network	268
2000-00664	CLESA	Cross-national determinants of quality of life and health services for the elderly	270
2000-00779	MEC	Minority elderly care	272
2002-00227	PROCARE	Providing integrated health and social care for older persons – issues, problems and solutions	274

2002-00251	ELDICUS	Triage decision making for the elderly in European intensive care units	276
2002-02341	CARMA	Care for the Aged at Risk of Marginalization	278
2002-02525	CareKeys	Keys for Quality Performance Management of the Care of Older Persons in Europe	280
2002-02647	EUROFAMCARE	Services for Supporting Family Carers of Elderly People in Europe : Characteristics, Coverage and Usage	282

### **SME-specific projects (CRAFT)**

<b>Project Number</b> QLK6-CT	<b>Acronym</b>	<b>Project Title</b>	<b>Page</b>
2002-70549	UROCT	Ultrahigh resolution ophthalmologic optical coherence tomography	286
2002-70587	HIPEDHIPS2	Development of a process for the manufacture of high performance near net shape orthopaedic prostheses	288
2002-70823	Rapi-HEAL	An affordable & more effective negative pressure closure treatment for chronic ulcers to improve patient mobility & quality	290
2002-70848	SCAFTCOE	Seaweed gels as fillings in pads/ mattresses for therapeutic use and care for the elderly	292
2002-71137	DOPATARGO	Dopaminergic partial agonist with potential against both Parkinson´s disease and Psychoses	294
2002-71584	ARMD	The potential of oligonucleotide submicron positively charged Emulsion ocular delivery system for age-related macular degeneration	296
2002-71851	TELEDOC	Telerehabilitation system using haptic interfaces and virtual Reality techniques	298

### **Abbreviations:**

CA = Concerted Action (coordination action)

CM = shared cost combined research and demonstration project

CRAFT = SME specific shared cost measure "collaborative research project"

CT = Contract

DM = Shared cost demonstration project

FP5 = 5th Framework Programme

KA6 = Key Action 6 "Ageing Population"

QoL = Quality of Life Programme

RS = Shared Cost research (R&D) project

SME = Small and medium sized enterprise

TN = Thematic Network Project (coordination action)

Area 6.1: Age-related illnesses and health problems

## **NERVOUS SYSTEM**





Project number:	QLK6-CT-1999-02004
EC contribution:	€1,399,985
Duration:	36 months
Type:	RS
Starting date:	01/02/2000

***Microglial activation in neurodegeneration in Alzheimer's disease:  
a therapeutical target ?***

**Abstract**

**Objectives:**

Chronic microglial activation and release of toxic mediators in CNS could explain neurodegeneration in Alzheimer`s disease. On the other hand, there are indications for a beneficial role of microglia in this disease (e.g. phagocytosis of amyloid peptide). This multidisciplinary European cooperation aims to understand the mechanisms and significance of microglial activation in Alzheimer`s disease and to evaluate strategies of therapeutic intervention in microglial activation in vitro and in vivo.

**Brief description:**

In workpackage (WP) 1, the effects of amyloid peptide (A $\beta$ ) on microglial cells will be characterized. Thorough information about extent and kinetics of microglial activation by A $\beta$  will be obtained by studies in vitro, in the living organism (in vivo-microdialysis experiments and studies in APP-transgenic mice) and in humans with Alzheimer`s disease (PET technique).

In WP2, the possible synergistic or inhibitory effects of “plaque-associated proteins” on microglial activation and the rate of neuronal A $\beta$  synthesis will be investigated.

In WP3, the hypothesis that innate immunity receptors (e.g. the LPS receptor) are crucial for A $\beta$ -mediated activation of microglial cells will be studied. Experiments in cells deficient for such receptors will be performed. In addition, the signal transduction mechanisms involved in cellular activation by A $\beta$  will be analyzed in this WP.

In WP4, we will study the biological relevance of microglial activation on a) toxicity for contiguous neurons and b) the rate of neuronal synthesis of A $\beta$ . Neuronal injury and increase of A $\beta$  release in response to microglial activation will be analysed also in vivo (in vivo microdialysis experiments).

In WP5, based on the results of WP 1-4, we will finally investigate the therapeutic consequences of our previous experiments. Then, COX-1 and -2 inhibitors, anti-cytokine strategies, anti-LPS receptor directed strategies, interferon- $\gamma$ , anti-mitotically active drugs and most importantly, further strategies that evolve from our experiments will be studied using our in vitro and in vivo models.

**Keywords:**

Alzheimer Disease – neuroinflammation – microglia - amyloid peptide

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Project number:	QLK6-CT-1999-02038
EC contribution:	€1,017,998
Duration:	36 months
Type:	RS
Starting date:	01/02/2000

***An Investigation of the Mechanism of Action of Growth Hormone Secretagogues for Improving Body Composition and Quality of Life in the Aged.***

**Brief Description**

The age-related decline in endocrine function plays an important role in many of the changes in body composition and brain function that form part of the ageing process. Our objective is to carry out studies in animals investigating how synthetic growth hormone secretagogues (GHS) act to improve body composition and brain function. Electrophysiological and neuroanatomical studies will determine how GHS interact with the brain pathways controlling growth hormone secretion, appetite and metabolism. Chronic GHS exposure will result in a new equilibrium of endocrine and CNS activity - we will study the consequences of long term GHS exposure on hypothalamic gene expression and body composition. Studies of GHS action in animals with deletions in specific genes will identify the key sites of action of these compounds. Studies in obese diabetic animals (ie with symptoms of syndrome X) will include effects of GHS agonists and antagonists on the progression of the disease. Finally, since GHS increase circulating levels of insulin-like growth factors, we will determine the effects of GHS in the central IGF system, that has a protective role against neurodegeneration

**Keywords:**

Growth Hormone Secretagogues, ageing, nervous system, cellular and molecular biology

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***Genetic and Behavioural risk factors for ageing-related coronary and cerebrovascular disease in Europe: A prospective interdisciplinary European multi-centre study***

**Abstract**

GENERALE is a unique European multi-centre prospective epidemiologic follow up study concerning both genetic and behavioural/ environmental risk factors for ageing-related atherosclerosis and cardiovascular events, focusing on antioxidative defences which ageing. Atherosclerotic cardiovascular events, cause of death and disability in Europe, and their occurrence increase as the mean age of the population rises. In this study we use existing population cohorts with DNA collected from six European countries (Finland, Germany, Italy, the Netherlands, Norway and UK). We will assess the impact and interactions of the major known coronary risk factors and 200 gene mutations with regard to atherosclerotic progression and cardiovascular events in cohorts with >20,000 subjects. The findings can be used to strengthen the competitiveness of the European research community, gene diagnostic and ultrasound imaging industry and to promote public health in Europe by new methods for prevention.

**Objectives:**

The main objective of the GENERALE study is to investigate the population impact, synergisms and antagonisms and pathophysiologically mediating role of risk factors associated with:

- 1) common genetic defects and family history,
- 2) socio-economic status,
- 3) lifestyle factors,
- 4) obesity, glucose metabolism and blood pressure,
- 5) lipids, lipid peroxidation, antioxidants, pro-oxidants,
- 6) folate metabolism with regard to ageing-related atherosclerotic progression and the incidence of myocardial infarcts, also whether genetic defects in antioxidative defence systems will enhance the atherogenic effects of smoking, high fat, alcohol intake, obesity, diabetes, hypertension, hyperhomocysteinemia and hypercholesterolemia.

The second objective is the European comparison:

- a) The prevalence of atherogenic gene mutations in different parts of Europe,
- b) To what extent differences in CVD in Europe are attributable to this genetic variability.

The third objective is to validate methods of assessment of lipid peroxidation in the human body.

The GENERALE study is based on the use of existing prospective population cohorts of middle-aged and elderly men and women, of which DNA has been collected. The cohorts are from five European countries (Finland, Germany, Italy, Norway and UK), enabling comparisons between the North, Middle and South of Europe. The study cohorts include over 20,000 subjects, which provides for the first time ever a sufficient statistical power to test gene-environment interactions in Atherosclerotic progression and CHD.

**Brief description**

The study involve the follow-up of atherosclerotic progression, assessed noninvasively with B-mode ultrasonography, and the incidence of coronary and cerebrovascular events, recorded and classified using MONICA criteria. Similar ultrasonographic technologies and protocols are used in the participating countries. This study will compete with American ARIC study, but is superior owing to a longer follow-up (up to 10 years), more genetic and behavioural variability, larger risk

gradient between centres and advances in DNA technologies. As the follow-up has mostly already been completed, this study will provide results quickly, in four years, and relatively inexpensively giving the Europeans a competing advantage study will provide results quickly, in four years, and relatively inexpensively giving the Europeans a competing advantage.

The co-ordinating and data-analysis centre will be the Research Institute of Public Health, University of Kuopio, Finland, with extensive expertise in cardiovascular epidemiology, arterial ultrasound imaging and statistical methods in population studies. Prominent European genome centres (Edinburgh, Helsinki) will participate in genotyping. Phenotypic biomarkers of lipid peroxidation (hydroxy fatty acids, cholesterol oxidation products, isoprostanes) and DNA oxidation will be measured by leading European laboratories (Copenhagen, Edinburgh, Stockholm). Most of the participating centres have already collaborated earlier.

This will be the first truly prospective study of genetic etiology of ageing-related atherosclerosis and CVD, not suffering from selection and survival biases that flaw the results of retrospective case-control studies generally applied in genetic epidemiology.

#### **Milestones and expected results:**

Follow-up for events and atherosclerosis will be completed in 2001, genotypings and lipid peroxidation assays in 2002, and statistical analysis and reporting in 2003. Time table for results:

- 1) The prevalence of genetic polymorphisms in 2002,
- 2) The role of defence systems-related polymorphisms,
- 3) Effect modification by genes on the pathophysiologic role of risk factors,
- 4) The role of lipid peroxidation as mediator and modifier of effects of major risk factors
- 5) The role of genetic polymorphisms and health habits in the European gradient in atherosclerotic CVD in 2003.

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## ***Interactions between oxidative stress and the activation of mitogenic signalling in Alzheimer's disease***

### **Objectives:**

Interactions between oxidative stress as a major driving force of degeneration and the activation of mitogenic signalling as a critical trigger of neurodegeneration in Alzheimer's disease (AD), modified by interactions and epistatic effects of AD-related genes will be studied. Research will be based on new models of the disease that allow to analyze the genetic, molecular and cellular mechanisms underlying neurodegeneration, to identify molecular switches that critically determine the fate of a neuron after injury and to test potentially protective strategies.

### **Brief description:**

The proposal presents a multidisciplinary approach on molecular and genetic factors that critically determine the pathomechanism of Alzheimer's disease (AD) and related chronic neurodegenerative disorders. It combines expertise in molecular biology, genetics, neurochemistry, neuromorphology, neuropharmacology, neurophysiology and behavioural biology. Based on new models of the disease that will be validated by comparative studies with postmortem brain tissue of AD patients, proposed research will analyse the genetic, molecular and cellular mechanisms providing the basis for the pathomechanism of AD and develop and test potentially protective strategies.

Major areas of research that will be covered by the proposal are:

Processes of intercellular signalling (e.g. mediators of oxidative stress, AGEs, AGE-receptor RAGE, cytokines, growth factors, NO) and intracellular signalling (e.g. p21ras, MAP-kinase cascade) involved in the pathomechanism, their role and interactions during the process of neurodegeneration, mechanisms of intercellular and intracellular signalling involved in the process of initiation and self-propagation of neurodegeneration and identification of targets for therapeutic interventions.

Mechanisms of cell differentiation in neurons, their regulation and dysfunction (e.g. mechanisms of cell-cycle-dysregulation in differentiated neurons) in the process of neurodegeneration, their involvement in aberrant repair in AD and their implications in apoptosis and cell death (e.g. mechanisms of oxidative stress-mediated cell death, relationship between cell-cycle-activation and cell death), possibilities of potentially neuroprotective interference with mechanisms of differentiation, de-differentiation and cell-cycle-regulation.

Involvement of immune mechanisms in neurodegeneration, mediators and mode of activation and their relationship to oxidative stress, intercellular and intracellular signalling mechanisms and cell-cycle-dysregulation in neurons, strategies for inhibition.

Modelling critical aspects of the pathomechanism through cellular, tissue and animal models (double transgenic mice overexpressing CuZnSOD/APP; transgenic mice expressing permanently activated p21ras; chronically adrenalectomized rats - ADX-model; specific two chamber culture system to analyse the effects of Advanced Glycation Endproducts).

Identification of new gene-defects causing AD or increasing the risk and analysing the interactions and epistatic effects of AD-related gene defects), genotype-phenotype relationships, mechanisms and mode of actions of genetic risk factors to induce their pathophysiological effects.

**Keywords:**

Alzheimer´ disease – AD-related genes – Cell Cycle - Immune mechanisms - Mitogenic signaling – Neurodegeneration – Neuroprotection - Oxidative stress – Transgenic animals

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## ***Connectivity in language rehabilitation in stroke and dementia***

### **Objectives:**

The project uses complimentary techniques, including Magnetoencephalography (MEG), EEG, Positron Emission Tomography (PET), and Magnetic Resonance Imaging (MRI) and combines these for the study of functional specialisation of brain regions at different time scales with a new approach to study functional integration. Structural imaging modalities like diffusion tensor imaging will be used to investigate the anatomical basis of cortical connectivity in patients. New tools for data analysis will be developed, for which several of the healthy individual participants stand in as the major expert for this technique world-wide. These include deformation field based morphometry for an objective detection of subtle morphological differences, the use of anatomical informed basis functions to improve spatial resolution and techniques to assess the effective connectivity between brain regions by means of structural equation modelling of fMRI time-series and to assess the long distance synchronisation of human brain activity by time-variant coherence analysis

With the combination of these different techniques it will be possible to get a clearer picture of the spatio-temporal dynamics of language production and comprehension in stroke and the effects of learning and rehabilitation. The combination of these different brain mapping techniques, sophisticated analytical tools, different languages (English, Finnish, German, French, Italian, Dutch, Portuguese, Greek and Swedish) and unimpaired as well as impaired speakers and listeners, is unique. This task requires a wide variety of very different methodological and technical expertise, a profound neuroscientific understanding and access and experience in the rehabilitation of patients. Therefore, we chose for a multicentre approach which pools expertise from all over Europe in an unprecedented way.

### **Brief description**

#### Theoretical work:

Development of diffusion tensor imaging to detect anatomical connections in language processing and its disruption, of anatomical informed basis functions to increase signal to noise and deformation field based morphometry to detect anatomical differences between groups

Description of effective connectivity in fMRI studies during language processing

Description of coherent EEG or MEG activities during language processing

#### Integration Work:

Standardisation and harmonisation of experimental designs

Data acquisition with the different methods (EEG/MEG; PET, MRI)

Data analysis

#### Clinical Work

Brain connectivity during language processing in fMRI or EEG/MEG in normal subjects

Brain connectivity during language processing in illiterates

Brain connectivity during language processing in stroke victims

## Key words

Language – Recovery – Rehabilitation - Diagnoses/prognoses - Neurobiological correlates - Effective connectivity - Diffusion tensor imaging - Cost-efficiency

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## ***High frequency stimulation of the subthalamic nucleus: a therapeutic approach to Parkinson's disease***

### **Objectives:**

High frequency stimulation (HFS) of the subthalamic nucleus (STN) has become a promising therapeutic option for patients with advanced Parkinson's disease (PD) who have severe motor fluctuations under levodopa medication. This project aims at optimizing the use and improving knowledge about the functional effects and possible mechanisms of this treatment through investigations in PD patients and in experimental rat models of PD.

### **Brief description:**

Clinical studies are dedicated first to the investigation of the best setting of stimulation parameters for the control of the cardinal motor symptoms of parkinsonism. The second objective is to evaluate the long term effects of the stimulation on cognitive functions in addition to motor scores. For this purpose PD patients are tested 1-4 years after surgery, under "off" and "on" STN HFS conditions, using a computerized motor screening test and a battery of neuropsychological tests selected on the basis to their sensitivity to PD and to levodopa withdrawal. The same tests are administered to other PD patients before surgery, under "off" and "on" levodopa medication conditions, and 3 months after surgery, under "off" and "on" STN HFS conditions, to compare the effects of STN HFS versus levodopa treatment.

As HFS has been developed to replace ablative surgery, the behavioural studies in experimental animals are conducted to analyse the effects of STN lesions and those of STN HFS in intact or parkinsonian rats using tasks assessing various aspects of motor and cognitive functions. The impact of STN HFS on STN neuron metabolic activity and outflow is investigated in experimental animals by means of in vivo microdialysis and in situ quantitative morphological approaches. The consequences of this stimulation on the functional alterations resulting from dopamine depletion in the basal ganglia structures are studied in parallel. Whether or not STN HFS can offer neuroprotection to dopamine neurons and influence dopamine metabolism and transmission is being investigated in a rat model of early PD (based on partial retrograde lesion of the nigrostriatal dopamine neurons) using neurochemical and morphological approaches. Finally, since the degeneration of dopamine neurons is progressive in the course of PD and since patients underwent long term levodopa medication before surgery, the possibility that the degree of dopamine loss and levodopa treatment may govern the therapeutic efficacy of STN HFS will be evaluated. For this purpose, the behavioural and cellular consequences of STN HFS will be compared between rats with partial or extensive dopaminergic lesion untreated or treated with levodopa.

### **Keywords:**

Parkinson's disease - Subthalamic nucleus - Deep brain stimulation - Basal ganglia

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contribution:	€1,706,355
Duration:	36 months
Type:	RS
Starting date:	01/02/2000

## *Network for Efficiency and Standardisation of Dementia Diagnosis*

### **Objectives:**

To improve and standardise the diagnosis of dementia at an early stage:

Use powerful and accurate functional imaging techniques, in particular positron emission tomography (PET) with 18F-2-fluoro-2-deoxy-glucose (FDG) as the current standard to assess the regional metabolic impairment that is characteristic for Alzheimer disease (AD).

Use this technique as an objective reference to improve and test the cost-efficiency of clinical tools for early and differential diagnosis of dementia.

Build a large FDG-PET data base of normal and dementia patients.

### **Brief description:**

The project is a multicentre study that now involves 10 centres with a memory clinic and access to advanced brain imaging technology, in particular PET. It involves analysis of retrospective data and, in the second phase, a prospective study.

For analysis of retrospective data (641 cases, including normal controls, Alzheimer disease, mild cognitive impairment, depression, vascular dementia, dementia with Lewy bodies, and fronto-temporal dementia), which were collected in the first year, we used advanced quantitative image analysis techniques to establish FDG-PET diagnostic criteria. A high accuracy (95%) was achieved for the distinction between AD and normal controls. Even very mild cases of AD were identified with 84% sensitivity and 93% specificity. Discriminant analysis is used for distinction between AD and other types of memory impairment.

Prospective data recruitment has started in Feb. 2001. It will cross-validate clinical diagnosis and associated PET findings and identify the metabolic correlates of diagnostic clinical and neuropsychological findings. The relation between FDG-PET and other biological diagnostic markers will be investigated and FDG-PET will be compared with other imaging and electrophysiological modalities. Diagnostic algorithms will be developed and analysed with respect to cost-efficiency. Specific neurotransmitter systems (dopaminergic and cholinergic) will be investigated. Finally, the FDG-PET data base and associated diagnostic procedures will be made available to the scientific community.

### **Keywords:**

Early diagnosis of Alzheimer disease – dementia – depression - mild cognitive impairment - functional brain imaging - positron emission tomography - cost efficiency - neuropsychological tests - prospective study.

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EC contribution:	€ 1,999,712
Duration:	48 months
Type:	RS
Starting date:	01/03/2000

## *Validation of single and multiple transgenic mice models for Alzheimer's disease*

### **Objectives:**

Fundamental research aimed at generating models for the molecular causes of Alzheimer's disease, and their in-depth analysis in vivo, i.e. transgenic and knock-out mice, and derived ex vivo systems. Transgenic mice are the “pre-clinical” models that allow invasive analysis of normal and deviating processes and interactions, at the molecular, cellular and tissue level. The models and the fundamental knowledge are needed to develop, test and optimise diagnostic and therapeutic procedures and novel drugs.

### **Brief description:**

The approach is essentially based on “experimental genetics” to develop transgenic mouse strain(s) and cell-lines, in which the expression or the inactivation of a mutant or wild-type human gene provokes a stable phenotypical defect or a marker. We have generated a transgenic mouse strain that overexpress specifically in the central neurons the human mutant Amyloid Precursor Protein (APP[V717I]). This mouse strain recapitulates almost perfectly the amyloid pathology of Alzheimer's disease patients, i.e. the amyloid plaques in the brain parenchym and vascular amyloid angiopathy. Other human proteins involved or related to Alzheimer's disease, i.e. Presenilin1 (PS1), protein tau, ApolipoproteinE4 (ApoE4),  $\beta$ -secretase (BACE) are additionally expressed in the central neurons in the brain of the APP transgenic mice by the use of recombinant DNA constructs or by viral vectors. The different single and multiple transgenic mice are further characterised and analysed by a multi-disciplinary approach to validate the models for the different pathogenic mechanisms in the neurodegenerative process in Alzheimer's disease.

Selected mouse strains with certified phenotypic characteristics of amyloid pathology are available and validated within the consortium. Parameters and test-systems include profiles of learning, memory, motivation, sensory and motor impairment, cognitive impairment. These are correlated to the molecular and neuropathological changes observed in the brain pre- and post-experiment.

The amyloid pathology is the major pathogenic mechanism and target to understand, therefore the APP [V717I] transgenic mice resulting from a preceding EEC-project, constitute the corner-stone of this consortium and is central to all its efforts. They are also the test-banks for developing, testing and refining viral vectors to deliver specified enzymes to the brain to define their potential for gene-therapy.

### **Keywords**

Alzheimer – Amyloid - presenilin - transgenic mice - model-validation

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Type:	RS
Starting date:	01/02/2000

## ***Targeting Astrocytes To Disrupt Inflammation-Neurodegeneration Coupling: Application To Alzheimer's Disease***

### **Abstract**

Increasing evidence supports the "inflammatory hypothesis" in Alzheimer's Disease (AD) according to which neuronal damages in this age-related disease are caused not only by the fundamental pathology it-self but also by the local inflammatory response to it sustained by reactive glia. Recent findings demonstrate sophisticated interaction and integration between neurons and astrocytes, a major glial cell population in the brain. Inflammatory astrocytes undergo morpho-functional changes which may perturb neuron-astrocyte interaction and result in neuronal sufference. By identifying and targeting harmful pathways in inflammatory astrocytes we will define potential new therapeutic approaches to prevent, or delay, AD progression. This consortium combines complementary expertise to: a) assess the "inflammatory hypothesis of AD" and the role of astrocytes in transgenic models; b) identify targets of inflammation-neurodegeneration coupling in astrocytes; c) validate drug strategies against them; d) test these therapeutical strategies in AD transgenic.

### **Objectives:**

The aims of the project are: to explore the hypothesis that local brain inflammation, sustained by reactive glia, participates in the neuropathology of AD, to understand the underlying cellular and molecular mechanisms in astrocytes; to design drug interventions directed against such mechanisms and to test their efficacy in transgenic models of AD. The final goal is to provide an original new strategy to prevent, or at least delay, the progression of neurodegeneration in AD. The overriding theme is "The age-related illnesses and health problems" addressed by studying AD. Cell communication in neuroscience will be studied by defining physiological and pathophysiological neuron-astrocytes interactions. Novel transgenic animal models of brain inflammation and AD will be generated or optimized. Defined drug strategies will be used to disrupt progression of degenerative brain disorders

### **Brief description:**

A new and exciting view of the CNS is that neuronal physiology depends on the presence and properties of the bystander astrocytes. Members of this consortium have importantly contributed to the recent understanding of neuron-astrocyte integration. Changes occurring in astrocyte functions during inflammation are bound to modify physiological neuron-astrocyte interactions and start pathological inflammation-neurodegeneration coupling. Molecular steps involved in this cascade may be targeted in order to disrupt such coupling and protect neurons. This consortium proposes 10 workpackages to define and test drug treatments against inflammation-neurodegeneration coupling in astrocytes and apply them to transgenic animals of AD. Workplan is the following:

a) to study, at cellular and molecular level, the impact of inflammation on astrocytic properties and astrocyte-neuron interactions; b) to select molecules acting on the harmful mechanisms in astrocytes as well as strategies to deliver such molecules to reactive glia selectively; c) to test the "inflammatory hypothesis of AD" utilizing transgenic animal models, in particular an AD model combined with genetic manipulation of inflammatory mediators; d) to characterise cellular and molecular properties of reactive astrocytes in AD transgenic models and human AD brains; e) to test whether targeting inflammatory astrocytes in vivo delays the progression neurological and cognitive decline in AD transgenic models.

This consortium is composed by a main core of 4 glia specialists, complemented by a neuropathologist, a genetist and a research group from a pharmaceutical company. Thanks to this composition, the proposal plans to perform a large spectrum of investigations requiring multidisciplinary competences and techniques, which cannot be provided by single laboratories. This can only be achieved through tight collaboration and interaction within the consortium involving 5 EU states and 1 associated member. A new and exciting view of the CNS is that neuronal physiology depends on the presence and properties of the bystander astrocytes. Members of this consortium have importantly contributed to the recent understanding of neuron-astrocyte integration. Changes occurring in astrocyte functions during inflammation are bound to modify physiological neuron-astrocyte interactions and start pathological inflammation-neurodegeneration coupling. Molecular steps involved in this cascade may be targeted in order to disrupt such coupling and protect neurons. This consortium proposes 10 workpackages to define and test drug treatments against inflammation-neurodegeneration coupling in astrocytes and apply them to transgenic animals of AD. Workplan is the following:

a) to study, at cellular and molecular level, the impact of inflammation on astrocytic properties and astrocyte-neuron interactions; b) to select molecules acting on the harmful mechanisms in astrocytes as well as strategies to deliver such molecules to reactive glia selectively; c) to test the "inflammatory hypothesis of AD" utilizing transgenic animal models, in particular an AD model combined with genetic manipulation of inflammatory mediators; d) to characterize cellular and molecular properties of reactive astrocytes in AD transgenic models and human AD brains; e) to test whether targeting inflammatory astrocytes in vivo delays the progression neurological and cognitive decline in AD transgenic models.

**Keywords:**

Alzheimer's disease – astrocytes - brain inflammation

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EC contribution:	€1,400,000
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Starting date:	01/01/2000

***The Fe65-APP-X11 protein-protein interaction network: towards the generation of new molecular tools for Alzheimer's disease diagnosis and therapy***

**Objectives:**

Deposition of amyloid beta peptide (A $\beta$ ) within the brains of Alzheimer's disease (AD) patients is believed to be central to the pathogenesis of AD. A $\beta$  is derived by proteolytic cleavage from the precursor protein APP. Recently, two families of adaptor proteins, the Fe65s and X11s, have been shown to bind to APP and to significantly influence APP processing and Ab production. The objectives of the proposal are:

- 1) to generate transgenic mice in which Fe65 and X11a are over-expressed and mice in which the Fe65 and X11a genes have been ablated, in which to study the effects of Fe65 and X11a on APP processing.
- 2) to identify the binding partners of Fe65 and X11a, other than APP, and to determine their possible effects on Fe65 and X11a modulation of APP processing and Ab production.
- 3) to identify synthetic molecules that modulate Fe65/APP vs. X11a /APP binding and which might assist the future design of novel therapeutics for AD.
- 4) to determine whether the "molecular misreading" of the APP gene observed in AD also occurs for Fe65 and X11 genes, and to determine the consequences of any such Fe65 and X11 gene misreading on APP processing and Ab production.

**Brief description:**

Most of the experimental approaches of this proposal are based on the observation that, in cultured cells, Fe65 overexpression causes an increase of A $\beta$  production while X11a overexpression leads to a stabilisation of APP and a consequent decrease of A $\beta$  production. To study these phenomena in vivo, A $\beta$  production and APP processing will be assayed in transgenic mice that overexpress Fe65 and X11a and in mice in which these genes have been knocked out.

Fe65 and X11a show the characteristics of adaptor proteins. The full complement of proteins binding to Fe65 and X11 will be determined by using the yeast two hybrid system and expression cloning methods with the protein-protein interaction domains of Fe65 and X11a used as "baits". The effects of the already known and of the newly discovered Fe65 and X11 interacting proteins on APP binding and on Fe65/X11a modulation of APP processing will then be investigated.

Synthetic peptides, based upon APP sequence, will be used to try to selectively disrupt Fe65-APP vs X11a -APP complexes.

To determine whether misreading of Fe65 and X11 genes occurs in AD, antibodies to Fe65 and X11 "+1 proteins" will be generated and used to probe normal and AD tissues for the presence of aberrant proteins. The presence of aberrant proteins and/or of antibodies directed against them will be evaluated in biological fluids of AD patients and in patients suffering from other types of dementia.

We have already obtained: i) founders of Fe65 transgenic mouse lines; ii) ES cell clones carrying the deletion of the Fe65 gene by homologous recombination; iii) vectors for the generation of X11 transgenic mice and X11 gene knock out mice; iv) antibodies against Fe65+1 and X11+1 proteins.

We demonstrated that: i) Fe65 is present both in the nucleus and in the cytoplasm and that APP regulates Fe65 nuclear translocation; ii) Fe65 interacts with Abl tyrosine kinase, which

phosphorylates and binds to APP through its SH2 domain; iii) X11 interacts with the copper chaperone for SOD1 and inhibits SOD activity.

Several ligands of Fe65 have been identified and are under study. We are currently developing procedures to interfere in vivo with Fe-X11/APP complexes. Antibodies directed against Fe65+1 and X11+1 are currently used to analyse the presence of these aberrant proteins in AD brains.

### **Keywords:**

Alzheimer's disease - adaptor proteins - amyloid deposition - transgenic and KO mice

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Type:	RS
Starting date:	01/01/2001

## ***The Role Of Neurosteroids In Healthy Ageing: Therapeutical Perspectives***

### **Objectives:**

The partners have shown that the administration of neurosteroids can reverse age-related memory deficits and abnormalities of myelin sheaths. Use of neurosteroids could thus become part of strategies for successful ageing and rehabilitation, by administering selective neurosteroid compounds or by increasing the synthesis of endogenous neurosteroids using agonists of the mitochondrial benzodiazepine receptor (MBR).

### **Brief Description:**

The project concerns preclinical research based on animal and cell culture models relevant to the ageing process of the nervous system.

Levels of neurosteroids are measured in the nervous system during ageing by gas chromatography - mass spectrometry, a new and extremely sensitive method. Levels of neurosteroids will be related to the expression of enzymes involved in their synthesis.

To reverse age-related memory deficits, we use stereotaxic infusion of neurosteroids and stimulation of their local synthesis with MBR ligands. The protective effects of neurosteroids on nerve cells and memory performance are studied after excitotoxic injury, to which the ageing brain is particularly sensitive. The mechanisms by which neurosteroids improve spatial memory performance and exert neuroprotective effects are examined, involving their influence on inhibitory GABAergic currents. The effects of neurosteroids on GABA<sub>A</sub> receptors are examined in slices of rat hippocampus, a brain region involved in memory. We try to find morphological correlates of ageing memory functions and the different actions of neurosteroids by quantifying GABAergic and non-GABAergic synapses in different parts of the hippocampus. These experiments are pivotal to an understanding of neurosteroid actions upon central nervous system function.

The breakdown of myelin sheaths is a reliable marker of the ageing brain and has been related to cognitive impairment. In addition, remyelination is considerably slowed in old rats. We examine whether the age-associated decrease in the rate of remyelination in the brain can be improved by treatment with neurosteroids or MBR ligands and whether neurosteroids and MBR ligands allow the age-related abnormalities of myelin sheaths in peripheral nerves to be reversed. The generation of transgenic mice provides the basis for studying the actions of neurosteroids and MBR ligands on the expression of myelin protein genes. These studies also provide important clues to the understanding of demyelinating neuropathies, which represent a serious problem in the elderly population.

### **Keywords:**

Steroids - Pregnenolone - Progesterone - Pregnanediones - Prasterone - Testosterone - Estradiol - Mass Fragmentography - Learning - Neuroprotective Agents - Receptors - GABA<sub>A</sub> - Demyelinating Diseases - Brain Injuries - Nerve Regeneration - Aging.

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EC contribution:	€1,195,923
Duration:	36 months
Type:	RS
Starting date:	01/02/2001

## *Nicotine, Nicotinic Receptors And The Ageing Brain*

### **Objectives:**

To study whether polymorphisms in nAChR genes influence the rate of cognitive decline in the general population and if nAChR gene loci contribute to the risk of age-related dementias, 2. to characterise the molecular mechanisms of nAChR-related neuroprotection and neurodegeneration using animal model systems, 3. the preclinical development of new nicotinic agents for the therapy of age-related neurodegeneration and cognitive deficits.

### **Brief description:**

The workplan includes :

1. The determination of the contribution of nAChR genes to cognitive decline in the elderly and in demented subjects, by means of the study of nAChR gene polymorphisms.
2. The study of the contribution of specific nAChR isoforms to brain ageing by means of gene targeting methods. Morphological, neurochemical, electrophysiological and behavioural parameters will be studied in nAChR subunit knock-out and knock-in mice during ageing.
3. The identification of new genes related to neurodegeneration induced by nAChR deficit, using subtraction libraries and differential screening techniques in nAChR subunit mutant mice. Attempts to identify human homologues of these murine sequences will be made using genomics databases available to the partner laboratories.
4. The study of the interaction between nAChR deficits and other pathogenetic factors active during ageing. Amyloid $\beta$  protein and glutamate receptor-mediated neurotoxicity will be studied in nAChR mutant animals. The influence of nAChR activation or deficit on brain trophic factor systems will be investigated.
5. The study of the influence of nAChR on programmed cell death and necrosis of neurones. The influence of nAChR on cell death will be studied in in vitro models of apoptosis. In parallel, apoptotic processes will be analysed in mice lacking specific nAChR isoforms.
6. Preclinical development of new nicotinic agents for age-related neurodegeneration and cognitive deficits. Development compounds arising from current research into nAChR ligands will be evaluated in the animal models of age-related deficits developed by the consortium.

### **Keywords:**

Nicotinic acetylcholine receptors - gene polymorphisms - neurodegeneration - amyloid neurotoxicity - neurotrophic factors - apoptosis - knockout mice - age-related cognitive decline - novel nicotinic agents.

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Project number:	QLK6-CT-2000-00384
EC contribution:	€270,000
Duration:	36 months
Type:	TN
Starting date:	01/05/2001

## *Early pathogenic markers of slow neurodegenerative diseases*

### **Objectives:**

Age-related disorders of the nervous system such as Alzheimer's, Huntington's and Parkinson's disease, and transmissible encephalopathies caused by prions are associated with changes in the conformation of proteins expressed in nerve cells. These diseases share in common the formation of misfolded proteins and the accumulation of aggregates and deposits in brain.

The ultimate goal is to use detection of protein aggregates or other early markers in easily accessible tissues as early diagnostic, prognostic, and therapeutic indicators of neuronal disease in Parkinson's, Huntington's and prion disease. Using cell cultures, living animals and clinical materials, the main objectives of this proposal are: 1) To define the pathogenetic significance of protein misfolding and aggregation and, to identify and characterize concomitant changes in cell structure and metabolism as early signs of neurodegeneration; 2) To validate in accessible tissues such as blood, these early, biologically relevant markers as predicting the onset and progression of brain pathology; 3) To test pharmacological treatments using the validated markers.

### **Brief description:**

This proposal includes basic molecular science and its translation to clinical application, especially with the development of pathogenetically relevant diagnostic markers. This is particularly relevant to 6.1 of the QoL Work Program of FP5, as it aims at reducing the impact of incurable, slowly progressing and disabling neurodegenerative disorders, by facilitating the development of treatments that reduce their morbidity by delaying their onset or halting their progression. The team's expertise includes cell and molecular biology, protein engineering, clinical neuropathology, and clinical neuroscience. We envisage 4 multidisciplinary Work Packages:

Cell culture models of slow neurodegeneration due to misfolded proteins.

Slow neurodegeneration due to misfolded proteins in animals.

Peripheral tissue changes due to misfolded proteins correlated to slow degeneration in the central nervous system.

Intervention in cell pathology caused by misfolded proteins.

The consortium will create model systems for Parkinson's, Huntington's and prion diseases using neuronal cells and transgenic mice. In these models, protein aggregate formation will be monitored in neurons. Changes in cell structure and biochemistry will be followed and defects in neural connections, transmitter release, neuronal firing and behavior examined. These changes will be related to the extent and nature of protein aggregate formation. The pathological findings will be correlated to changes in peripheral blood lymphocytes of mice and humans, as well as on muscle biopsies from affected patients. New pharmacological approaches to limit protein misfolding and inhibit development of cell pathology both in neurons and peripheral tissue will be developed. Modification of the peripheral early markers and, neuronal dysfunction and degeneration will be examined during the pharmacological treatments to validate the markers and possibly identify agents of therapeutic interest.

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EC contribution:	€600,000
Duration:	48 months
Type:	CA
Starting date:	01/03/2001

***Impact of age-related brain white matter changes on transition to disability in the elderly. Leukoaraiosis and disability.***

**Objectives:**

The main objective is to evaluate whether deep white matter changes, frequently detected on imaging (computed tomography or magnetic resonance) in the brain of aged individuals, is an independent determinant of the transition from a normal functional status to disability in the elderly. The role played by these changes in predicting death, dementia, gait impairment and cardiovascular events, all described in association with these images, will be also determined.

**Brief description:**

Eight hundred 65-84 years old subjects having brain images with white matter changes and showing no or mild disability will be enrolled and followed-up for 3 years.

These subjects will be identified in stroke centres, memory/dementia clinics, neurology/neurogeriatric departments and in random population cohorts.

Definitions of functional, clinical and brain imaging outcomes will be validated and harmonised in advance across the different national settings where the subjects will be enrolled.

Relative risks for the specified outcomes will be estimated in subjects with different severity of white matter changes, adjusting for confounding or modifying factors.

Progression of these changes will be followed-up on MRI images in relation to the variations in functional, including quality of life and clinical status.

At baseline and at yearly follow-up assessments data will be collected on: vascular risk factors; cardiovascular and neurological conditions; functional autonomy in the activities of daily living; quality of life; global and selective cognitive functions; behaviour; mood/depression; motor performance.

All the data collected by each enrolling centre will be electronically transmitted, and stored in a central database, checked in real time for completeness and quality, and analysed using methods of univariate and multivariate analysis.

The results are expected to provide information on causes of disability in the elderly, and indications on potential preventive strategies.

**Keywords:**

Ageing – disability - brain - white matter - changes.

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Starting date:	01/03/2001

## *Neuroreceptor changes in mild cognitive impairment*

### **Objectives:**

The objectives of this project are to be able to pose an early diagnosis and a prognosis for the development of Alzheimer's disease. Mapping of brain receptor in normal aged individuals, in patients with mild cognitive impairment, and in Alzheimer's disease will be compared to neuropsychological and psychiatric measures to establish the relationship between these measures.

### **Brief description:**

The early phase of Alzheimer's disease (AD) is manifested in a condition termed 'mild cognitive impairment' (MCI). MCI has recently become the subject of intensive investigations because earlier diagnosis of AD may allow for earlier intervention by, e.g., drug therapy. Currently, it is impossible to predict who of the patients with MCI later will convert into patients with AD.

This project involves investigations of normal elderly individuals as well as patients from memory clinic populations with MCI and AD. All subjects will in the single centres undergo the same complete neurological, neuropsychological and psychiatric evaluation. Blood testing and structural brain imaging with magnetic resonance imaging (MRI) will also be carried out. Positron emission tomography (PET) or single photon emission tomography (SPECT) will be used for mapping various brain neuroreceptor systems. Each centre has selected their individual receptor tracer ligand of probable relevance for MCI; these include five different markers. In some centres, previously validated methods such as cerebral glucose metabolism and cerebral blood flow measurements will be included. These measures will be compared to receptor distribution images. Since the collaboration is based upon a common protocol defining neuropsychological, neuropsychiatric and imaging criteria to be used by the individual partners a comparison between the mapping of the different receptor systems in the different centres is possible. Within the concerted action structure, a common platform for data exchange and a database for collection of relevant data will be constructed.

The final intention is to relate the findings from functional imaging with the clinical measures as well as the findings from functional imaging with progression rates and over-all prognosis. On the basis of these results, we will settle the diagnostic value of neuroreceptor imaging tools for an early diagnosis in the elderly patient with memory and/or emotional symptoms. Hopefully, we will also be able to point at new potential areas for drug development.

### **Keywords:**

Alzheimers disease - mild cognitive impairment - neuroreceptors - positron emission tomography - neuropsychology - disease progression - magnetic resonance imaging - brain imaging.

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## *European Multiple System Atrophy Study Group*

### **Objectives:**

Taking advantage of the European lead in international multiple system atrophy (MSA) research the proposed European MSA study group (EMSA-SG) aims to establish a European MSA Registry (EMSA-R) as well as a Core Assessment Program for Interventional Therapy in MSA (CAPIT-MSA).

The CAPIT-MSA trial protocol will be designed and validated through the first prospective natural history study of European MSA patients.

During the natural history study EMSA-SG will facilitate future research into ecogenetics and molecular pathology of MSA by virtue of decentralized DNA and brain tissue banking.

### **Brief description:**

Parkinson's Disease (PD) and/or MSA databases have been established by a number of centres participating in the project. Selected features of these will be combined to construct a novel MSA database for the purpose of patient recruitment, data acquisition and monitoring throughout the project and subsequent intervention trials.

CAPIT-MSA will be designed similar to previous EU sponsored concertation efforts in PD (CASIT-PD, Defer 1999) and Huntington's Disease (CAPIT-HD, Quinn 1996). CAPIT-MSA will comprise a novel set of EMSA-SG diagnostic criteria, a novel Unified Rating Scale (UMSARS) and additional investigations including autonomic function and urodynamic tests as well as structural and functional brain imaging.

The CAPIT-MSA protocol will be validated by a multicentre prospective natural history study of 120 MSA patients, recruited during the first year from 20 European University Hospitals. This study will generate prospective rates of disease progression in MSA, it will also identify important prognostic factors.

During the course of the natural history study EMSA-SG will coordinate decentralized DNA and brain tissue storage and processing in the participating centres according to standard protocols to facilitate future studies of ecogenetics and molecular neuropathology. Requests for DNA or brain tissue of patients dying with MSA will be reviewed by the EMSA-SG Steering Committee.

### **Key words:**

Multiple system atrophy, Unified MSA Rating Scale, Natural History, DNA/Brain Bank

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Type:	RS
Starting date:	01/01/2002

## *Rehabilitation In Parkinson's Disease: Strategies For Cueing*

### **Objectives:**

RESCUE aims to provide: 1 Effect of different cue types on gait parameters during stable conditions and after contextual manipulation in Parkinson's Disease (PD). 2 Optimal rehabilitation cueing and self management strategies. 3 Optimal characteristics of a cueing device facilitating to enable subsequent technological development. 4 Long-term and clinical benefits of the novel cueing methods in the home environment of patients with PD.

### **Brief description:**

Despite modern medical treatment, the walking disorders resulting from Parkinson's disease (PD) have a profound impact on the daily lives of sufferers and carers creating a spiral of immobility. RESCUE seeks to break this vicious circle by optimising, establishing and implementing a novel rehabilitation method. It will investigate the changes induced by auditory and visual cues on walking under various experimental conditions to determine which cues can best improve and sustain functional gait performance. By identifying the optimal behavioural and environmental strategies, it will promote self-management by patients and treatment by therapists. A prototype of a cueing device to be developed and tested complements the treatment package. RESCUE will test out the effectiveness of the optimised cueing package at home in the first randomised controlled clinical trial involving three EU centres, expert in this area. RESCUE will integrate knowledge into the best method for effective transfer and generalisation of cueing to activities of daily life enhancing the self-autonomy and quality of life of people with PD.

Phase I: Optimisation: Effectiveness and stability of visual and auditory cues on gait performance and identification of cognitive behavioural strategies and psychological, social and physical cost will be investigated in the laboratory and at home. Wash out periods will be defined, a portable prototype cueing device will be developed.

Phase II: Preparation: Guidelines will be developed for training patients at home. Physical therapists will be trained in the optimal cueing package and instrument. Independent observers will be trained.

Phase III: Generalisation: Efficacy of cueing package on functional gait will be investigated in a multi centre single blind cross-over randomised clinical trial (RCT) in the home.

Phase IV: Dissemination: Dissemination and duplication of optimal therapeutic strategies and self-management strategies to physical therapists in European countries as well as patient societies on Parkinson's disease. Production of educational packages and consensus conference. Guidelines for the use of a permanent cueing device and future developments.

### **Keywords:**

Rehabilitation - Cueing - Auditory and visual stimuli - Cognitive behavioural strategies - Fatigue - Contextual factors - Parkinson's disease - Mobility - Physiotherapy - Self-management strategies - Transfer of effect - Prototype cueing device - Gait - Functional performance.

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## *Collaborative Evaluation Of Rehabilitation In Stroke Across Europe*

### **Objectives :**

Rehabilitation of stroke patients is time consuming and expensive. The specific components of rehabilitation that affect outcome after stroke remain to be investigated. The aim of the proposed study is to compare the outcomes of stroke rehabilitation in four different rehabilitation centres across Europe. Differences in outcome will be related to amount and content of therapy, organisational characteristics and input of man-hours by the staff.

### **Brief Description :**

In each centre the pattern of recovery of 120 consecutive stroke patients will be documented. Measurements will be performed on admission and at discharge, and at two, four and six months after stroke resulting in complete assessments on five occasions on approximately 480 patients. Identification of differences in the provision of stroke services in the four centres will be based on time sampling of activities. An observation record will be used to register the activities, locations and social interaction of the patients on a random sample of 30 days in each centre.

Fifteen physiotherapy and 15 occupational therapy treatment sessions will be videotaped. The recordings will be made on 30 randomly selected days in the year. Video taping will be done on matched patients. The content of interventions will be logged to unveil the black box of physical and occupational therapy.

Analysis of the organisational characteristics of the different units providing rehabilitation requires the determination of the relative input of man-hours, the personnel and task characteristics for different patterns of organisation of stroke services and their respective relation to outcome.

The structural analysis will focus on management (pathway, planning, control system, etc.), task characteristics (standardisation of tasks, amount of formalism in organising the work), staff characteristics (level of specialisation of staff, structure of labour division, etc.) and physical environment (location, architecture, facilities, etc.). The data will be collected by quantitative and qualitative methods.

The pattern of recovery in the various centres will be compared. Case-mix will be used to control for the variation between patients treated in the four different settings. We will be able to identify which centre generates the best outcome. Multivariate analysis will be used to explore factors that contribute to the difference in outcome. The best clinical practice in stroke rehabilitation will be identified. The final goal is to improve the management of stroke rehabilitation and to reduce the level of long-term disability of stroke patients.

### **Keywords :**

Stroke - rehabilitation - recovery - prediction - quality control - organisational management - best clinical practice - physiotherapy - occupational therapy - multidisciplinary approach

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Duration:	48 months
Type:	CA
Starting date:	01/01/2003

## ***European Stroke Prevention in Reversible Ischaemia Trial***

### **Objectives:**

The aim of ESPRIT is to compare the efficacy and safety of two new treatment modalities (A and B):

A) oral anticoagulation (INR 2.0-3.0) and

B) the combination of 30-325 mg acetylsalicylic acid and 400 mg dipyridamole daily with that of the standard treatment

C) 30-325 mg acetylsalicylic acid daily to find a more effective treatment in the secondary prevention for patients with cerebral ischaemia of arterial origin

### **Brief description:**

Patients who have had a transient ischaemic attack or non-disabling ischaemic stroke of arterial origin have an annual risk of 7 to 12% for subsequent nonfatal stroke, nonfatal myocardial infarction or death (from all vascular causes) without treatment. The standard treatment acetylsalicylic acid (ASA) prevents only 13% of these events; this is far from ideal. ESPRIT is a randomised, international, multicentre trial in which three treatments are compared: a) AC (INR 2-3), b) ASA combined with dipyridamole c) ASA. The primary measure of outcome is the composite event 'nonfatal stroke, nonfatal myocardial infarction, death from all vascular causes or major bleeding complication', whichever occurs first. A total of 4500 patients will be enrolled.

Since cerebrovascular disease is one of the major European health problems, especially in the elderly, it is of utmost importance to look for more effective prevention than that by ASA. Data from secondary prevention trials in other cerebrovascular diseases suggest that oral anticoagulation (AC) or ASA combined with dipyridamole are more effective in the secondary prevention.

A more effective treatment will reduce disability, handicap and mortality and prevent loss of quality of life in many (especially elderly) patients.

### **Keywords:**

stroke - secondary prevention - European - trial - cerebral ischaemia - TIA

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Type:	CA
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***Role of Zinc Metabolism in Alzheimer's Disease. Elaboration of New Strategy for Prevention and Therapy of Alzheimer's disease.***

**Objectives:**

Refinement of research targets and task distribution between partners for collaborative research towards elaboration of a new therapeutic approach for Alzheimer's disease on the basis of knowledge about zinc metabolism in the brain. Coordination of research activities and accumulation of results into a common database. Dissemination of research results and inclusion of new partners into research network.

**Brief description:**

Zinc plays important roles in development and functioning of the nervous system and its homeostasis is disturbed in many diseases, including Alzheimer's disease. Elevated level of zinc is neurotoxic and according to the latest results zinc may play a crucial role in aggregation of amyloid  $\beta$  peptides and formation of amyloid plaques characteristic for Alzheimer's disease.

A present concerted action project will refine the research aims and functions and coordinate research between partners in the collaborative network towards understanding the fundamental principles of zinc metabolism in the brain and finding of key points of its regulation. The final aim of the research network is the elaboration of a new strategy and tools for prevention and therapy of Alzheimer's disease through normalization of zinc metabolism in the most critical regions of the brain.

Results of the concerted action project will be disseminated to community and industrial bodies during scientific meetings organized by consortium and through joint publications. New research centers and industrial bodies will be attracted into the research network.

**Keywords:**

Alzheimer's disease - amyloid plaques - zinc metabolism - metal chelation therapy.

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***Development of screening guidelines and clinical criteria  
for predementia Alzheimer's disease***

**Objectives:**

The primary goal of the study is to reach an evidence-based European consensus on the identification of subjects with Alzheimer's disease (AD) in the predementia stage. The secondary goals of the project will be to develop diagnostic criteria for predementia AD in a clinical setting and screening guidelines for predementia AD in the general population.

**Brief description:**

Alzheimer's disease (AD) is one of the most common neurodegenerative disorders in Europe. The diagnosis of AD can presently only be made when a patient is demented. Tools for diagnosing patients with AD before they become demented, i.e. when they are in the predementia phase, are urgently needed. This will create the opportunity to start therapeutic interventions in an earlier phase than it is possible now. This will improve the quality of life of patients with AD considerably. The project consists of 2 parts. In the first part, clinical criteria for predementia AD will be developed for use in the second line clinical setting. In the second part, screening guidelines for predementia AD in the general population will be developed. The clinical criteria for predementia AD will be based on the pooled data from 15 prospective clinical studies that will collect markers of predementia AD in 800 subjects with mild cognitive complaints. The markers of predementia AD that will be used for the development of the criteria are demographic variables, medical history, the score on the Mini-Mental State Examination, the degree of functional impairment, performance on cognitive tests, the degree of medial temporal lobe atrophy, the apolipoprotein E genotype, the number of white matter lesions, and the concentration of  $\beta$ -amyloid and tau protein in cerebrospinal fluid. In addition, blood and CSF samples will be collected that can be used for future research on markers of predementia AD. The screening guidelines will be based on pooled data from 5 population-based studies that have collected baseline markers of predementia AD in non-demented elderly and follow-up data with respect to cognitive outcome. The markers of predementia AD that will be used for the development of the screening guidelines are demographic variables, medical history, the score on the MMSE, the degree of functional impairment, cognitive test performance, and the apolipoprotein E genotype.

**Keywords:**

Early diagnosis of Alzheimer's disease - predementia Alzheimer's disease - mild cognitive impairment

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Type:	CA
Starting date:	01/09/2002

## ***European Carotid Stenting Network***

### **Objectives:**

To set up an European network of collaborating centres performing carotid stenting and surgery for the prevention of stroke, encourage harmonized clinical practice and standards for the investigation and treatment of carotid stenosis, and to carry out a randomised clinical trial within the network to compare the risks, benefits and economic value of carotid stenting and surgery.

### Expected results:

The results of the randomised trial will show whether stenting or surgery is preferable in terms of safety, economics and patient acceptability for the treatment of carotid stenosis

### **Potential applications:**

The dissemination of the knowledge and experience gained in the network of the procedures involved will inform the choice of doctors and health care funders in the EU when treating patients at risk of stroke due to carotid stenosis.

### **Brief description:**

Stroke is a major cause of disability in the ageing population. Atherosclerotic carotid artery stenosis is an important cause of stroke, which can be prevented by carotid endarterectomy. However, endarterectomy requires an incision in the neck and carries a small risk of operative stroke. Stenting, a new endovascular method of treating carotid stenosis avoids some of the discomforts and complications of surgery. However, stenting also risks procedural stroke and may have an unacceptable risk of restenosis. Evidence is required to inform patients' doctors and providers in the EU when choosing between these treatments. We have therefore started an international randomised trial to compare the risks and benefits of stenting with endarterectomy. A European network of centres will harmonise stenting techniques, safeguard the safety of EU patients thus treated and ensure the trial results are generalisable throughout the EU.

**Problem:** To determine whether carotid stenting and endarterectomy are similar in terms of costs and benefits as treatments for carotid stenosis or whether one treatment has significant advantages.

### **Keywords:**

Stroke - carotid stenosis - stenting – endarterectomy

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## ***Rapid Stroke Marker Detection via Immunosensors utilising Labelless Electrochemical and Resonant Mass Detection***

### **Objectives:**

The objective of this project is to develop an individually addressable array of labelless affinity biosensors for the rapid detection of biochemical markers for stroke, facilitating the rapid diagnosis essential for introduction of thrombolytic therapy. Labelless affinity address the problem associated with rapid diagnosis of stroke by allowing cost-effective (typically 10 EURO), rapid (in minutes), specific (using novel monoclonal antibodies and aptamers) and sensitive (ng-pg/ml), detection of stroke markers for use at the point-of-care.

### **Brief description:**

The project aims at the development of a generic platforms for labelless transduction of binding events. The particular application of the project is the labelless detection of biochemical markers for stroke so as to facilitate rapid diagnosis and subsequent introduction of appropriate therapy within the required 3 hours time frame. Novel biocomponents will be developed for detection of these biochemical markers, and further demonstration of the generic nature of the technologies to be developed will be realised via the use of antibodies and aptamers as capture biocomponents. Techniques for site-selective immobilisation of the biocomponents will be explored as will economic methods of producing microelectrodes. Following the ethos of the project, to have a successful commercialisable product, two technologies will be developed in parallel and are validated with the current gold standard of labelless detection, surface plasmon resonance. The two developed technologies will be evaluated and the technology exhibiting superior characteristics in terms of sensitivity, cost, applicability to mass-production, reproducibility and accuracy. Based on the outcome of this evaluation, a pre-production prototype will be developed and validated. This pre-production prototype will be clinically evaluated and a technology implementation plan drafted for post-project commercialisation. The consequences of the success of this project are immense. The rapid diagnosis of stroke, facilitating the intervention of thrombolytic therapy in the three-hours window following onset of stroke, will result in a massive decrease of unnecessary disability, morbidity and mortality and the associated economic burden. Additionally, the proposed multi-sensor arrays could be used by nursing-home staff, by homecarers, by the population themselves as well as by trained medical staff. Coupling the feasibility of the facile detection of stroke with a marketing campaign that highlights the need to treat strokes, as a condition requiring urgent medical treatment, could revolutionise the public perception of strokes.

### **Keywords:**

Stroke diagnosis - Biosensors - Antibodies - Aptamers - Microelectrode arrays - Site-selective immobilisation - Resonant mass - Impedance - Labelless transduction of binding events

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## ***The Impact of treatment with Acetylcholinesterase Inhibitors on Europeans with Alzheimer's Disease (AD)***

### **Objectives:**

Acetylcholinesterase inhibitors (AChE I) have been shown to afford modest benefits on cognitive functioning in patients with AD. A systematic review by the Cochrane Collaboration states “the practical importance of these changes to patients and carers is unclear”

The primary objective of this study is to find clinical evidence for the global efficacy of AChE I treatment. The secondary aim is to develop a comprehensive picture of the natural history of AD in Europe.

### **Brief description:**

This is a prospective 2 years observational cohort study, which will take advantage of the differences in prescription rates of AChE I across Europe. Patients will therefore be naturally predetermined to a treated or untreated group. Patients (n=1400) with AD will be recruited and reviewed 6 monthly. At follow up, well validated scales and questionnaires determining cognitive impairment, activities of daily living, behavioral disorders, dependency, caregiver burden, cost, and health care services use will be used. The primary outcome measure is a deterioration of one level on the “clinical dementia rating” scale (CDR). The study will be conducted within the setting of the European Alzheimer's Disease Consortium (EADC) which is a fully functional network of European centres of excellence specialised in AD.

### **Expected Results:**

Clinical evidence for the global efficacy of treatment of AD with AChE I. This evidence may then be incorporated into European Guidelines for AD.

A better understanding of the natural history of AD, and identification of criteria necessary to improve the quality and cost effectiveness of AD patient care in Europe. This is important not only for health professionals but also for families and caregivers for whom questions of prognosis, duration, and severity are amongst the most important.

Potential Applications:

Incorporation of results into treatment guidelines for patients with AD aiming to improve and standardise patients treatment and therefore quality of life.

Answers to questions about prognosis, duration, and severity of the disease.

Europe wide epidemiological data which will have applications for health policy planning.

### **Keywords:**

Alzheimers Disease – Dementia – Treatment - Acetylcholinesterase Inhibitors - Epidemiology

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## ***Obstacles and facilitators in diagnosing and managing early dementia in EU member states***

### **Objectives :**

This project aims to exchange experiences acquired in three RTD projects on early diagnosis of dementia and to make a research proposal based on these studies. The research proposal on obstacles and facilitators of diagnosis and management of early dementia will consider national circumstances. Therefore two workshops are needed to exchange national evidence, expertise and opinions. This exchange also enables EU member state to benefit from of each other's experiences. The exchange will contribute to the knowledge on which obstacles and facilitators are universal and which are country specific. The main objective of the workshops is the research proposal considering national circumstances. Specific additional objectives include: 1) To document evidence on obstacles and facilitators. 2) To compare international methodologies, procedures and techniques to diagnose dementia and to educate GPs on dementia-related problems. 3) To compare internationally the epidemiology of dementia, organisation of dementia health care and cultural norms regarding early dementia-related problems. 4) To document evidence on management of dementia-related problems and to exchange new developments.

### **Description of work**

The project comprises two interrelated workshops

Workshop 1: A two day workshop on basic obstacles in early diagnosis and management of dementia and on interventions to be linked to these obstacles.

These themes will be addressed in separate workshops:

a) Workshop on obstacles and facilitators. International comparison of evidence and opinions on barriers or obstacles to diagnosis and management of early dementia. These may be related to attitude, knowledge or skills and to social and financial conditions. Some countries have evidence on barriers, other countries will rely on supposed barriers. This will provide the basis for the interview guide and the questionnaire on obstacles and facilitators to be used in the research proposal.

b) Workshop on methodologies.

International comparison of methodologies, procedures and techniques to diagnose dementia and to educate GPs on dementia-related problems. This will provide the basis for a toolkit of interventions which can be linked to obstacles. Obstacles in one state can be addressed by methodologies, procedures and techniques used in another state.

c) Workshop on dementia-related national circumstances. Internationally comparison of epidemiology of dementia, organisation of dementia health care (e.g. presence of memory clinics), and cultural norms regarding early dementia related problems.

d) Workshop on management of dementia-related problems. International comparison of evidence and exchange of new developments regarding management of patients' and caregivers' dementia-related problems.

e) Workshop on research methodology

Selection of procedures and methodology for the study: 1) to study obstacles and facilitators of early diagnosis and management of dementia and for example focus groups and semi-structured interview

Four months in between

1. Set-up network of GPs to be involved in the study
2. Writing of research proposal adapted to the information from the two workshop days.

Workshop 2: Two days workshop on agreement on research proposal

Suitability of research proposal for use in EU countries regarding content and procedures. The project is co-ordinated by a central co-ordinator and a project manager. Each of the separate workshops is co-ordinated by a working group member who provides guidance and is responsible for the deliverables of the workshop.

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Area 6.1: Age-related illnesses and health problems

## **MUSCULOSKELETAL SYSTEM**





Project number:	QLK6-CT-1999-02024
EC contribution:	€1,199,998
Duration:	36 months
Type:	RS
Starting date:	01/01/2000

## ***Mechanical Integrity and Architecture of Bone Relative to Osteoporosis, Ageing and Drug Treatment***

### **Objectives:**

Aetiology of osteoporosis is in general related to age and estrogen deficiency. The aim of the proposed project is 1) to set up a method to measure in vivo in animals, the change of bone architecture, 2) to establish by which mechanisms age and estrogen deficiency diminish the strength of bone and 3) to establish how drug treatment can repair diminished bone strength.

From a pure mechanical perspective bone fracture risk is controlled by three parameters: the amount of bone, the architecture of the bone and the quality of the bone matrix tissue. The separated effect of each of these three aspects will be determined using finite element computer models and mechanical testing at different hierarchical levels. This will improve current understanding of the factors involved in bone degeneration, microdamage and fracture and will enable better testing of new treatment methods to cure osteoporosis.

### **Brief description:**

With current life expectancy, osteoporotic related fractures are a considerable health care problem. The precise anatomical changes which lead to diminished bone quality are unknown. Bone loss occurs within ageing and estrogen deficient patients and is generally measured by the amount of bone mass, which only partly explains the increased fracture risk. More accurate diagnoses can be made if bone quality is measured by geometry, architecture and matrix tissue properties also. However, these can not be measured in vivo, yet. The proposed project will use a newly developed micro-CT scanner to follow the architectural changes in the bones of animals as a function of ageing, estrogen deficiency and drug treatment. The mechanical consequences of architectural changes or matrix tissue changes will precisely be determined using computer models and micro mechanical testing. This will provide new information with respect to aetiology and osteoporosis treatment.

### **Keywords:**

Ageing – Osteoporosis - Bone Fracture

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Type:	RS
Starting date:	01/01/2000

***Investigation on mechanisms for maintenance and regeneration in the ageing muscle: Development of guidelines, diagnostic tools and a view to therapies***

**Objectives:**

The overall objectives are to evaluate:

Effects of ageing on a number of physiological and biochemical parameters of the muscle.

Muscle performance, repair and growth become less effective with increasing age.

Muscle fiber growth and repair are carried out by a stem cell, the satellite cell.

Calcium ion homeostasis and the process of electromechanical coupling is altered in ageing muscle.

**Brief description:**

Diminution in muscular performance is a major cause of disablement in old age. This loss appears to be a multi component phenomenon. We will investigate whether and which factors within the muscle itself are responsible for this decline.

Satellite cells are the only source for maintenance, growth and regeneration of muscle tissue. A major goal of our network is to determine changes in the behavior of the satellite cells during ageing (i.e. numbers, proliferative capacity in vitro and in vivo, myogenic program, calcium homeostasis). Important aspects of the contractile apparatus will be investigated as well. Most work will be performed on human tissue in a cooperation of outstanding basic scientists and clinical partners.

Tissue obtained from normal young and aged, exercised and sedentary old people, and for controls of hyperexercised athletes as well as people diseased with muscle wasting dystrophies will be characterized for frequency of satellite cells as well as biochemical features of the contractile apparatus.

Human satellite cells will be harvested from the biopsies and their proliferative capacity tested in vitro and in vivo, the latter by implantation and growth of human tissue in an animal. Trans-age transplantations in rats of extremely old muscle into young animals will be performed to understand the apparent superiority of a juvenile environment. Methods will be developed to biochemically quantify human proteins and human specific DNA in whole mouse muscle implanted with human myogenic cells. Combined with assessment of the presumed mitotic clock, the telomere, a diagnostic tool to predict the remaining capacity of muscle to grow, i.e. its trainability, will be obtained.

**Keywords:**

Muscle - Ageing - Human - Myoblasts - Satellite Cells

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EC contribution:	€1,799,999
Duration:	36 months
Type:	RS
Starting date:	01/04/2000

## *Role of Cytokines and Growth factors in cartilage destruction in Osteoarthritis (OA)*

### **Objectives:**

- 1 To identify therapeutic targets in various stages and forms of OA
- 2 To establish ways to interfere with the pathologic cartilage destruction in vitro
- 3 To establish therapeutic modalities in vivo

### **Brief description:**

Cartilage specimens from defined conditions of human OA and kinetic stages of experimental OA will be analyzed for cartilage matrix damage and concomitant cytokine and growth factor expressions. This includes the identification of shifts in receptor expression for these mediators in defined sites in the articular cartilage, which are more or less susceptible to OA development. This will identify known and novel cytokine/growth factor targets and will validate the use of animal models for particular aspects of human OA.

Since IL-1 is an obvious mediator in cartilage destruction, but proper therapeutic inhibitors are not available yet, we will establish novel ways to block IL-1 action, through interference with the recently identified IL-1R accessory protein and kinases in down-stream events and analyse whether disturbances are present in OA at that level. This approach will yield novel antagonists. Apart from the use of blockers we will use existing and develop novel transgenic and knockout mice to investigate the role of cytokine/growth factor pathways in animal models of OA in knee and temporomandibular joints. At present it is unclear whether growth factors such as TGF $\beta$  are protective or pathogenic in OA cartilage damage. To evaluate this we have developed novel, specific inhibitors and will apply these to the in vitro and in vivo model systems, using adenoviral overexpression systems.

A final approach in cytokine blocking will be to enhance natural of individuals to optimize the level of autoantibodies to adverse cytokines. First a screening will be done in OA patients, to correlate levels of existing autoantibodies with disease progression. Next, novel ways to enhance autoantibodies by vaccination will be done in OA models, with ultimate application in OA patients.

### **Keywords:**

Osteoarthritis - cytokines - growth factors - IL-1 - TGF $\beta$  - cartilage

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EC contribution:	€1,896,699
Duration:	36 months
Type:	RS
Starting date:	01/02/2000

## ***New Genes and Targets for Osteoporosis***

### **Objectives:**

To provide an integrated understanding of the genetic mechanisms that underlay the pathophysiology of osteoporosis and to transfer this new knowledge to benefit the aging population. In particular to: 1) Identify new mutations leading to altered bone density. 2) Understand the action of estrogen receptors in bone. 3) Generate models of osteoporosis through gene targeting. 4) Contribute to understand the molecular regulation of bone homeostasis and 5) Develop new diagnostic tests and treatments.

### **Brief description:**

To identify new mutations leading to altered bone density, we will take advantage of a large ENU mutagenesis screen which has been established at the GSF-Research Centre in Munich. A new screening for parameters involved in osteoporosis will be set up. To elucidate the molecular mechanism of bone homeostasis we will generate mice models in which key genes will be inactivated by homologous recombination by Drs. Owen, Charnay and Levi (London, Paris, Genova) who have already inactivated *Cbfa1*, *Krox-20* and *Dlx5*. Conditional gene targeting mediated by cre-recombinase will be used to induce tissue-specific inactivation in bone of genes which would otherwise cause a lethal phenotype. The possibility that genes identified in animal models are responsible for human pathology will be checked by Dr. de Vernejoul in Paris. The regulation of genes important for bone "well-being" will be studied in vivo and in vitro in order to design pharmacological approaches to affect bone homeostasis. These studies will also produce very important tools to direct gene expression in bone. The mode of action of the Estrogen Receptor in bone will be studied by Dr. Frank Gannon at EMBL. This is an essential part of the work because of the known correlation between Estrogen Receptor activity and bone defects (as illustrated for instance with the onset of bone loss in post-menopausal women). New immunodiagnostic and DNA-based diagnostic assays will be developed by Dr. Kane at Galway, Ireland while an industrial partner will develop new therapeutic and preventive treatments for human osteoporosis. To disseminate our results we have agreed to communicate them on a regular basis to the International Osteoporosis Foundation (IFO), which reunites more than 70 National Osteoporosis associations. IFO might be the best possible platform to make our results available to the end users.

### **Keywords:**

Osteoporosis – Genetics - Prevention.

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EC contribution:	€1,874,483
Duration:	48 months
Type:	RS
Starting date:	01/02/2000

## ***Opioid Treatment of Chronic Pain and Inflammation of the Locomotor System***

### **Objectives:**

The overall objective is to develop new pharmacological means of treating pain in degenerative and inflammatory disease of the locomotor apparatus. The project is an attempt to clarify the neuronal mechanisms in normal and pathologic conditions, to develop a new generation of opioid drugs and to test their therapeutical efficacy in adjuvant arthritis. The specific aims are to a) assess the expression and receptor characteristics of neuropeptides, representing nociceptive, anti-nociceptive and immune regulatory functions in bone, joints and muscle under normal and arthritic conditions, b) design, synthesise, pharmacologically characterise and experimentally test a new generation of opiates, which hypothetically combine potent anti-nociceptive and anti-inflammatory effects without the classical side effects.

### **Brief description:**

The expression of neuronal mediators in the locomotor system will be assessed under normal and arthritic conditions. In rats, the degree of adjuvant arthritis will be assessed by X-ray, paw volume measurement, serum markers and nociceptive tests. Tissues from bone, joints and muscle will be analysed with regard to neuropeptide expression, opioid receptor characteristics and immunologic features. The morphologic (immunohistochemistry) and quantitative (RIA) analysis will entail SP, CGRP (nociceptive), ENK, DYN (anti-nociceptive), VIP, NPY, NA (vasoactive), IL-1 and CRF (immunoregulatory). Receptor binding assays will characterise  $\delta$ ,  $\mu$ ,  $\kappa$ - opioid receptors with regard to number, specificity and affinity.

In the design and synthesis of new analgesic and immunosuppressive opioids for chronic locomotor disorders, it is important to minimise the CNS effects, while retaining their actions in the periphery. Hypothetically, a) delta-receptor opioids, antagonists as well as agonists, are useful templates for the development of novel drugs with analgesic (agonists) and immunosuppressive (agonists/antagonists) properties without side effects. b) derivatives of the mu-selective agonist 14-methoxymetopon are highly potent analgesics with mild side effects, which can be modified to act selectively in the periphery.

Biochemical and pharmacological characterization of the new opioid compounds will focus on agonist/antagonist properties in ileum and vas deferens preparations, and binding characteristics in brain tissue. In vivo studies will include anti-nociceptive and behavioural tests, and assessment of gastrointestinal transit (constipation) and CO<sub>2</sub> partial pressure (respiratory depression). The effect of the novel opioid drugs with regard to analgesia and immunosuppression in the periphery will be tested in rat adjuvant arthritis. Apart from in vivo assessment of nociception and degree of arthritis, tissues from bone, joints and muscle will be analysed with regard to neuropeptide expression and opioid receptor properties. Lymphoid and synovial tissue will be analysed for immunosuppressive effects.

### **Keywords:**

Pain - inflammation - musculo-skeletal tissues - arthritis - neuropeptides - opiates

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EC contribution:	€1,309,156
Duration:	36 months
Type:	RS
Starting date:	01/04/2001

## *Neuromuscular Assessment In The Elderly Worker*

### **Brief description:**

Neuromuscular (NM) problems reduce working ability of ageing workers, and increase cases of work loss and accidents. For this reason, elderly people throughout Europe are forced into early retirement and fail to be self-supporting. There is a need to identify and monitor work related NM disorders in order to a) reduce their consequences by monitoring the most vulnerable individuals, b) identify the determinants of NM ageing related to occupational conditions and c) evaluate methodologies for warning elderly workers when there is insufficient relaxation in vulnerable muscles. Preliminary results show the possibility of identification of NM problems through non invasive techniques, recently developed within the SENIAM and PROCID Concerted Actions, which can provide quantitative indices of NM performance. Substantial field tests and training initiatives are required to demonstrate that these techniques: a) can be used outside the research labs and may have a European market in the fields of ergonomics and occupational health and b) can be routinely used to monitor the relationship between occupational and NM system conditions in the working environment. Standardisation of methodology is needed and will be developed.

### **Keywords:**

Ageing workers, Neuromuscular system, Ergonomics, Electromyography, Muscle fatigue

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## ***Pan-European Network For Ageing Muscle***

### **Objectives:**

There are three main objectives:

- a) Evaluate to what extent healthy ageing and lack of muscle usage with age contribute to loss of muscle mass and function in the elderly.
- b) Optimise muscle training regimens to counteract loss in muscle mass, with special emphasis on the value of eccentric contractions.
- c) Evaluate whether intake of special nutrients can attenuate muscle damage and augment the muscle repair process as well as the exercise stimulus when performing muscle training.

### **Brief Description:**

The project is divided into three phases. Phase I will see the development of three nutritional supplements: 1) antioxidant product, 2) bovine colostrum product, and 3) protein product as well as an evaluation of three different exercise models in young and old people. The exercise forms are strength training to induce muscle hypertrophy, including resistance (eccentric) cycling exercise. The latter causes muscle damage and allows the study of repair processes. Muscle biopsies will be analysed for the influence of ageing on respiratory and leg muscles and of exercise on leg muscle force and power with a special focus on growth factors such as IGF-1 and a number of key cytokines. In Phase II, the ability of these nutritional supplements to amplify the exercise-induced responses on muscle growth factors and repair mechanisms in old people will be evaluated in randomised placebo-controlled designs. Phase III will use the information from Phase II, and the most potent nutritional supplement and the best training mode, i.e. the one causing the largest exercise stimulus will be applied in a multi-centre study of old subjects. Leg and respiratory muscle training will be the interventions, and muscle mass, strength, and ADL-functions will be end-point measures of efficiency of the applied regimen. Moreover, muscle force per unit area will be determined at the single muscle fibre level and we will particularly evaluate how large the differences are, when comparing skeletal muscle fibre types in relation to velocity and tension in old individuals and to what extent elderly people respond to training. At the whole-body level isometric and isokinetic dynamometry, and magnetic resonance imaging will be used to identify accurately changes in whole muscle volume. In addition, in all three Phases there will be a mechanistic approach using molecular and immunological techniques to identify growth factor and cytokine responses and the stimuli for evoking these responses.

### **Keywords:**

Skeletal muscles - elderly lack of muscle usage - loss of muscle mass - eccentric versus concentric contractions - antioxidants - colostrum - proteins - training response - immune response - local growth factors - gene expression

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## *Chondral And Osseous Tissue Engineering*

### **Objectives:**

Development of cartilage and bone in vitro. Development of their transplantation in vivo. Development of guided tissue regeneration. Use of biodegradable fixation devices. Development of microsurgical tissue transfer. Clinical application for joint resurfacing (osteoarthritis), treatment of large cranial bone defects and severe open tibial fractures.

### **Brief description:**

The project is transnational (5 EU countries), multidisciplinary, and involves both producers and users. It includes:

1) In vitro: Autologous chondrocytes, periosteal-derived and autologous stromal marrow stem cells are isolated, and expanded in a novel co-culture environment involving controlled oxygen tension. Novel scaffolds made of biodegradable biocompatible polymers (polyglycolide, polylactide, their copolymers, tyrosine polymer and bioactive glass and its lactide-composite) are used in the construction of cartilage and bone. In some experiments, growth factors may be used. The quality and characteristics of the obtained constructs are determined. Model bone/cartilage defects in experimental animals (rats, rabbits, sheep and pigs) will be studied. Biodegradable materials will also be used as barrier membranes for guided tissue regeneration.

2) Tissues constructed in vitro are transplanted as autogenous grafts. In other series, perichondrial or periosteal grafts/flaps are used with biodegradable scaffolds to develop bigger tissue grafts used to treat cartilage and bone defects as microvascularised flaps. Novel biodegradable fixation devices will be used to stabilise these grafts. Biodegradable devices containing biologically-active agents (e.g. antibiotics), will be developed. Bio-prosthesis will be also developed. The quality of tissues produced, and healing of the treated cartilage and bone defects will be evaluated using microradiography, histology, electron microscopy, biochemistry (e.g. DNA content, labelled collagens and proteoglycans, mass spectrometry, chromatography), histochemistry (e.g. the immunoperoxidase method using well-characterised monoclonal antibodies) and also X-ray, CT and MRI. Data will be handled using specific data capture program.

3) Clinical application at the end of the project, with the most successful methods will be applied as a pilot study in few patients depending on the results of the experimental phase and availability of cases. Indications include resurfacing in degenerative joint disease (osteoarthritis), to treat rheumatoid small joints, to treat large craniofacial bone loss, and free flaps are used to treat severe open tibial fractures, etc.

### **Keywords:**

Ageing - Biodegradable polymers - Bone - Cartilage - Co-culture - Coping - Data capture - Disabilities - Regeneration - Resurfacing - Microsurgery - Osteoarthritis - Oxygen tension - Perichondrium - Periosteum - Prosthesis - Rheumatoid - Self-reinforced - Tissue-engineering.

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## *Ageing-Related Muscle Wasting: Causes, Prevention and Reversal*

### **Objectives:**

This proposal establishes ATRONET, whose aim is to understand the reasons for atrophy in ageing muscle and the mechanisms by which it can be reversed. Expected outcomes of the work are a) definition of changes occurring in ageing muscle that cause atrophy, b) indications of how individuals may vary in their propensity to ageing-related muscle weakening, c) an improved understanding of the potential routes to mitigation of ageing-related muscle weakening.

### **Brief Description:**

The project commences with determination of the cellular changes occurring during ageing-related muscle atrophy. Human and rodent muscle samples from adult and poorly or successfully ageing individuals will be analysed for changes in multinucleate muscle fibre nuclear domain size, nuclear number, fibre number and capacities of associated mononucleate myogenic cells (satellite cells). These studies will determine what cellular events require explanation at the molecular level.

ATRONET will examine a series of rodent models of muscle fibre size control in order to select suitable models for further examination. Chief among these are a unique collection of genetically-modified mice with altered fibre size. Animals showing fibre size changes akin to those in ageing will be used subsequently.

Five lines of work will then determine the molecular mechanisms underlying muscle fibre size control. First, events intrinsic to the fibres will be examined, focussing on the signal transduction pathways recently demonstrated to control fibre size in vivo in rodents. Early markers of fibre size change will be established. Second, the transcription factor targets of signalling involved in size changes will be identified, Third, the effect of neural activity and how it impinges on the signalling pathways will be studied, in order to understand how best might size changes be reversed, for example by exercise. The effects of fibre activity and fibre stretch will be distinguished. Fourth, we will examine of the changing properties of satellite cells, their contribution to ageing-related muscle wasting and their potential reversal by treatment with growth factors or other agents. Fifth, the role of extracellular matrix in regulating muscle fibre size, modulating the effects of growth factors and affecting satellite cell and fibre behaviour will be analysed.

These studies will identify a) potential sites of mis-regulation in ageing individuals, b) potential routes for preventative or restorative measures and c) potential sources of individual variation in ageing prognosis.

### **Keywords:**

Muscle - innervation - weakness - wasting - exercise - satellite cell - myonuclei - fibre size - extracellular matrix - electrical activity - mechanical stretch - bedrest - transgenic mice

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***Physical Frailty And Loss Of Functional Independence In Old Age:  
Determinants And Adaptations To Physical Activity***

**Objectives:**

BETTER-AGEING aims to investigate the causes of frailty of the human motor system from whole body performance to single muscle fibre level, and the impact of an innovative 12-month physical activity programme on frailty prevention, well being and daily functioning.

**Brief Description:**

Fitness of the motor system is the limiting factor determining the ability of independent living until death. Indeed, even amongst the "healthy" old, it is musculo-skeletal frailty that is the limiting factor. Hence a major effort to understand and mitigate the phenomenon of frailty seems imperative for maintaining mobility inside and outside the home, postural stability (and thus the prevention of falls), the ability for self-care, well being and social inclusion.

The project BETTER-AGEING will therefore investigate the causes and reversibility of frailty in old age using a 12-month physical activity programme, specifically designed to increase muscle mass and strength, enhance postural stability and locomotory competence in a healthy European population aged 70+ years.

Specifically, the Partners of the BETTER AGEING Research Consortium seek to provide answers to the following questions: 1) What are the exact causes for muscle weakness in old age? 2) How much of the loss of strength and power is due to age-related muscle atrophy (sarcopenia) and how much to alterations of motor control? 3) Why is muscle weakness in old age contraction-specific? Is this due to a contraction-specific deficit in activation or is it just due to muscular factors? 4) Why are senile muscle fibres intrinsically weaker than young ones? 5) How much of the alteration in muscle strength and power in old age is due to changes in the muscle per se and how much to changes in tendon mechanical properties? 6) What are the implications of changes in muscle-tendon structure, muscle metabolism and motor unit recruitment on locomotory function and relative energy cost? 7) How do changes in motor system structure, function and control explain decrements in performance in common daily activities? 8) What is the degree of recovery of motor function, in its various expressions, induced by physical training? Are these reflected by an actual improvement in the perceived state of well-being and daily functioning?

In summary, BETTER-AGING will improve our understanding of the mechanisms involved in normal ageing and also in those with a history of falling by providing new information on 1) the causes and functional consequences of frailty of the very old, and 2) the improvement of motor function, whole body performance and psychosocial factors as a result of innovative, targeted exercise regime through exercise.

**Keywords:**

Ageing - frailty - sarcopenia - muscle weakness - muscle function - muscle contraction - falls - muscle fibres - motor control - skeletal muscle oxidative metabolism - exercise tolerance - strength - power - physical activity - daily activities - independence - well being - quality of life

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## *Network in Europe on Male Osteoporosis*

### **Objectives:**

To focus and to co-ordinate ongoing relevant European research initiatives on male osteoporosis (OP). To achieve major progress in the identification of men at high risk for osteoporotic fracture. This includes characterisation of men at high risk, definition of tools for risk assessment (i.e. clinical risk factors, physical bone assessment techniques, biochemical and hormonal markers, genetic markers). Assessment of these tools and the conditions for their implementation.

### **Brief description:**

Fractures are frequent in elderly men and carry a heavy burden in terms of mortality, morbidity and irreversible loss of quality of life and autonomy. However, male osteoporosis (OP) has been a neglected problem. Presently, there is no adequate evidence base for rational management of male OP and no consensus on diagnosis or treatment. In this context, NEMO will address the identification of men at high risk for fracture, the key to substantial progress in the management of male OP. The strength of the network lies in its multidisciplinary approach and the ability to take advantage of large European study cohorts. Expected achievements are a full characterisation of men at risk and assessment of tools for their identification with definition of conditions for optimal implementation. The results will be integrated in an outcome model that is broadly applicable to clinical risk assessment and modelling of effectiveness and economical impact of management strategies in male OP.

### **Keywords:**

Osteoporosis - bone fracture - men - ageing - risk assessment - risk factors - epidemiology - bone absorptiometry - quantitative ultrasound - bone turnover - hormones - heredity - environment - gene polymorphism - bone micro-architecture

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Type:	RS
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## ***The diagnostic validity of dental radiography techniques for identifying osteoporotic patients***

### **Objectives:**

To compare dental methods of osteoporosis assessment using ROC analysis. The first objective is to recruit 600 women in the 45-55 year age group and perform 'gold standard' bone densitometry of the hip and spine using DXA. Subjects will also undergo panoramic and intraoral dental radiography. The radiographs will be subjected to a battery of established and novel analyses, ranging from simple qualitative assessments to complex computer-aided diagnosis. The final objective will be to relate these radiographic data, alone or in combination with simple clinical risk assessment tools, to the bone densitometry data and perform ROC analysis to identify the optimal technique for diagnosis of osteoporosis.

### **Brief description**

Osteoporosis is a major European health problem. Diagnosis is primarily by dual X-ray energy absorptiometry (DXA) but access to this is limited in the European Union. Dental radiography is readily available; radiographs can be used as an indicator of low bone density. We aim to investigate the efficacy of dental radiographic indices in identifying patients with low bone density. We will recruit 600 perimenopausal women who will undergo bone densitometry to establish their osteoporosis status, and dental radiography. Dental radiographs will be assessed qualitatively and quantitatively using manual and computerised methods to deliver a range of radiographic data. The validity of each radiographic index in diagnosis of osteoporosis will be measured using ROC analysis. This will allow us to devise recommendations to dentists on appropriate criteria for referral to medical colleagues for bone densitometry.

### **Problem:**

How might radiographic and clinical information be used by dentists to identify patients at risk of osteoporosis?

### **Expected results:**

To provide the best dental method of radiographic and clinical risk assessment for those patients most at risk of osteoporosis.

### **Potential applications:**

By developing and assessing the diagnostic value of dental radiographic (and combined radiographic and clinical) methods in identifying subjects at risk of having osteoporosis, it is likely that dentists may be able to facilitate better access to accepted osteoporotic diagnostic procedures (DXA) for those patients at high risk of bone fractures.

### **Project web-site:**

This will be important in the future as part of our dissemination strategy.

### **Keywords:**

osteoporosis – bone - dental radiography

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## *Obesity and disease in ageing*

### **Objectives:**

To identify differences between white adipose tissue (WAT) depots and biomarker(s) for the development of age related obesity, type 2 diabetes and cardiovascular disease (CVD) and evaluate the effects of CLA plus n-3 PUFA (conjugated linoleic acid and polyunsaturated fatty acids) supplementation on these and the somatotrophic axis in humans and animal models of differing adiposity. Also to elucidate the cellular mechanisms underlying leptin “insensitivity”.

### **Brief description:**

The principle aims of this project are to evaluate a novel prognostic/diagnostic biomarker for susceptibility to age related obesity and associated diseases and to also evaluate a non-conventional, natural therapeutic agent (CLA plus n-3 PUFA) in the amelioration of these conditions. To fulfil these aims we will define the mechanism underlying obesity related type 2 diabetes and CVD in human dietary supplementation studies, diet induced obese rodents, spontaneously low body fat rats and cell cultures transfected with epitope tagged leptin receptors. Diet induced obesity in rodents closely mirrors obesity in the human, which is strongly influenced by diet composition, but is polygenic in nature, while the spontaneously low body fat rat has increased longevity and a healthy senescence, providing us with a model for the very lean individual. The transfected cells will allow us to study leptin receptor regulation at the cellular level. Using these models we will test the contention that leptin receptor desensitisation/down-regulation together with low serum adiponectin levels lead to ectopic lipid deposition and together form the key components in the development of obesity related type 2 diabetes and CVD. Thus, in the human we will measure leptin receptor expression on circulating monocytes and serum leptin and adiponectin levels to provide potential peripheral prognostic/diagnostic biomarkers. Pancreatic  $\beta$  cell function/insulin resistance and cardiovascular fitness (heart rate variability) will also be tested and the effects of CLA plus n-3 PUFA supplementation on all these parameters will be evaluated. In the rodent models cardiomyocyte, pancreatic  $\beta$  cell, hypothalamic neurone, somatotroph and WAT depot function will be measured with varying adiposity and with CLA plus n-3 PUFA supplementation. Regulation and function of the leptin receptor will be elucidated in transfected cells and in tissues from the rodent models defined above and in human monocytes.

### **Keywords:**

Age related obesity - cardiovascular disease - type two diabetes - insulin insensitivity - leptin receptor function - adiponectin - receptor regulation

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Project number:	QLK6-CT-2002-02363
EC contribution:	€556,954
Duration:	36 months
Type:	RS
Starting date:	01/01/2003

## *Advanced Detection of Bone Quality*

### **Objectives:**

Beside bone density, bone architecture and quality are main factors to assess the fracture risks and the evolution of osteoporosis. The objective of the ADOQ project is to evaluate the benefits of 3D peripheral Quantitative Computer Tomography linked to finite element analysis compared to the actual methods based only on bone density.

### **Brief description:**

The objective of ADOQ is to demonstrate the benefit of measurements based on the 3DpQCT technique to evaluate bone quality. Four 3DpQCT systems will support a multi-centre clinical study performed in five clinical centres. The systems will enable in-vivo examinations of the distal human radius and the tibia with a resolution of 100\*100\*100  $\mu\text{m}$ . Measurements will be associated to finite element analysis to determine bone mechanical properties. The clinical study will be realised on an average of 1500 persons with the objective of:

Defining normative data for bone architecture: reference data of 3DpQCT measurements in the radius and the tibia will be collected on a population aged from 20.

Demonstrating the contribution of structure to the fracture risk independently of the bone mineral density as measured by DEXA.

Evaluating the effects of physical activities on bone architecture as a prevention mean and as a support to treatment: in a cross sectional study performed at the age when peak bone mass is achieved, ADOQ intends to evaluate the effects of intense physical activity on peripheral bone macro and micro architecture, comparing weight bearing and non weight bearing sports.

Evaluating the effects of decreased physical activity: the study will aim at evaluating the influence of reduced muscle power on bone architecture in case of hemi- or paraplegia on bone structure, as well as evaluating the bone structure changes after peripheral fractures.

Identifying thresholds based on architectural and densitometric parameters to better detect patients at higher risk of osteoporosis and osteoporotic patients at higher risk of fracture.

Obtaining normative data on a population representative of astronauts and demonstrate the potential of 3DpQCT to foresee and monitor bone loss of astronauts before and after a space flight.

### **Keywords:**

Older people - elderly - ageing - public health - diseases - clinical survey - osteoporosis - bone - bone architecture - bone microarchitecture - medical imaging - micro-computed tomography - bone quality - finite element analysis - effects of exercise - space flight.

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EC contribution:	€1,399,714
Duration:	36 months
Type:	RS
Starting date:	01/01/2003

***Improvement of Hip Fracture Prediction in Osteoporotic Subjects by Low-Dose Volumetric QCT Assessment and Finite Element Analysis of the Proximal Femur***

**Objectives:**

To develop and optimise, in term of radiation and image quality, a volumetric 3D quantitative computed tomography (QCT) image analysis of the cortical and trabecular bone mineral density distribution as well as geometrical parameters of the proximal femur

To create and validate finite elements models of the proximal femur. Final goal is to improve fracture risk prediction in highly exposed subjects.

**Brief description:**

The project is split into three parts:

Determination of an optimal volumetric CT acquisition protocol. The best compromise between image quality and reduced radiation dose will be found. Image quality and radiation dose will be analysed by phantom and cadaver scans. Effective dose assessment will be calculated theoretically and will be verified by cadaver measurements. A semi-anthropomorphic phantom with realistic geometry, BMD, cortical thickness and volume values will be manufactured. For image analysis, an off-line PC-based workstation will be developed. The reproducible determination of analysis volumes of interest and geometrical parameters will be ensured by an anatomical co-ordinate system attached to the femoral neck.

In-vitro QCT analysis of excised femurs and subsequent bio-mechanical testing will be used to correlate volumetric BMD and geometrical parameters with bone strength. Forty excised femurs will be investigated. Volumetric parameters assessed will include BMD along the neck and the shaft axis, cortical thickness, cross-sectional moments of inertia, and length of the neck axis. The value of these parameters in fracture risk prediction will be assessed in a group of 120 elderly female patients.

Personalised FE models based on subject specific QCT data will be developed to improve the individual fracture risk prediction. With another type of models (parameterised), virtual loading schemes and influence of hip geometry on fracture risk will be studied. Both models types will be validated using the bio-mechanical tests of the excised femurs. The results of the models will also be used to optimise the analysis of the QCT measurements. Individual FE analysis will finally be performed in 10 patients to assess bone strength.

**Keywords:**

Osteoporosis - Quantitative Computed Tomography - Hip - Fracture - Finite element models - Bone - Bone Mineral Density

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EC contribution:	€2,082,620
Duration:	36 months
Type:	RS
Starting date:	01/01/2003

## ***Intervertebral Disc Degeneration: Interplay Of Age, Environmental And Genetic Factors***

### **Objectives:**

Our aim is to determine the influence of genetics, environment and age on intervertebral disc degeneration. We will assay blood samples from a twin-study, from back pain patients and from pain-free controls for gene-polymorphisms associated with disc degeneration. We will also examine disc tissue and cells from the patients. We will examine data from these studies to determine how genetic factors affect the behaviour and integrity of disc tissue and cells.

### **Brief description:**

The project will focus on age/gene/environment interactions in two groups of subjects. The first are subjects of a classic twin study comparing groups of monozygotic and dizygotic twin pairs discordant for the known major environmental risk factors for back pain. Their degree of disc degeneration will be monitored by MR imaging. The second group consists of back pain patients and their partners. Blood samples will be taken from both groups and assayed for disc-degeneration linked polymorphisms and for markers of cellular senescence. Tissue samples will be obtained from back pain patients undergoing routine surgical removal of their intervertebral discs for treatment of pain or deformity. Nutrient transport into the discs of these patients will be measured using needle microelectrodes to monitor nitrous oxide and oxygen levels. A sample and blood data base will record anonymous details of the patients such as age, sex, diagnosis, disc level, treatment, details of surgical specimen removed. The disc samples will be assessed histologically for degeneration and cell senescence. Samples will then be sent as appropriate for other assays. Biophysical properties of matrix macromolecules will be related to turnover measured by aspartic acid racemization. Tissue mechanical properties will be related to macromolecule degradation. The effect of matrix degradation on angiogenesis and neural ingrowth in a culture model will be determined. Cellular responses to mechanical and nutritional stress will be measured and the signalling cascades which are involved will be investigated. The information on the relationship between degeneration-linked polymorphisms and matrix and cellular properties will be used to develop a diagnostic grading scheme which can be used clinically. Novel 'risk genes' are likely to be identified and the aetiopathological of disc degeneration should be better understood..

### **Keywords:**

Intervertebral disc - gene polymorphism - disc degeneration - twin study - MRI - back pain - proteoglycan - aggrecan - collagen network - angiogenesis - neural ingrowth - intracellular signalling - mechanotransduction - cellular mechanics - cell senescence - cellular repair.

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Project number:	QLK6-CT-2002-02629
EC contribution:	€3,000,000
Duration:	48 months
Type:	RS
Starting date:	01/01/2003

## *Genetic Markers For Osteoporosis*

### **Objectives:**

Fractures related to osteoporosis account for a significant disease burden in Europe and this is set to increase in the near future. Since genetic factors play an important role in the pathogenesis of osteoporosis, identification of osteoporosis risk alleles represents a prime focus for research effort. This could provide new tools for risk assessment and identify novel biological pathways to be targeted for intervention. Association analysis of candidate gene polymorphisms is the most powerful approach to quantify risk conferred by genes which predispose to osteoporosis, because of the polygenic nature of the disease and the small contribution of individual alleles. We shall study genetic determinants of osteoporosis in several large European cohort studies, allowing accurate quantification of risk-allele effects and meta-analysis of sub-groups based on ethnicity, age, sex and other clinical endpoints. The long term objective is to increase understanding of the pathogenesis of osteoporosis and to identify genetic markers which can be used to help target preventative measures such as lifestyle modification and drug treatments more effectively.

### **Brief description:**

The research program will apply novel tools related to genomics, genetics, bio-informatics, and statistical analysis to establish a collection of osteoporosis risk alleles. The program strategy is focussed on identifying novel risk alleles through several approaches and on testing existing risk alleles, in relation to aspects of osteoporosis (bone mineral density (BMD), bone loss, fracture, gene-nutrient interaction, response to hormone replacement therapy (HRT)). The proposal combines excellent resources to perform such studies with >20.000 subjects by meta-analyses of the data, organisation of meetings, and workshops. Several closely related workpackages will be carried out:

1. Genotyping of already recognised candidate gene polymorphisms, in population studies involving perimenopausal women and older men and women.
2. A large collection of osteoporosis pedigrees will be used to compare linkage- vs. association analysis of osteoporosis risk genes.
3. Novel approaches in molecular and statistical analysis of multiple polymorphisms in a single gene (haplotyping) will be used for polymorphism evaluation.
4. We will identify polymorphisms of (novel) bone genes, implicated in rare monogenic bone diseases and analyse these in relation to osteoporosis in populations.
5. We will seek novel genetic determinants of bone mineral density by using linkage disequilibrium mapping to study loci syntenic to those which regulate BMD in mice. The resulting genes will be further investigated in association studies as described above.
6. Meta-analyses of genotype data in all populations will be performed to accurately quantify the risk estimates of risk alleles and perform sub-group analysis based on age, gender, ethnicity, and endpoint including fracture, BMD, and bone loss.
7. We will study the influence of dietary calcium intake on the effect of osteoporosis risk alleles among different European countries.
8. We will determine if there is a genotype-dependent response-to-treatment with hormone replacement therapy in women.

**Keywords:**

Osteoporosis - genetic analysis of complex traits – ageing - bone disease – diagnostics

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Project number:	QLK6-CT-2002-02700
EC contribution:	€662,692
Duration:	36 months
Type:	DM
Starting date:	01/01/2003

***Development and clinical evaluation of bioreplaceable small joint prosthesis for the correction of destructed small joints in rheumatoid arthritis and osteoarthritis.***

**Objectives:**

The objective of the demonstration project "JOINT SCAFFOLD" is to develop and demonstrate the performance and efficiency of a new bioresorbable joint implant (a "scaffold") in a large clinical study in Europe, in order to transfer rapidly the novel prosthesis from the primary development to the clinical practice. The new implant is designed to Osteoarthritis and Rheumatoid Arthritis elder people, with small destructed joints in fingers and toes. The project is based on strong preliminary scientific research and clinic results.

**Brief description:**

Bioreplaceable MCP-joint prosthesis is a new concept in joint surgery. The concept of bioreplaceable joint scaffold has been invented by two partners of this consortium in collaboration. Using the modern biomaterials technology, a new prosthesis is developed to prevent the harmful effects of silicone and to provide a method, which reliably corrects the deformities, and gives a potential permanent functional result in MCP-arthroplasty. The new prosthesis is only a temporary support in the joint until the spacer is bioabsorbed and replaced by the new fibrous-like tissue cushion. By using bioabsorbable materials, the long term foreign-body reactions caused by the wear debris of implant can be avoided. When using bioreplaceable prosthesis there will be no revisions due to the broken prosthesis and after healing patients are allowed to use their hands without load restrictions.

This new implant that overcomes the problems with currently used silicone prosthesis, i.e. the swanson implant, consists in highly porous cylindrical scaffolds made of fibres (filaments) for small joints, which enables on- and in- growth of tissue.

Preliminary first limited clinical studies with promising results need to be confirmed in a large scale study in Europe in the framework of a demonstration project. This demonstration project gathers partners from different profiles: industry, researchers, regulatory agency and above all, clinicians.

The implant is posed on fingers and toes joint of elderly Osteoarthritis and Rheumatoid Arthritis patients.

**Keywords:**

Joint surgery, MCP, arthroplasty, finger, toe, small joint, bioabsorbable, replaceable, implant, prosthesis, scaffold, clinical study, Osteoarthritis, Rheumatoid Arthritis.

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Project number:	QLK6-CT-2002-02710
EC contribution:	€546,774
Duration:	36 months
Type:	RS
Starting date:	01/01/2003

### *Femur ultrasound scanner*

#### **Objectives:**

Osteoporotic fracture incidence might be remarkably reduced if an accurate diagnosis of bone fragility is available. We will develop a new quantitative ultrasound (QUS) device for direct measurements at the proximal femur in vivo. Multiple QUS parameters will give a more comprehensive assessment of bone fragility, including aspects of density, structure, and material properties, exceeding the potential of radiological density measurements (e.g. DXA).

#### **Brief description:**

First in vitro studies at the partner institutions demonstrated the feasibility of ultrasound measurements at the femur and the potential of 3D rendering of a bone surface. We will further develop the three methods, surface rendering, ultrasound transmission and backscatter, to design and construct a prototype QUS scanner for assessment of femoral bone status. 3D surface rendering technique will enable us to find the optimal position of the ultrasound transducers for transmission and backscatter measurements relative to the bone precisely and consistent in all patients.

In the first phase the three centres will expand their development work to refine the methods for direct precise measurements at the proximal femur. According to know how and experience one participating centre will develop the methods for surface depiction, another centre will develop ultrasound transmission techniques and the third will develop ultrasound backscatter methods. In the second phase the three methodologies will be combined in one device, a research prototype for in vitro and in vivo measurements. This device will offer the potential of well-defined and precise positioning of the ultrasound transducers using the three-dimensional image of the bone. Transmission and backscatter measurements will provide a variety of parameters for the estimation of bone quality parameters, for instance bone density and bone structure. In the third phase this prototype for comprehensive assessment of bone status of the proximal femur will be used in an in vitro and an in vivo study to demonstrate the potential of this new device for the prediction of femoral fractures and monitoring of osteoporotic subjects. Dividing up these tasks reflects the knowledge and recent progress in these issues in the single centres. Subsequent commercialisation should enable strong progress in the diagnosis and monitoring of osteoporotic diseases and a remarkable decrease in the costs of osteoporotic fractures.

#### **Keywords:**

Quantitative ultrasound of femoral bone - acoustical surface rendering of bone -  
ultrasound transmission measurement - ultrasound backscatter measurement - acoustical structure  
assessment of trabecular bone

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**Partners:**

Project number:	QLK6-CT-2002-02285
EC contribution:	€1,402,505
Duration:	36 months
Type:	RS
Starting date:	01/01/2003

***European Network for Investigating the Global mechanisms  
of Muscle Abnormalities In COPD***

**Objectives:**

To evaluate the effect of COPD and its treatments, on physiological function, metabolic abnormalities and inflammation in the respiratory and peripheral muscle of patients with COPD. To develop an animal model of these muscles. To conduct pilot studies to assess the value of repetitive magnetic stimulation for the training of limb muscle and of an anti-oxidant nutritional supplement in patients with severe COPD

**Brief description:**

Technical expertise in the fields of muscle biopsy and physiological measurement will be shared between the partners. Using these techniques physiological aspects of respiratory and locomotor muscle function will be evaluated in patients with COPD and in age matched control subjects in 3 member states and 1 pre accession state. In the same patient population biopsy specimens will be obtained for analysis with regard to the impact of COPD on metabolic function and inflammation and redox imbalance. These same techniques will be used to evaluate the effects of acute exercise, pulmonary rehabilitation, lung volume reduction surgery and home mechanical ventilation. A novel magnetic coil capable of repetitive stimulation without overheating will be developed. This coil will be subjected to clinical evaluation to obtain pilot data with regard to therapeutic efficacy. An animal model of redox imbalance will be developed. This model will be used to evaluate the comparative efficacy of N-acetyl-cysteine and a novel anti-oxidant compound. The results of this study will be used to perform a pilot study of anti-oxidant therapy in patients with Chronic Obstructive Pulmonary Disease. As well as data collection, important additional goals of the study are transfer of technology and knowledge within members of the partnership as well as potential clinical and commercial application of the results

**Keywords:**

Chronic Obstructive Pulmonary Disease - muscle - diaphragm - quadriceps - biopsy - magnetic nerve stimulation - redox imbalance - pulmonary rehabilitation - home mechanical ventilation - nutritional supplementation - repetitive magnetic stimulation

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Area 6.1: Age-related illnesses and health problems

## **UROGENITAL DISEASES AND DISORDERS**



Project number:	QLK6-CT-2000-00064
EC contribution:	€1,044,004
Duration:	36 months
Type:	RS
Starting date:	01/01/2001

## *Hypoxic renal injury*

### **Objectives:**

Dysregulation of NO/O<sub>2</sub><sup>-</sup> occurs in association with ischemia reperfusion and promotes acute tubular necrosis. The objectives of the project are to know: 1) What causes dysregulated NO/O<sub>2</sub><sup>-</sup> formation; 2) Its impact on signal transduction mechanism related to apoptosis/ necrosis; 3) Protective principles (related to NO/O<sub>2</sub><sup>-</sup>) as a result of preconditioning regimes; and 4) The efficacy of pharmacological agents in preventing injury.

### **Brief description:**

Acute renal failure (ARF) is a very common disease affecting the ageing population. In ARF, the relative contribution of necrosis and/or apoptosis associated with the development of ischemia/reperfusion injury possibly depends on the severity of the initiating insult. It is known that the renal content of xanthine and adenosine changes with ischemia, as a consequence of ATP breakdown. The fact that adenosine may enhance NO release, whereas xanthine serves as a substrate for xanthine oxidase and thus promotes superoxide generation, predicts that different concentrations of xanthine versus adenosine (according to the period of ischemia) modulate the rate of NO versus O<sub>2</sub><sup>-</sup> production.

First, we will define the impact of initiating factors (inappropriate balance of xanthine/adenosine and NO/O<sub>2</sub><sup>-</sup>) on signal transduction mechanisms that provoke necrosis and/or apoptosis in the process of I/R in animals and hypoxia/ reoxygenation in cell culture.

Second, we will determine whether protective responses in isolated cells and animals associated with preconditioning are mirrored by an altered production of the above mentioned parameters or their cross-talk because it is known that protective responses of preconditioning are closely associated with a defined balance of these parameters.

Third, we will apply pharmacological strategies during progression of I/R injury in animals and hypoxia/ reoxygenation in cells to attenuate necrotic and/or apoptotic responses.

The methodology to be employed in order to achieve the objectives comprises cell culture experiments, isolated organs, and animal experiments. Besides analysing the formation of NO and O<sub>2</sub><sup>-</sup> (Griess reaction, redox-sensitive dyes) it is mandatory to determine the levels of xanthine and adenosine. Conditions of hypoxia/ reoxygenation will be simulated in cell culture as well as in animals. State of the art methods will be used to determine parameters of apoptosis/ necrosis (i.e. caspase activation) in all experimental systems. Established tools are used to follow activation of transcription factors (EMSA and histochemistry) and pharmacological inhibitors will be tested and verified in animals and cell culture.

### **Keywords:**

Acute renal failure, renal ischemia reperfusion, anoxia reoxygenation, preconditioning, xanthine, adenosine, nitric oxide, superoxide, apoptosis, necrosis, caspases, HIF-1, NF-κB, NOS inhibitors

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EC contribution:	€1,105,754
Duration:	48 months
Type:	RS
Starting date:	01/02/2001

## ***Prostate disorders: procurement of biomarkers and pharmaceuticals***

### **Objectives:**

Prostate disorders are a growing major socio-economic challenge because of our ageing population. We will identify changes in gene expression and proteins in prostate disorders. These changes will be used to develop diagnostic/ prognostics biomarkers and therapeutics for the painful and debilitating disorders of the prostate.

### **Brief description:**

New biomarkers and therapeutics for prostate disorders will have a major socio-economic impact. The disorders are debilitating, painful and incurable in their advanced stages. They affect a large proportion of men, are increasing in frequency with the ageing population and are a growing health-care cost burden. Proven performers from clinical, scientific and industrial backgrounds will undertake goal-orientated research. Human samples will be used, to avoid problems due to model systems. Alterations in expression will be detected by proprietary and established technologies, validated, and used to develop clinical markers and new treatments for prostate disorders. The project implicates new SMEs, presents opportunities for investors and job creation, and has the potential for continued growth. Different types of prostate samples will be used, which are normal, benign or malignant. They will be analysed for changes in RNA quality and quantity and alterations in proteins. The results obtained by our three approaches, and others that are publicly available (e.g. CGAP on the world-wide-web), will be compared. Candidate genes will be chosen on the basis of their propensity for the development of biomarkers and pharmaceuticals. They will be analysed in model systems and on archival prostate samples, to validate their importance. These analyses will draw on the different complementary strengths in the network. Validated genetic alterations will then be available to develop diagnostic kits and high throughput screens for pharmaceuticals, with the help and comprehensive expertise of our corporate partners.

### **Keywords:**

prostate disorders, benign prostatic hyperplasia, BPH, prostate cancer, biomarkers, therapeutic targets.

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Project number:	QLK6-CT-2000-00271
EC contribution:	€1,732,787
Duration:	36 months
Type:	RS
Starting date:	01/06/2001

## ***Specific Cytotoxic Agents to Treat Prostate Disorders in Elderly Males: Targeted Gene Therapy as an Alternative to Conventional Treatments***

### **Objectives:**

This projects aims to develop systems, which will precisely target gene therapy into human prostate cancer tissue. Tissue enhanced transcriptional control sequences, which drive the expression of genes in a secretory organ like prostate will be exploited to achieve one level of targeting. A detailed knowledge of the cell surface characteristics of prostate epithelium and the changes that occur in cancer, will also be used to target attachment of gene therapy vectors, focusing the therapy into the tumour cells, while sparing normal tissue.

### **Brief description:**

Prostate cancer will shortly become the leading cause of cancer mortality in the European male population. At present there is no effective therapy for metastatic androgen independent tumours. This project aims to exploit the state of the art in the generation of recombinant viral vectors, to produce safer gene therapy agents for the treatment of human prostate cancer in its most dangerous form. To achieve this aim, by means of gene therapy that can be applied intravenously, improvements in both the safety and specificity of tumour targeting will be necessary.

This will be achieved by engineering prostate specificity into the vectors firstly by driving therapeutic gene expression from prostate-specific promoters, and secondly by modification of viral cell tropisms to engineer preferential attachment to cancer cell surfaces. Novel techniques to minimise or eliminate anti-viral vector immune responses will also be investigated.

The optimisation of therapeutic gene strategies will provide a further prostate cancer-targeting element. Cytotoxic gene expression, prodrug activation and immuno-therapy are all available in the collaborating centres.

The consortium also has available a number of unique in vitro and in vivo model systems of human and animal prostate cancer, which will be used to provide a better pre-clinical testing regime for the targeted vectors prior to Phase I clinical trials in prostate cancer patients.

Singly targeted viruses will be examined for optimum specificity, safety and expression in these ex vivo systems, and various combinations of multiply targeted viruses will be tested comparatively in the different centres, using a common set of indicator genes, model systems and analysis parameters to achieve a true comparison.

The ultimate aim is to design better clinical trials and to bring the technology into the clinic for the benefit of prostate cancer sufferers in the shortest possible time, while minimising the risk of adverse treatment-induced side effects.

### **Keywords:**

Gene therapy, Prostate Cancer, Transcriptional targeting, Virus vectors, In vitro cell models, Adenovirus, HIV, Baculovirus

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EC contribution:	€1,136,508
Duration:	36 months
Type:	RS
Starting date:	01/02/2001

## ***Polymer-Virus Hybrid Vectors for Safe and Efficient Gene Therapy of Prostate Cancer***

### **Objectives:**

To demonstrate non-destructive surface modification of type 5 adenovirus with hydrophilic synthetic polymers and to characterise the composition of the coated viruses so-formed.

To optimise the polymer surface coating in order to completely abrogate normal binding of the adenovirus to its receptor (CAR) and prevent recognition by anti-adenovirus antibodies.

To introduce targeting ligands onto the surface of the coated virus, in order to restore recognition of prostate cancer-associated receptors, and promote cellular internalisation into receptor-positive cells.

To design the coating polymer for triggered intracellular release in order to maximise transgene expression within target cells.

To modify the polymer coating to inhibit binding of serum proteins and rapid clearance of the virus from the bloodstream, promoting extended circulation and effective access of the virus to disseminated target prostate cancer cells in vivo.

To combine all of these advances in formation of a vector capable of targeting prostate cancer cells (or tumour-associated endothelial cells) in vivo, following intravenous or intraperitoneal injection, and achieving useful therapeutic efficacy.

To establish preclinical data providing justification for clinical assessment of the targeted vector.

### **Brief description:**

This project will develop a “stealth” virus, capable of evading neutralising antibodies and infecting specifically target cells, notably prostate cancer cells. The stealth virus is made by reacting hydrophilic polymers on to the surface of adenoviruses, chemically modifying their phenotype. This layer of polymer will prevent the binding of neutralising antibodies, simultaneously preventing the virus from binding to and infecting via its normal cellular receptor. Linkage of ligands to the external virus surface then permits re-targeting to appropriate receptors, such as receptors associated with prostate and bladder cancer cells.

### **Keywords:**

Adenovirus-polymer coating-stealth virus-targeted vector-prostate cancer

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Project number:	QLK6-CT-2000-00565
EC contribution:	€2,164,896
Duration:	36 months
Type:	CM
Starting date:	01/02/2001

## ***Oestrogens and age-related urogenital diseases: basic and clinical approaches***

### **Objectives:**

Effects of estrogens and phytoestrogens on age-related urogenital diseases will be studied. Benign prostate hyperplasia and carcinoma in males, urinary incontinence in both sexes are in the focus of interest. Molecular biologic, animal experimental as well as clinical studies will be performed.

### **Brief description:**

1/3 of Europeans are over 55 years old, when conditions such as endometrial cancer, vaginal dryness, benign prostatic hyperplasia, prostate cancer and urinary incontinence are common, with increased healthcare costs and reduction in quality of life and mobility. The lack of oestrogens appears causally linked to the development and progress of such diseases. (E)UROESTROGEN(E)S aims to promote the development of selective estrogen receptor modulators (SERMs) with reference to phyto-SERMs. 5 partners at 4 universities belong to the European thematic network EUROSTERONE, with excellent laboratory infrastructure and access to patients. The research will lead to concepts for clinical trial and well-tolerated phyto-SERMs beneficial in the human urogenital tract. This will both aid the ageing population and be of great socio-economic impact throughout Europe.

### **Keywords:**

estrogens - prostate - urinary bladder

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EC contribution:	€1,399,997
Duration:	36 months
Type:	RS
Starting date:	01/06/2001

## ***Molecular Mechanisms of Androgen Resistance in Prostate Cancer***

### **Objectives:**

Prostate carcinoma is the second highest cause of cancer death in men in industrialised countries. No really efficient treatment exists for the late, metastatic stages. Androgens and the androgen receptor play a pivotal role in this disease but hormone ablation therapy usually only works for a limited time. It is planned to study the molecular mechanisms underlying the progression to the hormone-refractory stage in order to identify new drugable targets.

### **Brief description:**

Increasing evidence documents the essential role of the androgen receptor in the generation and growth of prostate carcinoma, even in late, androgen-independent stages. However, the mechanisms involved are still poorly characterised. In order to decipher the pathways implicated in this disease, tumour tissue originating from prostate tumor patients with different gradings will be obtained and thoroughly analysed. Genes that are differentially regulated in human prostate tissues, healthy or diseased, will be identified by the chip technology which allows the comparison of over 8.000 different transcripts in parallel. The results will be validated using several approaches, depending on the genes identified. Crosstalk with the androgen receptor signalling pathway will be analysed in detail, especially with regard to the role of growth factors. The interaction of protein partners with the androgen receptor will be analysed by several techniques, including two-hybrid methods. The impact of these interactions on androgen receptor function will be assessed in prostate cancer cell lines. Mutagenesis studies will be performed to identify receptor and co-factor regions important for the interactions. The role of phosphorylation and post-translational modifications in androgen receptor function will be studied. Finally the protein/DNA interactions responsible for the selective control of androgen target genes will be studied in detail. These complementary approaches should allow the selection of novel targets suitable for compound development in order to find new ways to treat therapy-resistant prostate carcinoma.

### **Keywords:**

prostate cancer - androgen receptor signalling - gene expression profiling

### **Co-ordinator**

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EC contribution:	€1,688,932
Duration:	36 months
Type:	RS
Starting date:	01/01/2001

***On Asymmetry in Sphincters: The role of functional asymmetry  
of sphincter innervation in incontinence***

**Objectives:**

The main objective of the project is to gather knowledge about pelvic floor asymmetry and its role in development, severity, diagnosis, treatment, and prevention of incontinence: a) Quantification of asymmetry in healthy subjects and in major patient subgroups with incontinence. b) To correlate asymmetry (by type and degree) to age and age-related changes in pelvic floor functions as assessed by functional diagnostic testing. c) To identify risk groups predisposed to become incontinent at higher age. d) To provide a scientific basis to treat incontinence by applying surface EMG measurement to routine diagnosis and therapy systems. e) To develop a clinical strategy (algorithm) to deal with incontinence especially in the elderly.

**Brief description:**

The project comprises 14 work packages, of which 2 are administrative, 6 are clinical, and 6 technical in nature. Initially, we will develop prototype hard and software tools, especially anal and vaginal/urethral EMG probes, which allow to record non-invasively individual motor units from each side of the pelvic floor muscles (based on surface-EMG technology) and to identify individuals with significant asymmetric sphincter muscle innervation. Subsequently, these tools will be applied to measure pelvic floor innervation and its symmetry/ asymmetry in subgroups of patients with urinary and/or fecal incontinence, as identified in major medical subspecialties (urology, gynecology, gastroenterology, surgery) in different countries in Europe. Furthermore, probe and system validation will be performed in patients in whom selective stimulation of left and right dorsal sacral roots is possible after sacral root stimulator implantation. Finally, in women undergoing childbirth the risk of developing incontinence after pelvic floor trauma is assessed and related to the existence and degree of asymmetric sphincter innervation. Surface EMG measurement will finally be used to develop easy-to-use clinical diagnostic and therapeutic system (based on biofeedback) for routine use, especially in the elderly.

**Keywords:**

incontinence – anal – urogenital - pelvic floor - innervation – asymmetry – surface EMG – biofeedback

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EC contribution:	€288.522
Duration:	36 months
Type:	CA
Starting date:	01/01/2003

## ***Contrast Enhanced Ultrasound Imaging In The Diagnosis And Treatment Of Prostate Cancer***

### **Objectives:**

To co-ordinate and disseminate the research in the field of contrast enhanced ultrasound imaging in the diagnosis and treatment of prostate cancer.

To increase the knowledge about the use of contrast-enhanced ultrasound imaging, and to determine its role in the diagnosis, biopsy guidance, treatment and follow-up of prostate cancer.

### **Brief description:**

Prostate cancer is the most common cancer in the elderly men. About 80% of all cases are diagnosed after the age of 65, and it has a major impact on the Quality of Life. Accuracy of the current diagnostic tools available to detect prostate cancer is disappointing low.

This concerted action approached the improvement in diagnosis and treatment of prostate cancer by the co-ordination and dissemination of the currently performed research of the partners in the field of contrast enhanced ultrasound imaging. This action will for the first time bring together the best European groups working in this field. All partners already have made a substantial contribution to the clinical research in this field during the last years. This action will co-ordinate these contributions to reach a critical mass, and will disseminate the results to the professionals, the industry and the users.

A possible continuation and expansion of the research during and after the end of this concerted action is one of key-topics of this action.

### **Keywords:**

Prostate cancer - Contrast agents - Ultrasound

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## **HEARING AND VISUAL IMPAIRMENT**



Project number:	QLK6-CT-1999-02094
EC contribution:	€1,673,004
Duration:	36 months
Type:	RS
Starting date:	01/02/2000

***Prevention of visual disability in elderly European populations: a multi-centre study of risk factors for cataract and macular degeneration***

**Objectives:**

The main objectives of the proposal are to identify lifestyle and environmental determinants of macular degeneration in the European setting with a particular focus on solar radiation and diet. The secondary objectives are to establish the health burden of this condition in different European countries and measure its impact on health-related quality of life

**Brief description:**

The study design is a multi-centre case-control study nested within a population based prevalence study. The study is being carried out in seven centres throughout Europe. Centre locations span a 27° latitude from south to north Europe covering a nearly three-fold gradient of UVR. In each centre, a representative sample of 1000 individuals over the age of 65 is invited to participate in a study which includes an eye examination and an interview with a fieldworker for risk factor assessment and vision-related quality of life. Risk factor assessment includes individual measures of lifetime outdoor exposure, current and past smoking and alcohol intake, and intakes of anti-oxidant vitamins measured both by dietary questionnaires and from blood samples. 20 ml of blood is taken in subdued light and sent immediately in an ice igloo by courier to a local laboratory for initial storage at -70 ° C and then transported to the laboratory of Professor Ian Young (Queens University Belfast) for analysis of antioxidant vitamins: ascorbate,  $\alpha$  and  $\lambda$  tocopherol, retinol,  $\alpha$ ,  $\beta$  carotene, lycopene, lutein and zeaxanthin. Buffy coats are extracted and stored for future genetic analyses. The eye examination by trained staff includes visual acuity and fundus image capture using digital photography. The digital images are sent to Professor de Jong in Rotterdam for grading of age-related macular degeneration using internationally accepted classification systems. Data on ambient levels of solar UVR (UVB and UVA) will be combined with the personal exposure histories from the questionnaire to calculate life-time ocular exposure to solar UVR for each individual. The data from the seven centres will be pooled and analysed using multi-level modelling to estimate the risks associated with each of the exposures at both the group and centre level. The study is designed to have adequate power to examine the study hypotheses and to investigate possible interactions between antioxidant levels, smoking and UVR.

**Keywords:**

Age-related macular degeneration, epidemiology, risk factors, UVR, antioxidants, smoking

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EC contribution:	€549,901
Duration:	36 months
Type:	CA
Starting date:	01/04/2001

## *Neuroprotection in the retina*

### **Abstract**

In the ageing population, the morbidity from blinding retinal neurodegenerations belongs to the most feared limitations of life quality. Blindness occurs in the main conditions i.e. glaucoma, ischemic diabetic retinopathy and age related macular degeneration as a consequence of both specific and common pathways leading to retinal cell, mainly neuronal, loss. The global objective of PRORET is therefore the development of therapeutic strategies aiming at blocking the cell death process triggered by genetic mutations or the ischemic process. The scientific and technical objectives of the PRORET project are:

to identify and characterise factors and mechanisms involved in retinal degeneration as a basis for the development of rational therapeutic approaches ; to design methods for therapeutic intervention and, as a prerequisite, for further develop models for retinal degeneration.

### **Objectives:**

The strategies termed under "neuroprotection" aim at limiting or preventing cell death. Such treatments can operate either directly on the degenerating cells or by acting on surrounding cells. Since cell death is mainly occurring through apoptosis we will particularly target this common pathway to find general neuroprotective strategies. The objective is to generalise and fully understand recent promising findings and screen new potential molecules on in vitro and in vivo models obtained through the cluster. Delivery system for applying molecules or cells to the retina will be developed in parallel to molecule screening. New neuroprotective strategies are expected to reach clinical trials during the course of this project.

The objectives are: to identify and characterise factors and mechanisms involved in retinal degeneration as a basis for development of therapeutic approaches; to design methods for therapeutic intervention and, as a prerequisite, to further develop models.

### **Brief description:**

Since cell death is occurring by apoptosis in these diseases, potential drugs and trophic factors that interfere upstream or directly with this process will be considered. Prominent targets belong to the apoptotic cascade e.g. caspases (3,4). Also we recently showed that neurotrophic factors and a Ca<sup>2+</sup>-channel blocker and a neurotrophic factor can postpone photoreceptor degeneration in the rd mouse. The first aim is to understand the molecular basis for these neuroprotective properties in order to identify or design more powerful molecules. The second aim results from the great heterogeneity of the disease is to generalise the neuroprotective properties trophic factors to other in vivo and in vitro models. In parallel, a systematic cloning strategy is initiated to isolate the trophic element implicated in the survival of cones. We need to gather and develop a panel of in vitro, in vivo models in order to assess the neuroprotective properties of potential molecules. We developed the culture of adult retinal neurones from the mammalian and human retina, that can be used to establish in vitro models of retinal dystrophy and ischemia. Animal models like the rds mouse rhodopsin (rho<sup>-/-</sup>) will be used to validate the neuroprotective treatment on other in vivo models with mutations in different genes than the rd mouse. Similarly, models of ischemia will be generated by partners 2 and 5. PRORET intends to improve drug or molecule delivery system to the

retina. These delivery system would enable to provide a constant concentration of the molecule during a long period and target the molecule to the retina with respect to systemic injections. This includes delivery by iontophoresis or non-viral gene transfer. The paracrine effects of transplanted photoreceptors will be further assessed on new animal models. Gene transfer may enable to promote long standing expression of trophic factors (GDNF) in the retina.

**Keywords:**

Neuroprotection – Retina – Degeneration

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Duration:	36 months
Type:	RS
Starting date:	01/01/2003

## ***Oculomotor Function and Self-Motion Perception in the Elderly***

### **Objectives :**

The objectives of the project are to sharpen movement detection skills in the elderly in order to prevent falls during walking and to improve their vehicle driving performance. Improvement in movement management will benefit either one of the initial shortcomings, i.e., the essential problems facing the elderly are basic movement detection and perception shortcomings. These will be attempted to be remedied via complementary sensory enhancement, strengthening of anticipatory behaviour, ergonomic vehicle and road designs and improvement in visual kinetic aids, as well as fall prevention/driving performance cross-training.

### **Brief description:**

An increasing number of elderly citizens are mainstreaming today in everyday life. For the elderly, as for the younger, mobility is an essential component of their quality of life. This project examines physiological, pathophysiological, behavioural and anatomical factors in humans and non-human primates to describe psychological and organic deficits leading to shortcomings in movement perception in the elderly and in patients. Experimental situations will simulate obstacle appearance while walking and vehicle driving situations under kinetic conditions, i.e., with the need to react within a given time frame. Human symptoms will be re-elaborated in comparable experiments in microlesioned and older non-human primates. The results will be used to propose and develop ergonomic training and rehabilitation programs to prevent falls in the elderly and to prolong their skills in vehicle driving. The programs will emphasise active and anticipatory behaviour rather than passive avoidance measures with the aim to allow the growing population of senior citizens in the European Union to retain their individual mobility and thus be able to continue to lead a fulfilling and satisfactory life.

### **Keywords:**

Aging – moving - driving

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Duration:	36 months
Type:	RS
Starting date:	01/05/2002

***Age-Related Macular Degeneration : "Assessment and optimisation of macular function with special regard to reading and motor control"***

**Objectives:**

The increasing number of AMD patients requires new approaches to assess macular function, specially those functions relevant for everyday tasks will be considered such as reading and motion control. The project plans to develop and evaluate new tests for early detection of AMD, assessment of macular function by psycho-physical and electrophysiological methods, optimisation of macular function, a standardised data acquisition, sensitive monitoring and a European standard test battery for a low vision examination.

**Brief description:**

Age-related macular degeneration (AMD) is a disorder of high morbidity in Europe and will be an increasing problem in the next decades. The main objective of the proposal is the development of tools for testing and optimising macular function, which consider the disabilities caused by AMD, mainly disability of reading and motion control, in order to maintain or restitute these functions and therefore quality of life. These tools will provide a high sensitive monitoring of preventive and therapeutic measures (screening for early detection and assessing residual function). These include psychophysical tests (e.g. contrast sensitivity, parafoveal letter recognition, figure/ground interaction, reading); eye movement recording with an eyetracker during fixation, reading, motion perception and exploration; assessment of fixation by Scanning Laser Ophthalmoscope (SLO); objective measurements by multifocal ERG linked with SLO for fixation control. The project will provide new knowledge about macular function and disabilities in AMD, which will be used for training. A test set will be established for a European standard for clinical low vision examination.

**Keywords:**

macular degeneration - reading disability - European standard test set

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EC contribution:	€1,631,713
Duration:	36 months
Type:	RS
Starting date:	01/01/2002

## *Neuroprotection in the retina*

### **Abstract**

In the ageing population, morbidity from blinding retinal neurodegenerations represents the most feared limitation of quality of life. The predominant causes of blindness, i.e. glaucoma, ischemic diabetic retinopathy and age related macular degeneration, occur as a consequence of both specific and common pathways leading to retinal cell, mainly neuronal, loss. The global objective of PRO-AGE-RET is therefore the development of therapeutic strategies aiming at blocking the cell death process occurring in these retinal pathologies. The scientific and technical objectives of the PRO-AGE-RET project are to identify and characterise factors and mechanisms involved in retinal degeneration as a basis for the development of rational therapeutic approaches; to design methods for therapeutic intervention; and, as a prerequisite, to further develop models for retinal degeneration.

### **Objectives:**

PRO-AGE-RET aims to prevent retinal cell death. We will identify general neuro-protective strategies through targeting apoptosis, widely implicated in death. We showed that neurotrophic factors, Ca<sup>2+</sup> channel blockers and receptor antagonists can postpone photoreceptor and/or ganglion cell degeneration in relevant animal models. The objective is to fully explore these promising findings and screen new molecules on in vitro and in vivo models circulating between member laboratories. Delivery systems for administering molecules or cells to the retina will be developed in parallel to molecular screening. New neuroprotective strategies are expected to reach clinical trials during the course of this project. The objectives are hence: 1) to further develop and circulate in vivo and in vitro models for retinal degeneration; 2) to characterise mechanisms involved in retinal degeneration as a basis for development of therapeutic approaches; 3) design methods for therapeutic intervention.

### **Brief description:**

Elucidating the mechanisms of cell death or rescue and screening potential neuroprotective molecules will first be performed in vitro, including adult mammalian and human retinal neurones and retinal explants. Candidate molecules will then be tested on in vivo models, the diversity of which reflects disease heterogeneity. Transgenic models of photoreceptor degeneration and experimental glaucoma inducing ganglion cell death are being generated in member laboratories. Since these models will be circulated, protocols for their morpho-functional characterisation will be rapidly standardised. To assess functional effects of different therapeutic strategies, clinical techniques (eg. multifocal electroretinograms) will be adapted to small rodents. The increased sensitivity of this technique should provide information on regional rescue as may occur with transplantation or viral injections. We will likewise adapt the confocal ophthalmoscope to visualise retinas of small animals. Since several neurotrophic factors have been found to be neuroprotective in member laboratories, their fields of application will be defined with the different in vitro and in vivo models. Their signalling pathways in specific retinal populations will be investigated by molecular cell biology and proteomics.

Calcium channel blockers which were found to be neuroprotective on photoreceptors, will be tested on different animal models to define their therapeutic fields of application and pharmacological profiles. The success of therapeutic strategies relies on both drug efficacy and delivery. PRO-AGE-RET therefore also intends to improve drug or molecule delivery to the retina. In contrast to systemic injections, these delivery systems provide constant doses over long periods, and permit targeting of molecules to the retina. These approaches include iontophoresis of pharmacological agents, non-viral gene transfer and cell encapsulation for in situ neurotrophic factor production.

**Keywords:**

Photoreceptor – Ganglion cells – Cell death & rescue

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EC contribution:	€2,256,710
Duration:	36 months
Type:	RS
Starting date:	01/01/2002

## ***CORTICAL VISUAL NEUROPROSTHESIS FOR THE BLIND***

### **Objectives:**

Visual impairment is included in the 10 most prevalent causes of disability in Europe. The project aims to develop prototypes in the field of visual rehabilitation and to demonstrate the feasibility of a cortical neuroprostheses, interfaced with the visual cortex, as a means through which a limited but useful visual sense may be restored to profoundly blind people.

### **Brief Description:**

While the full restoration of vision seems to be impossible, the discrimination of shape and location of objects could allow blind subjects to ‘navigate’ in a familiar environment and to read enlarged text, resulting in a substantial improvement in the standard of living of blind and visually impaired persons. Experiments will be designed to study population encoding of colour and luminance information in the retina and to develop a bioinspired system, which serves as part of a real-time neuroprosthetic test platform for processing visual information. Reconfigurable multichannel neurostimulators (128 channels) able to drive different current injections and waveforms through high impedance electrodes will be designed and developed as well as a multichannel transcutaneous power and data radiofrequency link to the intracortical microelectrodes. The safety and efficacy of permanent charge injection through multiple intracortical electrodes into cerebral cortex will be studied using histopathological and physiological techniques. We will use non-invasive transcranial magnetic stimulation (TMS), MRI and fMRI to study the degree of remaining functional visual cortex in blind subjects and to develop a systematic methodology for non-invasive investigation of the functional organisation of the occipital cortex in blind subjects. The results from this project will provide information regarding neuroprosthesis not presently available, as well as new information about the plastic changes in the adult nervous system, which has implications for rehabilitative training and device development. If we can understand more about the fundamental mechanisms of neuronal coding, and to safely stimulate nervous system, there will real potential to apply this knowledge clinically. Although we are still a long way from a perfect visual prosthesis, the success of the cochlear implant seems very promising also for this neurotechnological application.

### **Keywords:**

Neuroprosthesis, Retina, Multielectrode recordings, Visual pathways, Intracortical microstimulation, Blind, Visual information processing, Visual rehabilitation, Visual prosthesis.

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EC contribution:	€2,701,852
Duration:	48 months
Type:	RS
Starting date:	01/02/2003

## *Identification of environmental and genetic risk factors for Age Related Hearing Impairment*

### **Objectives:**

The general aim of this project is the identification of genetic and environmental risk factors contributing to age related hearing loss (ARHI). We will collect DNA and clinical and audiological data from 4800 patients and controls from 7 EU countries. Environmental risk factors will be identified by statistical analysis of clinical and environmental data. Susceptibility genes will be identified by DNA analysis (linkage and association studies).

### **Brief description:**

Patients, controls and family-based samples are collected by the 8 clinical partners. Our patient collection will include 1600 sporadic patients, 1600 normal hearing controls, and 1200 persons belonging to families containing at least two ARHI patients from 7 different EU countries, plus 400 patients and controls from the Saami (the Lapps in Northern Finland). A person is considered affected if, upon audiologic testing, the pure-tone average is at least 1 standard deviation above the age and sex-average median. A person is included as a control if he/she belongs to the better hearing half of the population. All patients and controls fill in a standardised questionnaire (in their native language) on clinical history and putative environmental risk factors for ARHI. The results of the questionnaire are fed into a database. Classical statistics (univariate and multivariate analysis) will be applied to elucidate the influence of environmental variables on ARHI.

The genetic analysis comprises genome searches on the Saami samples and the samples from the affected families, to identify candidate regions for susceptibility to ARHI. The databases from the Human Genome Project will indicate which genes (positional candidates) are located within each of the candidate regions. Additional candidate genes will be generated by constructing and analysing inner ear specific cDNA libraries. Among the positional candidates, a selection will be made to prioritise the genes that are known or suspected to have a function in the inner ear. Subsequently, a case-control association study will be performed using Single Nucleotide Polymorphisms (SNPs) analysis on the selected genes. Genes showing putative association with ARHI will be further analysed with a more dense set of SNPs, to identify the variations that significantly increase ARHI susceptibility.

Finally, the results from the genetic study and the environmental questionnaire will be integrated by modern computing technology (including neural networks and genetic algorithms). This will result in an ARHI model, which will enable us to formulate precise guidelines for the prevention of ARHI in the future.

### **Keywords:**

case-control - presbycusis - ageing - questionnaires - epidemiology - association study - genome search - computing - prevention - single-nucleotide polymorphism - susceptibility gene - non-parametric linkage analysis - quantitative trait - complex disorder - multifactorial

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Project number:	QLK6-CT-2002-02494
EC contribution:	€81,600
Duration:	36 months
Type:	CA
Starting date:	01/01/2003

***Photoreceptor Dynamics in Age-Related Macular Degeneration.  
Consequences for early diagnosis***

**Topic:**

The earliest changes in the photoreceptors caused by age-related macular degeneration

**Objectives:**

It is the purpose of the concerted action to elucidate the basic physiological processes involved in ARM/AMD. The participants will study the early changes in photoreceptor driven signals owing to ARM/AMD. This changes will be studied at different levels: the photoreceptor themselves, the retina, the visual cortex and at the perceptual level. It is anticipated that a better understanding of these processes will lead to improved clinical diagnosis and therapy of the patients.

**Brief description:**

The project will concentrate upon the implementation of new fundusreflectometrical, electrophysiological and psychophysical techniques for diagnosing ARM/AMD and advance the understanding of the involved pathophysiological mechanisms. This will be achieved by implementing new stimulation techniques, that enable selective stimulation of different photoreceptor types. The project is aiming at a complete description of the signals in each photoreceptor type and their mutual interactions at different retinal illuminances and temporal frequencies using electrophysiological techniques such as the recordings of electroretinograms and the visual evoked potentials. Furthermore, psychophysical tests of photoreceptor dynamics will be developed. The results from these studies will be used to further advance the available techniques to study more physiological and psychophysical properties of the healthy and diseased retina. The comparative study with the same technique in age matched normal and ARM/AMD patients will allow to draw conclusion upon the basic physiological mechanisms leading to ARM/AMD. Finally, the integrity of the photoreceptors themselves is studied by measuring the 'Stiles-Crawford effect' with a fundusreflectometrical technique. This is a non-invasive, objective and reliable technique to measure whether the internal organisation of the photoreceptors is still in tact or not. Fundusreflectometry can also be used to measure the density of the macular pigment.

**Keywords:**

ageing - macular degeneration - photoreceptors - electroretinography - psychophysics - visual evoked potentials - fundus-reflectometry.

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Area 6.2: Basic Processes of Physiological Ageing

## **CELLULAR AND MOLECULAR PROCESSES OF AGEING**



Project number:	QLK6-CT-1999-02237
EC contribution:	€1,799,811
Duration:	36 months
Type:	RS
Starting date:	01/03/1999

## *Prevention of iron storage disease in the ageing population*

### **Objectives:**

1. Guidelines for screening for haemochromatosis in the general population. 2. Guidelines for patient referral for genotyping. 3. Improved clinical awareness of iron storage disease in the ageing population. 4. Evidence for the contribution of haemochromatosis or carrier status in the following conditions present in the ageing population: cardiac disease, arthritis, arthropathy and hip joint disease, endocrinopathy and osteoporosis, liver disease, diabetes, Alzheimer's disease and cardiovascular disease. 5. The role of modifier genes and other genetic loci involved in iron storage disease.

### **Brief description:**

Many members of the Consortium have already actively collaborated and the work put forward in this proposal is based on our earlier work. New collaborations are underway. We are exploiting our wide expertise in the field of iron overload, in particular hereditary haemochromatosis (HHC). This disease is one of the most common genetic disorders in European populations. The majority of HHC is due to homozygosity of the C282Y mutation in the HFE gene, with contributions from the H63D mutation. The disease is easily treatable although frequently diagnosed after irreversible tissue damage has occurred.

We are continuing to recruit and analyse patient samples to provide us with a large database of information allowing us to compare the results from different parts of Europe. We are increasing the awareness of the disease and so encouraging early diagnosis. A large survey on 20000 subjects will provide the data on which to base screening strategies. We are pooling biochemical data (transferrin saturation and ferritin concentration), as well as genetic and clinical data from the different centres resulting from the phenotype/genotype studies. Many samples are referred to the different centres for genotyping based on a suspected diagnosis of HHC. Awareness of HHC now means that some clinicians refer samples unnecessarily for genotyping. As it is not clear what are the best parameters on which to base the decision to genotype we need to define guidelines for such referrals.

We are examining too the role that heterozygosity for either the C282Y or H63D mutations play in Alzheimer's disease, arthropathy, osteoporosis and cardiomyopathy. Experiments using transgenic mice will be performed to look at the role of modifier genes and their role in HHC. Compilation of our results will allow us to determine the nature of other loci involved in determining iron overload.

By developing protocols for HHC screening we will be able to improve the health of the ageing population in Europe by preventing tissue damage due to iron overload.

### **Keywords:**

Iron overload-haemochromatosis-genetics

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EC contribution:	€1,733,951
Duration:	36 months
Type:	RS
Starting date:	01/02/2000

## ***Role Of Oxidative Dna Damage And Repair In Ageing***

### **Brief Description:**

Principal molecular mechanisms underlying human ageing are unknown. Basic molecular understanding is required before therapeutic intervention can be applied to prevent the degenerative diseases associated with ageing. Such intervention will be required to meet the medical, social and economical challenges posed by a major increase in the percentage of old people in Europe. A major theory of ageing suggests that oxidative modifications of DNA increase with age. This theory will be tested by advanced chemical, molecular and biochemical analysis, by development and studies of new transgenic mouse models and by molecular characterisation of human premature ageing syndromes. The studies include detailed investigation of DNA repair processes, and their relation to transcription and to specific molecular ageing processes.

### **Keywords:**

Ageing - oxidative DNA damage - molecular biology

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## *Immunology And Ageing In Europe*

### **Objectives:**

To define and manipulate age-associated changes in human T cell immunity. To this end, this thematic network will co-ordinate research on basic cellular and molecular mechanisms underlying human T lymphocyte ageing in a longitudinal model of specific ageing processes. T cell clones will be produced in a central facility and distributed to members for identifying and validating age-associated changes in a multidisciplinary, quality-controlled fashion using a workshop approach with central data analysis. Characteristics jointly identified as relevant to the ageing process in vitro will be validated in vivo using the unique donor materials of the participants. Manipulation to influence immuno-senescence in vitro will be tested with a view to intervention in vivo. The interdisciplinary synergistic interactions of the participants will enable the identification of the critical cellular and molecular changes underlying T cell senescence and begin to develop interventions to ameliorate these changes.

### **Keywords:**

Ageing, Intervention, Immunosenescence, cellular and molecular biology.

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EC contribution:	€1,574,023
Duration:	36 months
Type:	RS
Starting date:	01/02/2000

***Identification And Characterisation Of Genes Controlling Longevity  
And Ageing In An Animal Model.***

**Brief Description:**

An understanding of the molecular and physiological mechanisms that cause ageing is essential for the rational intervention of age-related disease. Simple model systems that exhibit ageing provide an economical means to obtain this understanding. Our objective is to determine the genes and physiological mechanisms that cause ageing in *Caenorhabditis elegans* with a view to targeting processes that underlie age-associated disease in humans. This will be achieved by an extensive, interdisciplinary analysis of a series of genetic variants that exhibit greatly slowed rates of ageing resulting in life span increases of up to 300% (Age mutants). This analysis will reveal both regulatory mechanisms that control ageing rate and downstream mechanisms that constitute the molecular and physiological causes of ageing. We predict that many of the mechanisms we uncover will be universally linked to ageing in all animals and that consequently the targeting of these mechanisms will ameliorate age-related disease or postpone its onset.

**Keywords:**

Ageing, gene, nematode, molecular biology, animal model

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EC contribution:	€1,536,763
Duration:	36 months
Type:	RS
Starting date:	01/01/2001

***Age-Related Changes In Learning And Memory: Neural Cell Adhesion Molecules, Associated Carbohydrates And Ligands***

**Brief description:**

The aim of our joint study is to investigate the roles of the neural cell adhesion molecules, NCAM and L1, in aged rodents with regard to the efficacy of acquisition, retention and recall of learned tasks versus that in young and adult animals. We wish to examine the contribution of the two molecules to synaptic plasticity using LTP in vitro and learning paradigms in vivo in wild type and transgenic animals. We also wish to characterise the functional properties of sub-domain fragments of these molecules including their cognate ligands and carbohydrates in modifying learning and memory. Further, we wish to identify novel ligands of NCAM and L1 by means of rational design and combinatorial chemistry and to evaluate of such ligands to preserve and promote the capacity for learning at old age and under stress

**Keywords:**

Ageing, learning, memory, regeneration, neural cell, adhesion molecules, ligands, cellular biology

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## ***THE ROLE OF PROTEASOME IN HUMAN AGEING: IMPLICATIONS FOR ANTI-AGEING STRATEGIES***

### **Brief Description:**

Accumulation of damaged proteins is a hallmark of ageing. Proteasome is the main proteolytic system in charge of damaged protein degradation within the cell. Recent data on human keratinocytes and dermal fibroblasts have shown that proteasome alterations may be responsible for the age-related drop of quality in cellular proteins. Our project is a concerted attempt to understand this phenomenon, and to find appropriate handles to keep it under control. We will analyse the expression of genes coding for proteasome subunits and proteolytic activity. We will use phage-display and antibodies to identify age-associated modifications in cellular proteins. We will construct human cellular model systems to investigate the role of proteasome in senescence and apoptosis. Finally, we will develop a test to screen substances for their potential effects on age-related proteasome alterations

### **Keywords:**

Ageing, proteasome, gene, cellular senescence

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Type:	RS
Starting date:	01/01/2001

## ***Testing The Mitochondrial Theory Of Ageing***

### **Objective:**

The mitochondrial theory of ageing proposes that the accumulation of somatic mutations in mitochondrial DNA (mtDNA) during life results in a progressive decline in energetic function and eventual cellular and organismal degeneration. We propose to test this idea directly, by engineering a mtDNA mutator that will be expressed in various model systems, including yeast, cultured human cells and the fruit fly *Drosophila*. The phenotypic consequences of an enhanced mtDNA mutation rate will be evaluated on cellular and physiological function gene expression, senescence and lifespan.

### **Brief Description:**

Mitochondrial DNA mutator strains will be created in the various biological model systems to be used, based on the expression of a defective mitochondrial DNA polymerase (POLG) enzyme, lacking proof-reading exonuclease activity. The mutator polymerase gene will be engineered by in vitro mutagenesis and re-introduced, e.g. into cultured cells or *Drosophila* embryos, using standard transfection and microinjection methods, yielding transformed lines expressing the mutator. The rate and pattern of accumulation of mtDNA mutations will be evaluated in the various model systems, to confirm that the mutator works, and to measure the altered dynamics of somatic mutation of mtDNA. The phenotypic effects of an enhanced rate of mtDNA mutation will then be investigated at the cellular and organismal levels via methods appropriate to each model system. In yeast, genetic crosses will be used to test roles of other genes and parameters in the phenotypic expression of the mtDNA mutator, and effects of the mutator on vegetative lifespan will be measured. In mammalian cells, we will evaluate effects on respiratory phenotype, cell viability and senescence. Susceptibility to agents inducing DNA damage, respiratory stress and apoptosis will also be investigated, as well as a variety of physiological parameters of ageing. Global effects on gene expression related to ageing will be studied using hybridization to cDNA microarrays. In flies, effects on lifespan over many generations, and under various types of stress, will be evaluated. Interactions with other mitochondrial functions and the tissue-specificity of observed phenotypes will be tested using appropriate genetic crosses. The major results expected will be a detailed profiling of the effects of an enhanced mtDNA mutation rate on cellular and organismal phenotype, gene expression patterns and overall lifespan, in key model systems relevant to biological ageing.

### **Keywords**

mitochondrial DNA - somatic mutation - gene expression - biological models

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Duration:	36 months
Type:	RS
Starting date:	01/10/2001

## *Molecular Mechanisms Of Senescence And Ageing*

### **Objectives:**

The major goal of the current application is to determine the major factors governing ageing at the cellular level in vitro and in vivo. We will clarify the role of programmed cell death in cellular and organismal ageing. We will attempt to design new strategies for the diagnosis and treatment of age-related dysfunctions in experimental animals and humans.

### **Brief Description:**

We will try to identify new genes, which are related to replicative senescence in vitro. To establish a cause-effect-relationship for selected senescence-associated genes, it is planned to over-express candidate genes in young cells and study consequences for their phenotype. It is also planned to abrogate the function of candidate genes in senescent cells and thereby override the senescent phenotype. Furthermore, the expression and function of a defined set of genes, implicated in cellular growth regulation and in the regulation of cell death, will be analysed during in vitro ageing. We will analyse expression and function of these genes at various levels, including transcription, post-transcriptional control, and a biochemical determination of gene function. We will also identify new cellular genes that are capable to break the senescent phenotype at M1 or M2 stage. Besides genes that are acting in the so far unknown senescence pathways, we also anticipate to identify upstream regulators and downstream effectors of the p14(ARF) and p16(INK4A) senescence-inducing pathways. In a complementary approach, genes and gene products that are involved in transcriptional regulation of these genes will be characterised. Finally, we will address the question which of the changes observed in the cell culture models are relevant for ageing in vivo. To this end, the expression and function of selected senescence-associated genes will be determined in biopsies; these biopsies are available from an already existing bank of skin and vascular biopsies that have been obtained from young and old healthy volunteers, as well as in clinical samples from patients with intrinsic or extrinsic skin ageing, biopsies from patients with vascular disease of various grades, and fibroblasts taken from patients with premature ageing syndromes, i.e. Werner syndrome and Down syndrome. These experiments will allow to discriminate age-dependent alterations that occur in cell culture only from those alterations which occur in a similar way in aged human beings.

### **Keywords:**

senescence - cell cycle regulation - apoptosis - premature ageing syndromes - longevity - cDNA screening - gene identification - skin ageing - arteriosclerosis - fibroblasts - endothelial cells - human ageing - gene expression profiling

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Project number:	QLK6-CT-2001-00175
EC contribution:	€1,576,657
Duration:	36 months
Type:	RS
Starting date:	01/01/2002

## *Mechanisms of ageing in extracellular matrices*

### **Objectives :**

During the ageing process, the changing structure, composition and properties of extra-cellular matrices such as tendon, skin, blood vessels, etc., reflects a gradual change in expression by matrix-forming cells. The mechanisms controlling this change in expression are not at all understood. The proposed work aims to (1) provide knowledge on the mechanisms controlling the ageing process in extra-cellular matrices, (2) differentiate the effects of 3 hypothetical pathways by which matrix-producing cells alter their expression with age, and (3) to formulate strategies to manipulate of cell activity which could form the basis of anti-ageing strategies. Anti-ageing strategies to be investigated will include ultrasound, cell transplants, protein expression, and novel drugs.

### **Brief description**

Three hypotheses are presented as to what makes matrix-forming cells change their expression in ageing tissue:

1. Ageing extra-cellular matrices show gradual and accumulating differences in structure, composition and properties due to a basic difference between the processes of matrix tissue formation and of matrix tissue turnover and remodelling evident as a change in the expressed protein profile, or proteosome.
2. Ageing represents gradual and accumulated injury repair responses to either overt or sub-critical damage in the matrices, and age induced mRNA changes detected by transcriptome.
3. Ageing arises from progressive changes in the magnitude or nature of the mechanical signals passed from the matrix into the matrix-forming cells, or a changing sensitivity of the transduction of these signals.

The work is divided into 3 work-packages, each designed to test one hypothesis. Differences in structure, composition and molecular packing in young versus mature tendon will be related to expression of both anabolic and catabolic products from young and old matrix-forming cells to test (1). The expression of anabolic and catabolic products from young and old matrix-forming cells in response to sub-critical and severe mechanical injury will be examined to test hypothesis (2). The response of young and old matrix forming cells to mechanical stimulation and their expression of cell surface transduction molecules will be examined to test hypothesis (3). Cell expression in pathological tissue and abnormal tissue (gene knock out models) will also be studied to deduce mechanisms of age-related changes.

Arising from the knowledge gained in terms of each putative mechanism, we propose to finish the work with preliminary formulations of possible ways in which matrix-forming cell expression could be manipulated in order to combat age-related degradations in extra-cellular matrix properties and to combat age-related diseases of matrix tissues.

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Project number:	QLK6-CT-2001-00310
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Duration:	36 months
Type:	RS
Starting date:	01/01/2002

***Functional Genomics And Proteomics In Human Molecular Gerontology And Geriatrics (Development Of Ad Hoc Microarrays, Diagnostic Applications And Molecular Screening)***

**Objectives:**

Human gerontology is entering the post-genomic era where amounts of genomic data must be transformed into functional information. We shall clarify the role of genes previously discovered to be associated with ageing in the process of successful (longevity without overt diseases) and unsuccessful ageing (pro-inflammatory status, age-related diseases, disabilities) by functional genomics and proteomics. We shall develop and exploit a reliable multi-functional microarray.

**Brief Description:**

In this project we shall clarify the role of genes previously discovered to be associated with ageing in the process of successful (longevity without overt diseases) and unsuccessful ageing (pro-inflammatory status, age-related diseases, disabilities) by applying advanced functional genomics and proteomics on complementary in vitro models of human ageing, and on cells from centenarians and patients struck by major age-related diseases. With an SME we shall develop and exploit a reliable multi-functional microarray 'SeneChip' suitable for molecular gerontology in vivo and in vitro, and for diagnostic in geriatrics, to evaluate the pro-inflammatory status of patients, particularly those at high risk for impending disability, and their morbidity and chance for survival after stressful conditions (surgical operations). Moreover Senechips shall be commercialised for helping the development of novel cosmeceuticals/anti-ageing drugs.

The objectives of this project "Functionage" are :

To find the functions of genes recently identified as being associated with human ageing.

To identify and find the functions of novel proteins, interacting with the products of these genes or not, in different models of human ageing, namely by proteomics analyses.

To assess their contribution to successful or unsuccessful ageing by using an existing collection of biological samples from healthy centenarians and patients struck by major age-related diseases.

To find out the molecular mechanisms of stress induced premature senescence and to test whether it occurs in vivo.

With an SME, to develop a reliable multi-functional microarray 'SeneChip' for molecular gerontology and for diagnostic to evaluate the pro-inflammatory status and morbidity of geriatrics patients at risk for impending disability. Senechips will be commercialised for helping the development of novel cosmeceuticals/anti-ageing drugs.

**Keywords:**

gene function - human ageing - diagnostic - functional genomics - proteomics - centenarians - in vitro - pro-inflammatory status - cosmeceuticals

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Duration:	36 months
Type:	RS
Starting date:	01/01/2002

## *Towards The Maintenance Of Tissue Elasticity For Healthy Ageing*

### **Objectives:**

The control of elastic fibre assembly and remodelling holds the key for healthy ageing through the maintenance of dynamic elastic tissues (blood vessels, skin, lungs, elastic cartilages) and the treatment of many age-related disorders or poor repair processes. Specific aims of this project are to identify mechanisms at the molecular and cellular levels leading to 1) the synthesis of elastic fibre components (elastin, fibrillins, microfibrillar-associated glycoproteins) and their three-dimensional organisation in the extra-cellular matrix, and 2) elastic fibre disorganisation in human tissues.

### **Brief Description:**

The programme comprises 4 complementary workpackages : in WP1, elastic fibre changes will be compared in human samples, in young and old wild or genetically-deficient rodents, by immunocytochemistry, ultrastructural and biochemical analysis, and related to physiological/biomechanical parameters. Using several rat strains, the search for specific genes that define the elastin quantity in the aorta will be carried out as well as the analysis of the differential gene expression in aortic cells from these rat strains, in treated versus untreated smooth muscle cells and fibroblasts, in skin equivalent versus dermal equivalent models. WP2 will tackle the three-dimensional structure and assembly of the elastic fibre, from individual structural domains to interactions of elastin and fibrillins with other elastic fibre components. WP3 will focus on the emerging family of lysyl oxydases, enzymes that confers to elastin and collagen their elastic properties and tensile strength, respectively. The aim is to identify the elastin-specific lysyl oxydase and its activation mechanism. This WP will also focus on the regulation of the elastin and lysyl oxydase genes, and the identification of factors and corresponding signal transduction pathways that may be activated in the main elastic-fibre-producing cell types, myofibroblasts and smooth muscle cells. These cells and skin-equivalent model will be used to test the effects of cytokines and potential therapeutic drugs on the co-expression of the two genes. WP4 will identify the proteinases involved in elastic fibre degradation using normal and pathological human samples, and corresponding animal models; elastin and fibrillin fragments produced in tissues will be characterised. This will lead to the rational design for docking site antibodies or peptide mimics which will be used to inhibit elastic fibre degradation in ageing skin and aorta. The results should lead to new ways to sustain elastic fibre function, to stabilise and regenerate elastic fibres during ageing and age-dependent elastic tissue disorders by understanding the mechanisms that govern the well-controlled assembly of functional elastic fibres, controlling the cross-linking pathways that determine the property of elastic fibres, encouraging the neosynthesis of functional elastic fibres, and preventing elastic fibre degeneration in old patients.

**Keywords:**

Elastin - fibrillins - microfibrillar-associated glycoproteins (MAGP) - lysyl oxydases (LOX) - elastic fibers - elastases - matrix metalloproteinases (MMP) - tissue inhibitors of matrix metalloproteinases (TIMP)

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EC contribution:	€1,096,560
Duration:	36 months
Type:	RS
Starting date:	01/01/2003

## *Ageing and the biological clock in the brain*

### **Objectives:**

The objective of the present project is to decipher basic cellular and molecular processes that underlie disturbances in the control of biological rhythms of an individual during ageing. In mammals, the suprachiasmatic nucleus (SCN) plays a role of biological clock and offers unique potentials for studies of ageing phenomena at the cellular and molecular level that can be correlated to a distinct function, the regulation of biological rhythms, which undergoes major changes with ageing to deteriorate the quality of life. Despite the clinical evidence that disturbances in biological rhythms disrupt the life of elderly people, little is known about the molecular, cellular and functional changes occurring in the SCN during ageing. In the proposed project the Partners will study changes of factors intrinsic to the neurons in the SCN as well as extrinsic factors in humans and experimental systems. The latter includes effects on the SCN by cytokines that increase in the blood and the brain in aged individuals.

### **Problem:**

Disturbances in sleep patterns and biological rhythms is a problem that increases with ageing

### **Aims:**

To analyse molecular, cellular and functional changes in the pacemaker in the brain for biological rhythm in aged humans and experimental animals

### **Expected results:**

Establishment of factors both within the biological clock and from the environment that causes the disturbances in sleep patterns

### **Potential applications:**

Know-how methods for treatment of a disabling condition with ageing

### **Keywords:**

Ageing - Biological clock - Cytokines - Nervous system - Hypothalamus

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Duration:	36 months
Type:	RS
Starting date:	29/01/2002

## *T cell immunity and ageing*

### **Objectives :**

T-CIA will network EU laboratories from Universities and Industry, together with one NAS member to focus on biomarker discovery for monitoring immune ageing in vivo. Normal physiological ageing processes as opposed to results of underlying disease will be studied separately in males and females by comparing samples from young and old, healthy and less healthy, in longitudinal studies and cohorts characterised by genetic epidemiology. In this way, proteomic, genomic, genetic or functional biomarkers will be identified which are informative for the T cell ageing process. Interventions in vitro will provide clues for exploiting novel agents in vivo to slow down or reverse immunosenescence. The objectives are to recommend strategies to measure immunosenescence in vivo, assess its clinical relevance and contribute to prevention and reversal.

### **Description:**

Each partner will provide samples and data to a central facility (CF) which will catalogue and redistribute them for analysis. Each partner will thus receive a wider variety of materials than available from their own resources, and, reciprocally, each sample will be assessed by a much wider variety of techniques than available in one centre. Data will be returned to the CF for analysis and correlation with clinical status and other donor information, particularly the genetic epidemiology data generated by one of the partners. Biomarkers informative for age-associated changes must not be influenced by disease and should also be observed in in vitro culture models. The degree to which they are influenced by gender will be assessed. Interventions which are beneficial in vitro should be reflected at the level of such biomarkers. This project will test the hypothesis that such biomarkers do indeed exist and can be exploited for monitoring levels of immunosenescence in vivo, allowing identification of persons who might benefit from that category of interventions found to be advantageous in vitro. The project thus consists of three components: 1) collection of samples, generation of T cell clones, cell and data banking, redistribution of samples, data gathering and analysis (at the CF); 2) biomarker discovery at the genomic, proteomic and functional levels; 3) testing novel interventions in vitro. The CF will provide cell and data storage capacity and manage the logistics of sample distribution, data collection and collation, and will organise meetings for discussion of these matters. The CF will also act as a training centre for young scientists from the other partners, and as a clearing house to mediate placements within the consortium. Interactions with a large ongoing 5th Framework Thematic Network co-ordinated by the present applicant will be encouraged to generate synergistic interactions going beyond this single RTD project.

### **Keywords:**

Ageing, T-lymphocytes, Intervention

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Area 6.2: Basic Processes of Physiological Ageing

## **GENDER-RELATED DISORDERS**



Project number:	QLK6-CT-2000-00736
EC contribution:	€153,564
Duration:	36 months
Type:	RS
Starting date:	01/03/2001

## *Burden of disease in old age*

### **Objectives:**

The main aim of this network is to help the better usage of existing data resources and to explore the information gaps in understanding of the disablement process. The early modifiable predictors of disability will be addressed from different perspectives. These include physiological, hereditary vs. environmental, gender and life-span approaches. Recommendations for good practice will be given. The need for a new collaborative cross-national study on the disablement process will be evaluated.

### **Brief description:**

A network of centres representing recognised expertise in ageing research and previously established cross-sectional and longitudinal studies with up to 35 years of follow-up will be formed. The new cross-sectional studies involved in the network employ up-to-date methodology in capturing the most essential levels of the disablement process. They will enable hypothesis-building analyses to be carried out. The participating longitudinal studies are a unique data resource. They will enable hypotheses to be tested in prospective analyses. Using data from previously established studies will make it possible to examine whether earlier life influences will have an effect on the health and functional capacity of older people. The use of pre-existing data from the network studies will make it possible to capture the stability of and change in various modifiable exposures (such as physical activity, body weight and smoking) and their effect on age-related health outcomes. The twin studies in the network will provide important material for testing the relative contributions of hereditary vs. environmental components to the variability in the disablement process and other health outcomes. The network will also study, why some people with similar disease are functionally independent while others suffer from a heavy burden of disease and are in need of care. The network participants will exchange researchers, data, expertise and produce collaborative publications. A background document describing the participating studies will be produced. Based on the analyses carried out evidence-based policy recommendations and recommendations for good practice will be given. The need for a new comparative cross-national study focusing on the disablement process and burden of disease in old age will be evaluated. If further collaborative research is deemed necessary a proposal for a new study with internationally harmonised and standardised data collection procedures will be suggested.

### **Keywords:**

Burden of disease in old age - disablement process - previously established cross-sectional and longitudinal studies - twin studies - hereditary and environmental influences - modifiable exposures - collaborative publications - evidence-based policy recommendations

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Duration:	36 months
Type:	RS
Starting date:	01/01/2001

## ***EARLY DEVELOPMENT OF OVARIAN FOLLICLES – TIMING OF MENOPAUSE IN WOMEN***

### **Objectives:**

Identification of the role of anti-müllerian hormone (AMH), growth and differentiation factor-9 and -9B (GDF9/9B) in the selection of primordial follicles in the ovary. The production of AMH, GDF9 and GDF9B. The development of assays for AMH, GDF9 and GDF9B. The relation of AMH, GDF9 and GDF9B levels and ovarian functioning with age. The effects of AMH, GDF9 and GDF9B on ovarian functioning in vivo and in vitro. The identification of genes regulated by AMH, GDF9 and GDF9B.

### **Brief Description:**

Menopause is a major milestone in the ageing process in women. The cessation of ovarian function causes the almost complete absence of female sex steroid hormone production by the ovaries in postmenopausal life. Consequently, before and after the menopausal transition very different physiological hormonal regimens prevail, which have a major impact on healthy ageing of women and their quality of life. Since the age of menopause affects the length of the period of postmenopausal life, it is of utmost importance to describe the process of menopause and to identify predictors to monitor the timing of menopause. Menopause is caused by the exhaustion of the follicle stock in the ovary, and the efficiency by which primordial follicles are recruited into the growing pool of follicles is one of the main determinants of the age at which menopause occurs. This project aims at understanding the role of anti-müllerian hormone (AMH), growth and differentiation factor-9 and -9B (GDF9, GDF9B) in primordial follicle loss.

AMH, GDF9 and GDF9B have each been implicated in the regulation of early follicular growth. They are members of the large superfamily of transforming growth factor  $\beta$  (TGF $\beta$ )-like growth and differentiation factors. An important consideration in the choice of these factors is their specificity toward the ovary.

In the first stages of the project efforts will be focussed on the development of tools. In the middle stages the endeavours will be geared more to the in vitro and in vivo physiological studies, while in the last stages of the project the efforts will concentrate toward the screens of AMH, GDF9 and GDF9B regulated genes which may serve as monitors of healthy ageing in women.

### **Keywords:**

Ovary - menopause

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Duration:	36 months
Type:	RS
Starting date:	01/01/2001

***Sleep Disorders In Menopausal And Postmenopausal Ageing Women: Prevalence, Biological Mechanisms, Animal Models, Social Aspects, Treatment And Prevention.***

**Objectives:**

The objective of the proposal is to clarify why menopausal and postmenopausal women suffer from a considerable number of sleep disorders that adversely affect their quality of life and their efficacy in daily performance, and how these disorders can be treated. The problem is divided into the following aspects, each addressed in a work package: 1) What kind of sleep disorders ageing women suffer from, 2) Do the changes in the sleep quality correlate with changes in hormonal levels in the course of ageing, 3) Do the changes in sleep quality correlate with changes in the circadian system in the course of ageing, 4) How vulnerable are ageing women to sleep loss, 5) What is the role of the GABAergic system in sleep disorders of ageing women, 6) How can we treat sleep disorders in ageing women.

**Brief Description:**

Based on focus group interviews, a sleep questionnaire that is specifically suited for studies of sleep disorders in ageing women will be developed and validated for social epidemiological research. The questionnaire will assess the prevalence and type of sleep disorders, as well as the psychosocial and health status of women over 30 years. The sociological data from focus group interviews and the sleep questionnaire, will assist to interpret biomedical data. Their integration will provide the basis for prevention strategies and treatment of sleep disorders in ageing women.

Oestrogen, progesterone, prolactin, melatonin and growth hormone levels will be correlated with sleep quality in menopausal women. Hormone profiles of women with satisfactory sleep will be compared to those who have sleep disorders verified by polysomnography. Sleep will be investigated in gene targeted mice lacking specific hormones. The data will provide the basis to evaluate possibilities of hormone therapy. The ability of ageing women to recover from the effects of prolonged wakefulness will be investigated in sleep deprivation experiments, and their capacity to obtain deep sleep will be evaluated.

The decreasing sensitivity to light in the course of ageing may be associated with disturbed circadian rhythms. Light-induced melatonin suppression will be tested in normal women and compared with women suffering from sleep disorders verified by polysomnography. The data will be used as the basis for planning light therapy and melatonin treatment to alleviate sleep disorders in ageing women. In addition, hormone replacement therapy will be evaluated. Analysis of women's hormonal status will be related to the type and severity of sleep disorder and/or circadian rhythm disorder and will precede the treatments. The results of these experiments will serve to formulate treatment recommendations for sleep disorders in ageing women.

**Keywords:**

Ageing - actigraphy - women - benzodiazepine - focus group - GABA - hormone therapy - knockout - light therapy - melatonin - menopause - microdialysis - oestrogen receptor - orexin - polysomnography - restless leg syndrome - sleep deprivation - sleep disorder - sleep quality - sleep questionnaire

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Starting date:	01/01/2002

***European Male Ageing Study: Prevalence, Incidence And Geographical Distribution Of Symptoms Of Ageing In Men, And Their Endocrine, Genetic And Psychosocial Correlates***

**Objectives:**

The proposed study aims to assess the impact of an ageing-related decline in endocrine anabolic functions on the health status in elderly men. The hypothesis is that regional and inter-individual variability in dysfunctions, body composition and health outcomes in ageing men can be explained by different rates of decline in anabolic hormones, which are in turn influenced by epigenetic and/or genetic factors.

**Brief Description:**

A cross-sectional survey of a random population sample of 4800 community-dwelling apparently healthy men aged 40-79 years in 12 different areas of Europe will be undertaken to determine baseline hormonal and clinico-physiological status together with assessment of some key predictor variables. These men will then be followed prospectively for 5 years to determine their changes in both hormonal and general health status.

Participating centres: - Manchester (England) Co-ordinating, Malmo (Sweden), Tartu (Estonia), Lodz (Poland), Szeged (Hungary), Leuven (Belgium), Santiago de Compostela (Spain) and Florence (Italy).

Each of the 8 centres will recruit 400 men (100 in each decade after 40 years) from the random sample of community registers (with an additional 200 men from ethnic minority communities in Manchester) and collect the following data either in- home or in-hospital.

Clinical - demographic, co-morbid condition, medications, nutrition, physical activity, ageing male symptoms, physical functioning (SF-36), moods, cognition, sexual dysfunction, prostatism score; Physiological - fat and fat-free mass by physical anthropometry (height, weight, regional circumferences and skinfold thickness) and bone density by ultrasound of the heel; Hormones – Testosterone, sex hormone binding globulin, free testosterone, bioavailable testosterone, oestradiol, bioavailable oestradiol, Dihydrotestosterone, Dehydroepiandrosterone sulphate, LH, Variant LH and FSH, insulin, insulin-like growth factor-1 and its binding protein 3, leptin, parahormone, thyroxine, thyroid stimulating hormone; Polymorphisms in selected genes - androgen receptor, oestrogen receptor a, vitamin D receptor, aromatase, steroid 17a hydroxylase/17-20 lyase, 5 $\alpha$  reductase 2, sex hormone binding globulin, LH ?, LH receptor and FSH Receptor.

All will be repeated in the same subjects 5 years later (except DNA analyses).

**Keywords:**

Ageing - ageing men - testosterone - androgens - hormones - muscle function - frailty - osteoporosis - bone ultrasound - fractures - body composition - cognition - mood dysphoria - sexual dysfunction - prostate - nutrition - secular trends - regional variation - quality of life

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Area 6.3: Demographic and social policy aspects of population ageing

## **DETERMINANTS OF HEALTHY AGEING**



Project number:	QLK6-CT-2000-00211
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Starting date:	01/03/2001

## ***A Multi-Disciplinary Approach To Healthy Ageing And Its Determinants In 11 European Countries***

### **Objectives:**

Changes in and determinants of usual and healthy ageing in terms of mortality and morbidity outcomes as well as in terms of physical, psychological, cognitive, and social functioning will be investigated in 11 European countries. Special attention will be given to differences in the above-described relationships between Northern and Southern European populations.

### **Brief Description:**

For 11 European countries the participants will bring in data on about 7600 subjects, collected in the period 1959-2000. The data are collected by means of physical examinations, blood sampling, interviews, questionnaires and death certificates. Data on indicators of healthy ageing (mortality, morbidity, self-perceived health, physical functioning, psychological functioning, cognitive functioning, social functioning) will be extended by information on determinants, e.g. socio-demographic factors, biological risk factors and lifestyle factors. The work in the context of the present proposal can be divided in the following tasks:

Construction of two databases: 1) on biological determinants of healthy ageing concerning the European cohorts of the Seven Countries Study, 2) on data of the FINE and SENECA Study relating to indicators and socio-demographic and lifestyle determinants of healthy ageing.

Investigation of age, period and cohort analyses of blood pressure, cholesterol, BMI and heart rate in the general population and a healthy subgroup of men followed up from 40 to 99 years of age. Also the impact of these changes on coronary heart disease, stroke and all-cause mortality will be studied (Seven Countries Study).

Investigations of gender-specific interrelationships between dietary factors and their impact on healthy ageing (self-perceived health, psychological and cognitive functioning and mortality) in persons aged 70-99 in European countries. Special attention will be given to dietary patterns, nutrients, biomarkers of nutrient intake and nutritional status (FINE and SENECA study).

Investigations of gender-specific age-related changes in and determinants of functioning in people aged 65-99 in European countries (FINE and SENECA study).

Reporting in peer reviewed journals and to the EU. Based on a workshop with participants and health policy makers a final report will be prepared containing the most relevant results. This report will also be made available as an Internet site to support health policy makers.

### **Keywords:**

Healthy ageing - blood pressure - cholesterol - BMI - heart rate - coronary heart disease - stroke - diet - physical functioning - psychological functioning - cognitive functioning - social functioning - socio-demographic factors - prospective study - international study

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Duration:	36 months
Type:	RS
Starting date:	01/05/2001

## ***The Measurement Of Quality Of Life In Older Adults And Its Relationship To Healthy Ageing***

### **Objectives :**

To review the existing literature and measures on quality of life and healthy ageing in older adults. To adapt the existing WHO measure of quality of life, the WHOQOL, for use with older adults. To use the adapted WHOQOL in a study of healthy ageing. To consider the relationship between healthy ageing and a variety of lifestyle, psychological, and cultural factors.

### **Brief Description :**

The first main aim of the research will be to develop a reliable and valid measure of quality of life for older adults. An existing measure that has been developed simultaneously across a wide range of cultures, the WHO's WHOQOL, will be adapted for use with older adults. This process will include an initial collection of focus group information from older adults, their carers, and relevant professionals, in 17 different participant groups. The focus group information will be used to devise a pilot Older Adults WHOQOL. Data will then be collected from 300 older adults in each centre and the data will be used to test the psychometric properties of the pilot measure. A revised version of the measure will then be included in field trials. The second main aim of the research will be to use the Older Adults WHOQOL in a cross-cultural study of healthy ageing. This study will examine a variety of characteristics of healthy ageing that include lifestyle factors (such as diet and exercise), psychological factors, family and other social factors, and cultural factors. Of particular interest will be the examination of attitudes to ageing in different cultures and how these impact on different aspects of quality of life such as psychological and physical health, and personal and spiritual values. Taken together, the research programme will provide a reliable and valid cross-cultural measure of quality of life in older adults that can be used in a variety of normative population, policy evaluation and clinical outcome studies. The programme will also offer guidelines on healthy ageing and quality of life that should impact on policy making and research in this area.

### **Keywords :**

Quality of Life - Healthy Ageing - Attitudes to Ageing - Cultural Factors - Measurement.

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Type:	RS
Starting date:	01/01/2002

## *European Challenge For Healthy Ageing*

### **Objectives:**

The “European Challenge for Healthy Ageing” project aims at improving the criteria to define frailty, that is emerging as a major characteristic of elderly people. The project will then develop two quantitative indexes ("Frailty index" and "Functional Activity Index") that will express the degree of frailty and activity level in elders. In addition, a correlation of the "Frailty index" and the "Functional Activity index" with the genetic variation will be studied. The project includes also a plan to disseminate the results throughout Europe among organisations operating with elders.

### **Brief Description:**

Frailty is emerging as a major characteristic of elderly people. It is characterised by an impending disability and high risk of morbidity and mortality. The relative impact of environment and genetics on frailty is presently unknown. The “European Challenge for Healthy Ageing” project will address this question by taking advantage of the results emerged from studies in human longevity. It will be characterized by a completely new experimental design. In fact, to avoid the problems connected with the classical association studies (such as the diversity of environmental conditions, social classes across short geographical distances and so on) we will use a set of intrafamily comparisons as well as interfamily comparisons. In particular, a sample of pairs of first cousins whose parents are born between 1890 and 1905 and are either concordant or discordant with respect to the longevity trait will be recruited. In addition, if possible, alive parent will be recruited too. The recruitment will be carried out in populations from Italy, France and Denmark, where genetic and environmental history are known and documented. All the individuals enrolled in the study will be analysed for gerontological parameters that can be correlated with the health status. All the information will be then analysed to develop quantitative synthetic measure of frailty and activity level ("Frailty index" and a "Functional activity index"). The DNA of the recruited individuals will be extracted and a set of genes that are involved in stress response will be analysed (APOE, HRAS1, HSP gene family, IL6, Sirt gene family, TH). The purpose of this step is to evaluate the relevance of this important class of genes in the quality of ageing. New algorithms will be developed to explore the correlation between health status indexes and genotypes of the stress responder genes. Within the project time the dissemination of the results among the organisations dealing with elders will be carried out.

### **Keywords:**

Ageing, Centenarians, Frailty, discordant sib pairs, concordant sib pairs, intrafamily comparisons, interfamily comparisons.

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Duration:	36 months
Type:	RS
Starting date:	01/01/2002

***The Role Of Diet On The Longevity Of Elderly Europeans- A Study In The Context Of The European Prospective Investigation Into Cancer And Nutrition.***

**Objectives:**

The objectives of the study are the identification of an optimal overall dietary pattern for the elderly Europeans and the development of a nutrition score that will describe this pattern. The project will also evaluate the proximity of the dietary patterns of the European population to the optimal diet, identify the influence of socio-demographic factors on diet, assess the necessity for and nature of dietary advice and the feasibility of altering existing dietary habits.

**Brief Description:**

Most causes of death and disability among the elderly have strong nutritional components. The project aims at identifying dietary patterns of elderly that maximises longevity and their socio-demographic determinants.

Data on diet, medical history, somatometry and socio-demographic characteristics for 4000 Europeans, from Denmark, France, Germany, Greece, Italy, Netherlands, Sweden and the UK, aged 65 or more will be transferred from the EPIC databank to the coordinating centre. In this databank for the elderly, mortality data already recorded at IARC will also be transferred and incorporated. The project, based on the above information, will assess the extent to which the dietary habits affect the health of elderly Europeans.

Dietary patterns in various European regions will be identified and their socio-demographic determinants will be examined. An optimal nutrition score for the elderly will be determined based on food group intakes that best predict longevity. The dietary patterns of the elderly in the various European regions will be compared with the identified optimal diet allowing assessment of the proximity of their diet to the described one. Analysis of diet in relation to various causes of mortality will also be performed.

Finally, results on the necessity and nature of dietary advice for the elderly in various European regions will be elaborated. Information material in lay language will be prepared and made available to elderly people and those who care for them.

**Keywords:**

Nutrition – elderly - longevity

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All other EPIC centers contribute data and scientific expertise to the EPIC-Elderly project, without financial obligation on the part of the project.

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Duration:	24 months
Type:	RS
Starting date:	01/01/2002

## *Ageing Well: European Study Of Adult Well-Being*

### **Objectives:**

ESAW shall produce a European Socio-Cultural Model for Ageing Well which estimates the direct causal contribution of five key components (physical health and functional status, mental efficacy, life activity, material security and social support) along with personal characteristics and culture to the outcome variable ageing well. It shall support domestic and international policy development, and guide the delivery of professional care and services to older people across Europe.

### **Brief Description:**

ESAW shall conduct a parallel study simultaneously in six countries. A population sample of between 2000-2400 people will be drawn in each country. Face-to-face interviews shall be conducted by trained interviewers using a structured interview schedule. Data from each country shall be amalgamated into a European data set. The data shall be analysed to produce seven reports which shall recount the status of older people in Europe. Five reports shall focus on physical health and functional status, mental efficacy, life activity, material security and social support. These reports shall highlight differences between and within countries in the situation of older people especially with regard to age, educational levels and gender. A sixth report shall examine cultural differences between the countries in terms of their political structure, welfare and health services. LISREL modelling shall provide the evidence to produce the seventh report which shall summarise the European Socio-Cultural Model for Ageing Well in terms of the impact of the five domains on the outcome variable representing ageing well.

The study is broken down into three phases. In Phase 1 each country shall translate the survey instrument, train interviewers and select the community sample of older people. Phase 2 represents the data collection and preparation phase. Phase 3 shall consist of data analysis, writing and dissemination (including a European conference). To stimulate discussion about Ageing Well in the European context a 2-day conference will be held in Sweden in the 24<sup>th</sup> month to report the findings from ESAW to a diverse European audience.

### **Keywords:**

ageing well - socio-cultural model - policy-making - gerontological education - professional care - physical health - functional status - mental efficacy - life activity - material security - social support

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EC contribution:	€2,188,374
Duration:	36 months
Type:	RS
Starting date:	01/01/2002

## ***Enabling Autonomy, Participation, And Well-Being In Old Age: The Home Environment As A Determinant For Healthy Ageing***

### **Objectives:**

The main aim of the ENABLE-AGE project is to examine the home environment as a determinant for autonomy, participation and well-being in very old age in a longitudinal perspective. More specifically, e. g. to explore country specific housing-related societal support as represented in personal situations; to provide an update of housing policies and legislation; to provide a home assessment standard methodology; to provide policy recommendations in housing issues across the EU.

### **Brief Description:**

The novel scope of this project is to explicitly consider subjective and objective person-environment relationships as important determinants to healthy ageing, in a European perspective. A macro level update on housing policies (the ENABLE-AGE Update Review) will support the project process, integrated with the knowledge generated by the ENABLE-AGE Survey Study (N=2000) and the ENABLE-AGE In-Depth Studies (N=200). A wide range of well-proven measurements will be administered at home-visits with very old people, randomly sampled in five partner countries. The design is longitudinal, comprising two measurement points (T1 and T2) with a one-year interval. For the qualitative ENABLE-AGE In-Depth Studies, 200 in-depth interviews followed by consultation interviews with a sub-sample (n=60) will be effectuated. The synthesis of results from the different parts of the project will provide the basis for producing a Home Assessment Methodology Package and policy recommendations and guidelines in housing policies for use across the EU.

Results will concern national and comparative data sets and reports at T1 and for T2-T1, the Home Environment Assessment Package, final reports and scientific publications presenting new knowledge on transactional processes involving objective and subjective housing circumstances as determinants for healthy ageing in terms of autonomy, participation, and well-being, especially as they concern very old people. Furthermore, the results will support theoretical development within the field. The results will be disseminated at scientific as well as practical levels in order to underfeed the provision of updated housing policies and service provision across Europe.

### **Keywords:**

activity - ADL - environmental assessment - functional health - housing accessibility - home assessment - housing policies - well-being.

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Area 6.3: Demographic and social policy aspects of population ageing

## **SOCIO-ECONOMIC IMPACT**



Project number:	QLK6-CT-1999-02161
EC contribution:	€500,000
Duration:	36 months
Type:	CA
Starting date:	01/01/2000

## ***Socioeconomic determinants of healthy ageing: from description to explanation***

### **Objectives:**

The general aims of the project are:

- to provide a comprehensive description of socio-economic differences in health expectancy among the elderly in different European countries;
- to contribute to the explanation of these differences, by looking at risk factors, at specific diseases, and at accumulation of disability and selection by mortality over the life-course.

### **Brief description:**

Throughout the European Union, socio-economic factors are important determinants of healthy ageing: persons with a higher socio-economic status not only live longer, but also spend a smaller portion of their life-time with disability. This phenomenon offers good opportunities for identifying specific factors, which promote successful ageing. This project therefore aims to describe socio-economic differences in health expectancy among the elderly in 11 European countries, and to contribute to the explanation of these differences.

This study will be performed on the basis of the following data sources: (i) survey data on the prevalence of disability, diseases and risk factors, available in 11 participating countries; (ii) census follow-up data on mortality by cause-of-death, available in 11 participating countries; (iii) longitudinal studies of disability and mortality occurring in the same individuals, available in at least 3 participating countries. All data will be cross-classified by age, gender and educational level. Data-sets will be prepared according to common specifications, and sent to the co-ordinating centre for centralised data-analysis.

For each country and gender, the following analyses will be performed:

Cross-tabulation of disability-prevalence and mortality by educational level and age among the elderly (60+);

For each educational group, calculation of health expectancy (i.e. life expectancy, total/with/without disability) from age 60;

Cross-tabulation of disease- and risk factor-prevalence and of cause-specific mortality by educational level and age among the elderly;

Calculation of the contribution of specific diseases and causes of death to educational differences in health expectancy among the elderly;

Calculation of the effect of accumulation of disability and selection by mortality at younger ages to educational differences in health expectancy among the elderly.

The results are expected to increase our understanding of how socio-economic factors promote healthy ageing and postpone the onset of disability. This knowledge is important for the development of policies leading to a compression of morbidity, and for an accurate prediction of the future size and nature of the ageing population.

## **Keywords:**

Ageing - Health expectancy - Socioeconomic factors

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EC contribution:	€1,395,841
Duration:	36 months
Type:	RS
Starting date:	01/02/2000

***Research action for improving elderly workers safety, productivity, efficiency and competence towards the new working environment***

**Objectives:**

The overall aim is to promote the health, working capacity, and well-being of ageing employees by a series of cost-effective methods and work policies.

It is intended a) to develop reliable assessment criteria, strategies, and tools to evaluate existing work models, b) to develop new work models so as to improve the productivity, safety, and work satisfaction of elderly workers, and c) to propose policies for improving the older workers' position on the labour market.

**Brief Description:**

To begin with, existing studies and work models will be assessed, and the key problems of elderly workers extracted from these studies. Based on these findings, new work models as well as criteria and tools for their assessment will be developed. Thereafter, two laboratory studies, extensive questionnaire studies in three countries, and a number of on-site work interventions are planned in six companies. At the end of the project, guidelines on work organisation for elderly workers, vocational training schemes for elderly workers, best-practice examples on work organization of elderly workers, and recommendations for policy interventions will emerge.

Each newly-developed and implemented work model will be validated in a comprehensive cost-effectiveness analysis. The full cost of each proposed work model assessment methodology (first equipment costs, estimated tool development and upgrading costs, application costs in relation to human resources and time) will be evaluated and translated into monetary terms. The associated benefits will be weighed against the costs.

**Key Words:**

Elderly workers (older than 45) - cost-effective new work models - evaluation criteria and tools - recommendations for policy interventions

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EC contribution:	€2,758,630
Duration:	24 months
Type:	RS
Starting date:	01/01/2002

## *Survey on health, ageing and retirement in Europe*

### **Objectives:**

SHARE -- a longitudinal Survey of Health, Ageing and Retirement in Europe -- will collect interdisciplinary data on European citizens older than 50 years. Data to be collected will include health variables, psychological variables, economic variables and social support variables. The current proposal aims at several preparatory surveys in a selected number of European countries culminating in a main test survey of about 12000 individuals.

### **Brief Description:**

Core of the work is the iteration between questionnaire development and data collection. Point of departure will be the US HRS, the UK ELSA and other survey instruments (e.g., in Germany, Italy and Sweden) which have addressed relevant questions.

Data will be collected in three stages. First small-scale experiments include trials with a number of important design elements (e.g. sample design, questionnaire design, interview modes, comparison with administrative data). Then full-questionnaire pilots will be run. Based on these experiences a medium-scale test survey will be held in all participating countries. They are a balanced representation of the various regions in Europe, ranging from Scandinavia (Denmark and Sweden) through Central Europe (France, Germany and the Netherlands) to the Mediterranean (Spain, Italy and Greece). Belgium, Switzerland, the UK and the US are part of SHARE but are not funded under this project.

This survey will follow a common set-up across all countries with the goal of collecting data that are strictly comparable to allow cross-country research. The outcomes of the project, including the collected micro-data, will be made widely available, subject to legal and confidentiality restrictions. The surveys will be big enough to allow initial cross-country analyses in their own right, and, hopefully, also some within-country analyses.

Specifically, the project will develop sample designs that are feasible in different countries, potentially making use of the sampling frames that are already available; develop survey instruments and sample designs that are most suitable for each country and optimally adapted to the various sample strata; investigate response effects and feasibility of interviewing modes in experiments and pilots; and finally recommend a survey design and instrument for a ready-to-go pan-European longitudinal SHARE on a full scale.

### **Keywords:**

Longitudinal survey design - data collection on ageing

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EC contribution:	€1,760,816
Duration:	34 months
Type:	RS
Starting date:	01/02/2002

## *Sustaining Working Ability in the Nursing Profession*

### **Objectives:**

Today's working conditions in nursing often do not allow healthy ageing at work. Most nursing staff leaves the nursing profession prior to regular retirement age. In the NEXT-Study the reasons for and the circumstances of premature departure from health care work are being investigated. The study shall provide the basis for targeted workplace health promotion designed to assure sustainable work ability in the nursing profession.

### **Brief description:**

Within the frame of the NEXT Study, similar parallel cohort studies will be performed in each of the 8 participating countries (Belgium, Finland, France, Germany, Italy, Sweden, The Netherlands, United Kingdom). Between 5000 and 8000 nurses of all categories will be followed by means of self-report questionnaires during a period of 12 months beginning in September 2002. Hospitals, old peoples' homes and health care institutions in primary care will be included to represent the national distribution of nursing work.

Topics of interest of the assessments are the participants' working conditions and health, as well as attitudes and private circumstances relating to job and working perspectives. Furthermore the nurses' intent to leave the present health care institution will be assessed. Those leaving the work place within the one year investigation period will receive additional assessments at the time of their exit and after further 12 months to assess the circumstances of this step as well as the consequences. Further data will be gathered by a structured analysis of the participating institutions to assess factors of relevance for premature departure from nursing work such as the economic situation and attitudes or activities concerning workplace health promotion and sustainability of the workforce.

The NEXT Study adopts a unique approach. By assessing premature departure from health care work, it will provide knowledge about (i) risk factors, (ii) risk groups for premature departure, (iii) the impact the exit has on the individual, (iv) the age dependency of risk factors, and (v) factors of relevance for normal ageing in health care work.

### **Keywords:**

demographic development - healthy ageing - nurse - nursing - premature departure from work - risk factors - self-report questionnaire - shortage of nursing labour - sustainable work ability - work and health.

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EC contribution:	€931,331
Duration:	30 months
Type:	RS
Starting date:	01/01/2002

## *Ageing, health an retirement in Europe*

### **Objectives:**

To document the improvement in the health of the elderly in Europe (ideally since 1950), based on a systematic collection of existing national data.

To provide projections for this process into the future (e.g. until 2050).

To analyse retirement decisions and the demand for health care as a function of age and health (in addition to the usual economic variables).

To combine these results with the projections for the health of the elderly into estimates of the future evolution of health care and pension costs.

### **Brief description:**

Recent bio-metric research, based mainly on US data suggests that people not only live longer, but also in better health. This project will first document to what extent this trend exists in Europe as well and make projections for health of the elderly over the coming decades. These projections will be used to asses the sustainability of social security system based on a detailed analysis of the influence of better health on the demand for health care and retirement decisions.

The data search and compilation constitutes the first important phase (Phase1) of the work programme. Existing national socio-economic panels will be used first, they have the advantage of being modern and roughly comparable. The project will also search for data from the 1950s and 1960s from different sources, e.g. insurance companies and national health services.

This will be undertaken by a team composed of researchers from a majority of EU member states and with an intimate knowledge of the national environment and statistical sources.

On this basis, the second phase will start with the compilation of alternative scenarios for the health of the elderly and indicators of 'active' life expectancy for the EU up to 2020 and 2050.

At the same time there will be theoretical and empirical work on the influence of health on retirement decisions and the demand for health care. This will show the sensitivity of projections for health expenditure and retirement benefits to alternative assumptions concerning the health of the elderly.

Finally the implications for public policy, notably with health care and pensions will be examined in the light of the bio-demographic data.

By incorporating a number of bio-dynamic and health factors into the demographic projections it will provide the European Commission, other Community institutions and national decision-takers with new tools of analysis and new arguments in policy debates. The findings will be disseminated in the form of working papers, conferences and academic publications.

### **Keywords:**

Ageing - health - retirement - longevity.

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Duration:	36 months
Type:	RS
Starting date :	01/01/2003

***Socio-economic and occupational effects on the health  
inequality of the older workforce***

**Objectives**

The proposed interdisciplinary research will provide detailed evidence on the association between individuals' socio-economic status and physical or mental health for the older workforce, highlighting the direction of causation of this relationship and examine how this affects labour force participation. It will compare the above relationships across the participating EU countries to identify institutional differences that might influence these relationships.

**Brief description**

The research will provide detailed evidence on the association between individuals' socio-economic status and physical and mental health and sense of well being of the older workforce (those above the age of 50) and highlight the direction of causation of this relationship. A number of issues will be investigated relating to differences between sexes with respect to the effects of individuals' socio-economic and occupational status on the physical and mental health at the later stages of working life. The assessment of the impact of the socio-economic and occupational differences on physical and mental health is crucial, not only for our understanding of the development of age-related diseases and disability, but also how these may be avoided by controlling contributory socio-economic factors. The project comprises 6 work packages:

The first encompasses the tasks required for scientific co-ordination: monitoring and management of scientific progress and general day-to-day communication within the project. The second draws together the available literature and data sources in a survey of the current state of knowledge on the relationship between health and individual socio-economic and occupational status indicators of the older workforce, in the participating EU countries and identify the important unanswered research questions. The third uses a variety of available datasets to assess in descriptive terms the importance of the age-health-employment status relationship and organises the collection of primary data for the participating countries. The fourth uses appropriate statistical/micro-econometric methodology to identify associations between various past and present social and economic parameters and their impact on disease, impairment and health for the older workforce by gender. It will explore the interactions of mental and physical health and labour market participation and explore causality issues. The fifth brings together the different results on the impact of socio-economic and occupational status on individuals' health for the older workforce, across the participating EU countries. The sixth, communicates project activities and results to the EU, end-users and the public in meetings, conferences or symposia.

**Keywords**

Ageing – health - socio-economics

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Type:	CA
Starting date:	01/01/2003

## *The dynamics of income, health and inequality over the life cycle*

### **Objectives:**

To estimate the causal effect of income on health around the age of retirement, distinguishing between the impacts of transitory and permanent poverty and deprivation on health.

To analyse the dynamics of individual health, with an emphasis on the degree of persistence of ill-health over the life cycle.

To estimate the reverse effect of health on income through reduced earnings, early retirement and the varying pension schemes.

To estimate the causal effect of income on the use of health care services, using longitudinal data.

To estimate the impact of policy interventions and pension schemes on the degree of income-related inequalities in health and in access to health services in all European Union countries.

### **Brief description:**

This project aims to apply advanced econometric methods to analyse an unusually rich source of information (the European Community Household Panel) in order to provide some answers to questions of great policy relevance. The underlying question is: what explains the European cross-country differences in the degree to which health and health care utilisation are unequally distributed by income? Our previous work has developed some useful methods to measure and quantify the degree to which health and health care are unequally distributed between rich and poor, and what contribution do the different age groups make. It showed that these inequalities have persisted despite decades of policymaking were aiming at equal access, combating poverty and social exclusion. Furthermore, we were able to show that the age groups around the retirement age made the most important contribution to these inequalities and inequities.

Effective policymaking requires a proper understanding and a quantification of the causal mechanisms generating these inequalities. The availability of a new rich panel data sets offers hitherto unseen possibilities for finding causal relationships by exploiting the changes in health and income around retirement, and by dealing with endogeneity and unobserved heterogeneity. This should enable us to shed further light on the causality of the associations found so far in cross-sectional analyses. The data will allow for the estimation of both the dynamic relationships between income reduction, health and health care at the individual level and for the identification of the effects of intertemporal changes in these variables. In addition, several country teams have access to country-specific datasets with linkages to tax registers, mortality and hospitalisation registrations which offer ample opportunity to validate and extend the 'common core' ECHP findings on income, health and health care relationships to other health and utilisation parameters.

### **Keywords:**

Income – health - inequality - retirement

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EC contribution:	€1,553,206
Duration:	36 months
Type:	RS
Starting date:	01/01/2003

## *Future Elderly Living Conditions In Europe*

### **Objectives:**

From 2000 to 2030, EU population aged 75+ will have increased by three quarters. These trend in numbers will be amplified or balanced by changes in other spheres: health and socio-economic conditions of the elderly, potential support from their partner or children. The choices for future living arrangements at old ages and associated needs for care are the result of these interacting influences. The project is to forecast them for the next 30 years. It will lead to proposals for the adaptation of family and elderly policies, to be debated with policy makers and civil society.

### **Brief Description:**

The project is centred on a 2000-2030 forecast in a selection of nine European countries of the population aged 75+, classified by sex, age, marital status, together with health, family and socio-economic conditions. It will result in a quantification of living arrangements and an estimate of the future needs of old-age populations.

Work will follow four main lines:

1. An assessment of the past and present position of the elderly (by sex and age) on various living conditions aspects. Marital status is first dealt with, together with sex and age. Health, family and socio-economic conditions are then considered. Statistical material is analysed through age-cohort-period models. The data needed are extracted from vital statistics, censuses and population registers, large panels and repeated surveys. Most of them are national and an important attention will be devoted to comparability and reliability. All data will be organised in an interactive data base.
2. Development of sets of projections till 2030 along the same dimensions, through three complementary methods and various assumptions, respectively micro-simulation with life-course events, dynamic multi-state based on movements from status to status and a combined static/dynamic method.
3. Inference of future choices for living arrangements and estimation of care needs, from the cross-characterisation of the elderly by their health/ disability status, family potential support and socio-economic resources.
4. Debates of the results with policy makers and civil society, developing propositions for adjustments of the elderly and family policies. Implications of the numerical trends are debated with policy makers and civil society in workshops at national level, then in a European Forum. A specific web-site will be developed in order to disseminate findings of the project, advertise for the venue of the European Forum and open the related discussion.

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EC contribution:	€2,999,612
Duration:	36 months
Type:	RS
Starting date:	01/01/2003

## *Advanced Multidisciplinary Analysis Of New Data On Ageing*

### **Objectives:**

The main objective is to develop policy tools in the field of ageing. Specifically, we will conduct statistical and econometric analyses of individual behavioural responses to public policies influencing active and healthy ageing, health care services utilisation, retirement, and social participation, and we will develop indicators for key concepts relevant to EU policy such as retirement incentives, savings adequacy, well-being and disability status of the elderly.

### **Brief Description:**

Focus of our statistical and econometric research methodology is the analysis of individual behaviour. We study decisions made by individuals or households, and we analyse how individuals respond to their socio-economic environment, including institutions and policy measures. We estimate behavioural reactions ("feedback effects") to changes in public policy, e.g. changes of health care utilisation and its implications for health status in the wake of a health care reform, or changes of the retirement age and the level of savings in the wake of a pension reform.

The data we are using are non-experimental and come from (large) surveys such as SHARE, ELSA and HRS. We employ a number of well-known and also of advanced statistical techniques, including regression types of analyses, multinomial choice models of various kinds, robust, semi-parametric and non-parametric estimation methods, duration analysis, and bio-statistical methods, paying attention to the nature (particularly selectivity) of the samples and the endogeneity of explanatory variables.

In addition to the behavioural analyses, we construct indicators designed to inform policy in the area of ageing. The choice of indicators will be motivated by both policy relevance and the cross-country reliability and validity as inferred from the above behavioural analyses. For example, an indicator of work-related disability will reflect validated measures of incapacity to work that are comparable across countries and not administrative data that would confound individual circumstances with legal eligibility rules. We place particular emphasis on inequality or distributional measures, to an extent not possible with aggregate data.

### **Keywords:**

Quality of life of the elderly - retirement behaviour and active ageing - retirement incentives - health, disability and well-being of the elderly - health services utilisation - intergenerational family solidarity - income and savings adequacy among the elderly.

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Starting date :	01/01/2003

## *Demographic uncertainty and the sustainability of social welfare systems*

### **Objectives:**

This study focuses on the sustainability of welfare systems in EU countries in the face of ageing and demographic uncertainty. Although population ageing is expected and its consequences to the sustainability of the welfare systems have been widely explored, it is much less recognised that the degree of ageing is highly uncertain. Unexpected demographic development poses particular problems that emerge slowly, but are potentially of considerable importance and may have several implications. This study addresses these problems. The extent of demographic uncertainty and the effects of unforeseen developments on welfare expenditure and its financing are demonstrated and analysed. The effects of demographic uncertainty on the risks different groups and cohorts face are also studied.

### **Brief Description:**

The main tools employed will be six different overlapping-generations models, two generational accounts, one model establishing the socio-economic and demographic determinants of individual health status and the determinants of health care expenditure for a given health status and one mechanistic model, with a detailed description of the institutional features of the country's social security system, used in budgetary cost analysis of population ageing.

The project consists of five parts. The first part comprises the set-up phase, preparing country-wise stochastic demographic projections and economic models to work together. It also includes surveying relevant recent literature both on the role of uncertainty in economic decision-making and on the state of applied economic models used in ageing research. Part two consists of country-wise calculations of age-related public expenditure and income, and global analysis of macroeconomic outcomes, describing quantitatively the effects demographic uncertainty has on the economic assessments of the consequences of population ageing. In the third part of the project the country results are compared and the differences analysed and explained. Part four examines how demographic uncertainty could and should be taken into account in ageing policies. Part five transforms the results and experiences from the other four parts into methodological conclusions on the desirable and feasible interplay of demographic and economic ageing analysis.

### **Keywords:**

Population ageing - demographic uncertainty - sustainability of welfare systems - risk sharing policies

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Area 6.4: Coping with functional limitations in old age

## **COPING WITH FUNCTIONAL LIMITATIONS/TECHNOLOGIES**



Project number:	QLK6-CT-1999-02236
EC contribution:	€1,000,000
Duration:	36 months
Type:	RS
Starting date:	01/01/2000

***Enhancing outdoor mobility in later life: personal coping, environmental resources, and technical support***

**Objectives:**

The objective of the MOBILATE project is the comprehensive description and explanation of the outdoor mobility among older adults in urban and non-urban settings in northern, southern, central, and eastern Europe, the description and explanation of both age-related and cohort-related changes in mobility, and the enhancement of the outdoor mobility in old age by providing varied dissemination material for concrete application.

**Brief Description:**

The MOBILATE project aims to better understand the complex interplay between personal competencies and coping efforts of older people and aspects of the physical and social environment, all of which significantly impinge upon the outdoor mobility of ageing men and women.

In order to achieve this goal, the project combines different data sources (person, environment, including urban versus non-urban regions) as well as different data-collection strategies (generation of a cross-sectional and cross-country data set MOBILATE Survey and MOBILATE follow-up data). In the survey, patterns of outdoor mobility and activity are examined in roughly 300 men and women aged 55 years or older from six urban and rural regions, representing five European countries (eastern and western Germany, Finland, Italy, Hungary, and the Netherlands). The sample of altogether 3,941 respondents is disproportionately stratified according to gender and age. The MOBILATE survey is based on a standardised questionnaire including items on the basic personal and environmental components of mobility as well as psychological measures on coping, well-being and cognitive functioning, and a mobility diary which spans two days.

The MOBILATE follow-up covers a total of 862 participants and uses the same instruments applied in the first data collection wave (1995).

At one research site, an evaluation of a demand-responsive transport system is conducted. Furthermore, a comparative analysis of mobility-relevant European regulations will be provided.

**Keywords:**

Outdoor mobility, quality of life, individual changes, activities, health, social network, environment, neighbourhoods, urban settings, rural settings, transport modes, automobile, public transportation, mobility regulations.

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Type:	RS
Starting date:	01/04/2000

## ***Robotic Assistance In Neuro And Motor Rehabilitation***

### **Objectives:**

Explore machine mediated neuro-rehabilitation therapies for older persons.

Develop a clinical prototype machine for reach and grasp therapies and evaluate the therapeutic impact.

Establish the acceptability of robot mediated neuro-rehabilitation to older patients, physiotherapists and allied healthcare professionals.

Exploit results for the benefit of the European community and its citizens by moving towards a practical commercial device, supported by the clinical evidence.

### **Brief Description:**

For a person who has just had a stroke, recovery to full health is a slow, tedious and often painful process. The more the person can exercise and the better the quality of the exercise, the better the persons recovery will be, however it is costly to provide this level of assistance with current physiotherapy services. The GENTLE/S project is investigating robot mediated neuro-rehabilitation that can provide high quality therapeutic interventions and at the same time monitor the patient recovery so to assist with determining prognosis and diagnosis. The system is targeted for upper limb rehabilitation and is appropriate for people who have had a stroke, a traumatic brain injury, or similar insult effecting motor and sensory control of the upper limbs.

Treatments can be tailored to the individual patients needs, and allow for repetitive, task oriented movements that challenge the patient yet provide a high level of motivation. The aim is to re-educate movement, recover the muscle strength in the limbs and achieve goals that improve the patients independence. This is done both by real tasks and also through virtual reality with computer graphics where the user manipulates objects on a computer screen through a simple 'reach and touch' technique. The robot reinforces the correct movement pattern and they combination of visual and haptic support engages the patient in the therapy. The patient's physiotherapist can customise the exercise to each user's specific needs and selects the appropriate level of assistance required.

The design of the robot itself is such that all those involved in the patient's rehabilitation are included in the process from physiotherapists, to physicians, to family members to healthcare managers. This design technique has lead to a robot that could deliver treatment at a special stroke rehabilitation centre, or would be equally effective at a rural centre where a centralised specialist can down load suggested exercises and upload data on the persons progress. The technique has also led to an easy and reliable user interface for both patient and therapist.

### **Keywords:**

machine mediated stroke rehabilitation, neuro-rehabilitation, machine, therapy, CVA, cerebral vascular accident, haptic, rehabilitation robot, minimum jerk theory.

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Project number:	QLK6-CT-2000-00375
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Duration:	36 months
Type:	CA
Starting date:	01/04/2001

## *The Role Of Home Respiratory Ventilators In The Management Of Chronic Respiratory Failure*

### **Objectives:**

The specific objectives are as follows:

Comprehensively to survey custom and practice (including reimbursement policies) in relation to HRV in all States of the European Union

To derive guidelines for HRV use appropriate for patients and their carers both professional and domestic

To create a web site to facilitate HRV use in Europe

To carry out a comparative economic evaluation of the cost of use of HRV in the various environments in which it is adopted. To move towards the establishment of a small but effective HRV Advisory body capable of surveillance of a higher level of use of HRV machines.

To make recommendations in relation to quality control of HRV machines and procedures and the training involved in their safe and effective use

The long-term aim, in addition to reducing health care costs, will be to create an advisory authority with the capacity to monitor usage and if warranted arrange clinical trials. The project will be carried out with the active assistance of the European Respiratory Society

### **Brief Description:**

Chronic respiratory failure (CRF) affects many of the citizens of Europe particularly the aged. The management of these cases is increasingly expensive. In the USA home respiratory ventilators (HRV) are commonly adopted as a technology contributing to less dependency and greater patient empowerment of those with CRF. In Europe this is a practice moderately well developed in a few countries but with wide variations in custom and practice. Against this background, as part of a Concerted Action, it is proposed to carry out a survey in sixteen European States and, on the basis of the information gleaned, to move towards better standardisation of HRV practice. The long-term aim, in addition to reducing health care costs, will be to create an advisory authority with the capacity to monitor usage and if warranted arrange clinical trials. The project will be carried out with the active assistance of the European Respiratory Society

### **Keywords:**

Home ventilators - espiratory failure - Home care

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Duration:	36 months
Type:	RS
Starting date:	01/04/2001

## ***The Prerequisites Of The Elderly For Living At Home: Criteria For Dwellings, Surroundings And Facilities***

### **Objectives:**

The purpose of the project is to improve the conditions of living at home of the elderly. The project will make an inventory of the state of the art of products and facilities necessary for independent living, identify the wishes and needs of the elderly, identify the criteria for manageability of housing and accessibility of services, and suggest new developments in order to contribute to future independent living.

### **Brief Description:**

In order to reach its objectives the project progresses in three phases. In the first phase, the present situation is clarified, with regards to the regulations and standards of the living conditions of the elderly, the market situation for dwellings, products and services, and the administrative and organisational practices in providing these to the elderly. In this phase also the wishes and needs of the elderly are studied. These surveys are carried out for all participating countries, Denmark, Finland, The Netherlands and Spain, which represent different parts of Europe and different practices. At this phase a co-operation network with the relevant market and public actors is established, for purposes of the latter phases of the project.

In the second phase development challenges are identified. In the practices that were identified in the first phase, improvement needs are identified, taking into account the wishes and needs of the elderly, especially as regards living independently in existing dwellings. Criteria are developed to articulate these improvement challenges.

In the third phase the criteria are tested and developed further in real-world development situations, in co-operation with the members of the network that was identified in the first phase. The cases will be development, renovation, experiment or other projects carried out and financed by organisations working with the elderly housing issues. This project will participate in these cases by consulting in the planning phase and observing and analysing during and after the realisation of the case project. The selection of cases will aim at adequate variety, for example representing a range of building types and methods as well as local community types.

In the final phase the results and conclusions are reported and disseminated among the network and outside it. Specific exploitation plans, proposals and guidelines are made.

### **Keywords:**

Elderly people - independent living - criteria - dwelling - surroundings of dwelling - services - facilities - wishes and needs - existing dwelling stock - user evaluation

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Starting date:	01/04/2001

## ***ENABLING TECHNOLOGIES FOR PERSONS WITH DEMENTIA***

### **Objectives:**

The objectives of ENABLE are to:

- develop prototypes and provide test series of enabling technological products
- develop methodology for assessment of effects of using the products, including cost/ benefit analysis
- examine whether the products can enable people with dementia living in their own home

### **Brief Description:**

ENABLE concerns development and adaptation of technological products which people with dementia (e.g. Alzheimer's disease) can use to carry out daily tasks which they previously were unable to do, due to the dementing disease. The selected products fall into three categories:  
 devices to support memory (time orientation, taking medicines etc.)  
 devices to provide pleasure and comfort (multimedia programmes)  
 devices to facilitate communication (pre-programmable telephone)

People with dementia will test the products in practice for up to one year, and the effects of using them will be studied through interviews with the users and their carers. Mitigation or solving problems for people with dementia, enhanced self-esteem and well-being as well as costs and benefits at individual and society level will be focused. Ethical issues will also be addressed. Methodology for assessment of effects will be developed as part of the project. The ICIDH-2 model developed by WHO will be used as the analytical framework. The methodology will provide a basis for outlining the protocol for the intervention trial with technological products, and will include a set of methods and tools related to assessment of health condition, functional abilities, personal factors (personality, attitudes, education etc.) and environmental factors (home environment, level of care services). Also, qualities of the products as well as other factors of importance for the observed effects will be examined. Companies will be contacted to promote the commercialisation of products which are found useful, user-friendly and acceptable by the user group.

### **Keywords:**

Dementia - assistive technology - independent living - cost/benefit - memory support - time orientation - locator for lost objects - cooker usage monitor - water level and temperature controller - automatic bedroom light - remote day planner - multimedia programmes

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## ***FRIENDLY RESTROOM FOR ELDERLY PEOPLE***

### **Objectives:**

Carrying out the necessary research and designing, building and testing several prototypes for a Friendly Rest Room for older persons and people with disabilities. All the elements of the FRR (toilet bowl, grab bars, sink) will adjust to the individual needs of the users, allowing them to gain greater autonomy, independence, dignity, improved self-care and, therefore, experience better quality of life.

The measurable objective is to establish a minimum of 70% of older or disabled persons who, after having used the prototype of FRR, find it highly valuable and use worthy.

### **Brief Description:**

Friendly Rest Rooms where all the components are adjustable to the needs of older or disabled persons with varying degrees of functional impairment will be designed and tested.

The methods and technologies involved to fulfil the above objective will range from contactless smart card technologies with read-write capabilities, voice activation interface, motion control and sensor systems, mechanical engineering and robotic techniques, mathematical modelling, as well as ergonomic research, design for all philosophy and medical and social sciences.

The FRR-Consortium brings together end-user organizations representing a wide range of European countries (more than 25), universities, research and rehabilitation centres needed for the scientific, technical and professional aspects of the project.

The project involves a broad research base needed to define the user-parameters for designing and developing the FRR systems. User involvement in all the stages of the research and problem solving process of the FRR prototype development and testing is ensured, including involvement of secondary users, care takers and rehabilitation professionals. Testing the prototypes will take place with involvement of external industrial companies and end-user organizations in preparing plans for dissemination and exploitation. Databases of new knowledge and know-how will be created and wide exposure of the new perspectives of the FRR systems to improve the independence, dignity, self-care and quality of life of the older persons in the European community will be developed.

### **Keywords:**

Intelligent toilet - fall prevention - caring home - independent aging - individually automated adjustable facile environment - User driven research - design for all

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Duration:	36 months
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Starting date:	01/04/2002

## ***Dynamically Responsive Intervention For Tremor Suppression***

### **Objectives:**

Tremor can be a significant problem to sufferers of Parkinson's disease, Multiple Sclerosis (MS), and other neurological problems resulting in movement disorders, when engaged in activities of daily living, requiring particular dexterity such as eating, dressing, and writing. The objective of this project is to create a prototyping and evaluation platform for the future development of wearable ambulatory devices (orthoses) that mechanically suppress upper-limb tremor while preserving, as far as possible, natural movement. The categories of tremor to be addressed are those resulting from progressive neurological disorders, such as Parkinson's disease and multiple sclerosis as well as tremor resulting from cerebellar trauma, and atypical essential tremor.

### **Brief Description:**

The project will apply a holistic approach to the development of practical tremor suppression orthoses prototypes. They will integrate a range of candidate technical solutions for kinematic sensing, control, and actuation. The prototyping platform, once developed, will be used to evaluate and compare the relative efficacy of available sensing, actuating, and control technologies for suppressing tremor. The project will identify design benchmarks for tremor suppression aids that meet the requirements of the widest range of users and severity of disability in its various aetiologies and manifestations. Several of the mechanical tremor suppression techniques to be prototyped and evaluated depart demonstrably from earlier attempts to mechanically damp tremor. The project will draw upon a wide spectrum of technological and clinical disciplines in the areas of materials science, biomechanics and rehabilitation engineering, sensors, feedback and control, neuroscience, and systems engineering. There is to be substantial user involvement in all phases of the project, from requirements analysis through system development, to clinical evaluations. Through a series of user trials, viable technical solutions for practical orthosis construction will be identified, evaluated, and compared with respect to the cardinal product characteristics that meet the requirements of the widest range of users and severity of disability. The differential requirements relating to materials, aesthetics, performance, functionality, and reliability are to be addressed. Once user-validated, the development platform will provide a benchmark system for evolving improved, commercial, versions of the laboratory prototype orthoses developed in the project.

### **Keywords:**

Neurological tremor - Active orthotics - Assistive technology - Rehabilitation robotics.

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Starting date:	01/04/2002

## ***Aged People Integration, Mobility, Safety And Quality Of Life Enhancement Through Driving***

Objectives:

AGILE aims to develop a new set of training, information, counselling and driving ability assessment and support tools for the elderly, evaluating their full range of physical, cognitive, behavioural and interactional abilities, targeting a fair, inclusive and cost-effective, standardized, pan-European elderly drivers assessment procedure.

### **Brief Description:**

The mean number of elderly drivers on European roads is currently approximately to 12% of all drivers and is estimated to reach 20% of them by 2010. Although older drivers as a group do not have higher accident frequencies, when their accident statistics are corrected for yearly mileage, they seem to be over-represented in specific accident types (i.e. turning left at a T-junction, changing lane, merging or leaving from a parking position). Moreover, 5%-7% of them seem to suffer from undiagnosed dementing diseases, that make them dangerous drivers, unless properly helped. AGILE focuses on two key milestones: developing the required knowledge to establish national policies for delivering certification of fitness to drive to the elderly and, at the same time, helping as much as possible older age groups to continue driving safely, as enhanced mobility leads to increased well-being for them.

This task is approached by establishing a clear identification of elderly problems in relation to various driving tasks and an aetiological classification of their traffic accidents. Then, a proper set of elderly driving ability assessment criteria will be selected (with quantified thresholds) and they will be assessed through a low-cost pre-screening tool (for self-assessment or by family doctors) or (if needed) by an integrated driving assessment system, including various tools, such as a neuropsychological test battery, driving simulator scenarios and on-road tests; as well as an expert tool for decision support. They will be evaluated, towards a reference detailed test drive scheme, through Pilots in three European countries (Belgium, Greece and Sweden) with around 100 elderly per country.

All developed assessment methodologies and tools will be optimised towards their cost-assessment and their viability will be pre-checked. The overall assessment methodology of the project will be proposed as a standardised pan-European elderly drivers assessment scheme.

Last but not least, appropriate training and consultation courses will be developed, to help the elderly overcome their driving problems as well as a methodology to embattle current negative stereotypes about elderly drivers and towards enhancing public awareness and acceptance of elderly driving abilities.

It should be emphasised that the assessment methods targeted are not meant to present a new barrier for elderly drivers, but instead they are expected to simplify and rationalise the currently used assessment process for most of them and help the rest to find appropriate methods and aids to

remain safe drivers. Due compensatory policies will be proposed for the few that may still ultimately need to be excluded from further driving.

### **Keywords:**

elderly drivers - driving ability assessment - neuropsychological test battery - driving simulator - reference driving test - decision expert tool - elderly training courses - elderly traffic safety.

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## *Life quality of senior citizens in relation to mobility conditions*

### **Objectives:**

The general objectives of our project are: To explain and describe the present mobility situation of senior citizens from their own perspective; To motivate action from the side of the authorities and other relevant groups in society who are, or feel, responsible in this area, among others by making discrepancies in problem identification transparent; To provide guidance for setting up and implementation of policies towards “keeping the elderly mobile”.

### **Brief description:**

European policy regarding the elderly aims at maintaining their mobility. This is a central element of integration in society. Senior citizens want to stay autonomous and independent as far as possible. Without the possibility to maintain mobility, senior citizens cannot lead an independent life, with many other problems as a consequence, such as isolation, health problems, etc. The focus of this project lies on the present mobility situation, the problems, needs and wishes of different groups of senior citizens compared to the experts' (i.e. sociologists, psychologists, traffic experts, experts on gerontology, politicians, policy makers, experts of other related EU projects) points of view.

The research work starts with a state of the art report, which functions as a frame of reference for all the research tools needed in the project. The comparison of the user-perspective with the expert assessment of situation and problems will be elaborated on with the help of qualitative and quantitative survey instruments combined. The collection of qualitative materials will be validated with the help of standardised interviews. The resulting picture will consist of a description of problems, in combination with their distribution and weight in society. The third major tool will be a heuristic one; multidisciplinary discussions in the frame of four workshops, in which industry, policy makers and politicians will discuss the results of this project together with senior citizens representatives and the consortium. In the centre of the discussions the following questions will be raised: How can experts adjust their knowledge of facts and their view on the user situation to the users' own perspective? How can the users' perspectives be translated into practical measures and incentives? How can perspectives be changed with the help of communication? Contradictions between senior citizens' and experts' views on things will be one motor of the work-process in this project. Eliminating barriers for the implementation of sensible solutions will be very much related to this contradiction, and to the question of how to improve the situation in this respect in the future. The final product will be a model which includes a list of problem types and respective solution types for mobility and transport problems of senior citizens, the adequate methodology for dealing with this including dissemination and lobbying activities, in the sense of communication concepts like the marketing model.

### **Keywords:**

Senior citizens - mobility - user needs - enhanced life-quality - multidisciplinary approaches - prevention of accidents - improved living-conditions - public safety - heuristic methods - qualitative survey - focus groups - narrative interviews - standardised interviews - user-perspective

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Type:	RS
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## *Improving implant fixation by immediate loading*

### **Topic:**

Improvement of the fixation (i.e. osseointegration) of permucosal and percutaneous implants through controlled immediate loading

### **Objectives:**

The project will investigate the mechanical aspects of osseointegration of metallic implants used for permucosal and percutaneous fixation of prostheses.

An oral rehabilitation protocol will be developed to control the mechanical conditions to optimise the speed and quality of osseointegration, thereby maximizing the success rate of implant-retained prostheses while minimizing the rehabilitation time for patients.

The oral rehabilitation protocol, combined with a “smart prosthesis”, should lead to a rehabilitation period that is significantly reduced when compared to control patients. The implant failure rate in patients using the smart prosthesis should also be significantly reduced when compared to controls.

### **Brief description:**

A series of animal experiments will be set up to study the mechanical stimulation of bone response around implants. In these animal experiments, screw-shaped implants will be installed in the mandible of mini pigs (after extraction of the teeth) and in the distal tibia of guinea pigs. Well-defined mechanical stimuli will be applied and the bone response will be monitored. For the follow-up of the bone remodelling around the implants, several techniques will be used: micro focus computed tomography (micro-CT), conventional histology, histomorphometry and vibration analysis.

With micro-CT, a fully three-dimensional characterization of the bone tissue around the implant can be obtained. By applying vibration analysis as a second follow-up technique at the same time, the results of vibration analysis can be interpreted by comparing them with micro-CT. Mechanical devices will be developed to apply a well-defined loading to the implant. Computer models will be developed to investigate the loading at the implant - bone interfaces and to correlate the results with the observed bone remodelling. In addition to the more conventional finite element models where the trabecular bone is modelled as a continuum with site dependent mechanical properties, high-resolution finite element models of the trabecular architecture will be developed as well. For this purpose, micro CT scans of mini pigs mandibles will be taken post mortem, prior to histological preparation of the samples.

Micro-computer tomography based finite element models will also be developed to model and simulate the bone reaction in the experimental guinea-pig model. Here the models will be based on micro-CT scans obtained in vivo and post mortem.

A limited pilot study on patients will be integrated in an advanced stage of the project. The exact protocol for this will be subject to evaluation of the animal experiments. For use during the pilot study, a “smart prosthesis” will be developed.

## **Keywords:**

implant fixation - mechanical stimulation - osseointegration - finite element modelling - FEM - micro focus computed tomography - micro-CT -  $\mu$ CT - smart prosthesis - custom suprastructure - rapid prototyping - miniature sensors

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## ***Research, development and demonstration of a novel non-invasive continence management system***

### **Objectives:**

Review the existing NICMS and develop it into a robust and acceptable device. Review currently available female urinals and design and produce a device that is easy for disabled people to use in conjunction with the NICMS. To design appropriate day and night time pad interfaces for use with the liquid-handling system. To provide Europe wide critical testing, to produce an acceptable and reliable continence management system.

### **Brief description:**

The work for this proposal is divided into four phases. The exploratory phase looks at a number of features that have been identified in the previous work on the liquid handling system as needing development. These features make the device unreliable, heavy, and noisy or are not easy and economical to manufacture. These features will be investigated and solutions will be proposed. Investigations will also proceed to provide the information necessary to successfully develop three user/ device interfaces.

The development phase will use information gained during the exploratory phase to develop the different elements of the non-invasive continence management system. This will involve extensive redesign of the filters, noise reduction and ergonomic improvement to the liquid handling system. The user/ device interfaces will also be developed during this phase.

During the Prototyping phase, the different elements of the non-invasive continence management system will be produced using the information gathered during the two previous phases. This phase extends into the demonstration period because feedback from the testers will be used to improve the device during the course of the project. It is anticipated that the test centres will have many recommendations for improvements to the all parts of the system when they have received feedback from their test subjects. During the demonstration phase, the 20 liquid handling systems will be distributed amongst the testing partners. The devices will be tested at first on healthy volunteers before proceeding with patient testing. The demonstration non-invasive continence management systems will be clinically evaluated to assess the strengths and weaknesses of the designs. Adjustments and improvements will be made during the course of this phase.

### **Keywords:**

Continence management - non-invasive - incontinence.

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Type:	RS
Starting date:	01/01/2003

### *Patient education in Parkinson's disease*

#### **Objectives:**

A patient education and treatment programme for people with Parkinson's disease and their carers will be developed and evaluated for effectiveness. The newly developed programme will provide education materials which can be used throughout the different European countries taking into account the specific cultural backgrounds and local health care conditions.

#### **Brief description:**

The patient education programme is aiming at the empowerment of patients suffering from Parkinson's disease as well as their carers. It is objected to the major goals of (a) transmission of knowledge, (b) teaching and training of instrumental skills and (c) integration of knowledge and self-management of the chronic disease.

Throughout the life of the project, research and development work will pass 2 major stages:

The basic development stage.

The application and evaluation stage.

During the basic development stage, the overall objective is the development of the 7 key components of the patient education programme:

Information

Self-monitoring,

Health empowerment

Stress-management

Anxiety and depression

Assertiveness

Social support.

Within the application and evaluation stage the major objective is to apply the innovative patient education programme in each of the participating European countries and to evaluate the feasibility using a formative evaluation process.

As a final result of the project, an innovative education manual will be provided in 7 European languages. It will allow flexible application taking into account cultural and regional differences, and it will improve quality of life in patients and carers with a chronic neurological disease.

#### **Keywords:**

Quality of life - Parkinson's disease - patient education - psychological treatment - psychosocial support.

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Duration:	48 months
Type:	TN
Starting date:	01/01/2003

## *Prevention of Falls Network Europe*

### **Objectives:**

PROFANE aims at improving Quality of Life of the ageing population by focussing on a major cause of disability and distress: falls. The aim is to bring together workers from around Europe to focus on a series of tasks required to develop multi-factorial prevention programmes aimed at reducing the incidence of falls and fractures amongst elderly people.

### **Expected results:**

A coherent multidisciplinary multinational network committed to conducting future research and implementing best evidence with the objective of reducing injurious falls amongst elderly people. A series of “state of the art” statements, consensus statements and best evidence management protocols. In vivo gait and balance monitoring techniques/ technology. Agreement on a series of psychological measures.

### **Potential applications:**

Best evidence management protocols to improve care and interventions. Self-help materials for older people.

### **Brief description:**

PROFANE is a thematic network with 25 members focusing on the issue of prevention of falls and improvement of postural stability amongst elderly people. It comprises 4 work-packages taxonomy and co-ordination of trials clinical assessment and management assessment of balance function 4 psychological aspects of falling.

The work of PROFANE is practical. It will advance the science but it will also aim to change health care procedures to introduce best practice widely across Europe. Each work package will undertake a series of workshops bringing together experts and observers around specific topics. The network will conduct two network meetings to synthesise work from packages and mount a website to disseminate information.

### **Problem:**

Falls are a common problem for older people, and cause considerable distress morbidity and mortality. This network brings together clinicians, researchers and technologists to work together towards the goal of reducing the incidence and impact of falls.

### **Keywords:**

Falls - Fractures - Prevention - Postural Stability - Old Age - Balance - Psychology - Randomised Trials

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Area 6.5: Health and social care services to older people

## **CARE SERVICES**





Project number:	QLK6-CT-1999-02035
EC contribution:	€898,532
Duration:	36 months
Type:	RS
Starting date:	01/03/2000

## ***Implementation Of Patient Involvement Instruments To Improve General Practice Care For Older People In Europe***

### **Objectives:**

This project aims:

- To document and compare internationally which are barriers for patient involvement.
- To develop and select programmes that implement patient involvement instruments.
- To assess and compare internationally programmes that implement patient involvement instruments.
- To prepare a toolkit of materials to implement the patient involvement instruments.

### **Brief Description:**

Active involvement of patients requires tools, such as instruments to measure patient views of care or education of care providers. Effective implementation programmes are needed to implement these tools in general practice in Europe. Workpackage 1 (Barriers Study) identifies barriers for patient involvement in general practice, using semi-structured interviews with purposeful samples of 20 general practitioners of 30 patients in each of the 11 participating countries. Workpackage 2 (Programme Development) develops five specific tools for patient involvement, based on the results of workpackage 1, and tests their feasibility in small scale pilotstudies in each of the countries. Workpackage 3 (International Evaluation) evaluates the implementation of selected tools with respect to acceptability, costs and behaviour change, using stratified samples of 12 general practitioners in each country. This international comparative study will show the relevance of specific barriers and facilitators for implementation in different countries. Workpackage 4 (Toolkit development) prepares valid and attractive materials for the implementation of patient involvement in general practice care for older people.

### **Key words:**

General practice - quality improvement - patient involvement

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EC contribution:	€863,038
Duration:	36 months
Type:	RS
Starting date:	15/05/2000

## ***A European Project To Devise A Hospital Admission Case-Mix System For Elderly Patients, Plus A Standardised Method Of Recording Hospital Outcome***

### **Abstract**

Many older people entering hospital have multiple medical problems and disabilities. They often require multi-disciplinary assessment by a range of health workers, including doctors, nurses, and other therapists. In addition, workers in the fields of social care and housing may need to be involved (1) in the assessment process and (2) in supporting care arrangements on hospital discharge. Inadequate assessment, particularly when it occurs early in the hospital admission, may have important long-term implications, both for individuals and for health and care services. For example, treatable conditions may be overlooked, and older people may lose their independence unnecessarily.

An important way to improve quality and equity of medical care in older people, is to carry out European-wide research, comparing the experience of different countries with different medical and social systems. For older people entering hospital, comparative research of this type needs to examine differences in:

- (a) the OUTCOME of hospital admissions, while taking into account
- (b) differences in CASEMIX\*.

European-wide comparative research needs standardised systems of measurement. Unfortunately, no existing casemix or outcome system is designed specifically for use among large numbers of older patients early in the hospital admission.

### **Objectives**

The ACMEPLUS Project therefore aims to produce a brief, European-standardised system for measuring case-mix and outcome of people aged 65 years and over, who have recently been admitted to non-surgical hospital specialties (principally General Medicine, Medicine for the Elderly [geriatric medicine] and Rehabilitation).

### **Details of the ACMEplus project**

The three-year project will use two Phases of data collection, with at least 200 patients being studied in each Phase by each of the eight participating centres. Over 3200 patients aged 65 years and over will have been evaluated by the end of the project.

PHASE I will use a wide range of potential case-mix and outcome variables chosen as the result of

- (a) a Systematic Review of the literature,
- (b) previous work of two of the partners on casemix assessment plus a new (predominantly graphical) method of recording outcome,
- (c) an initial Consensus Conference of all partners

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\* Casemix refers to patient-based, disease-based and other factors that can affect outcome, including the type and severity of physical/mental problems, and new or pre-existing disabilities. Casemix classification systems attempt to divide groups of patients into different sub-groups which are homogeneous in the sense that they have similar outcomes or require similar amounts of resources.

PHASE II will collect data using a subset of variables from Phase I. This subset of variables, which will be known as the ACMEplus instrument, will be selected by a combination of

- (a) a clinical consensus involving all the partners, which will be strongly influenced by
- (b) a series of statistical analyses of Phase 1 data\*

Phase II will also establish the acceptability, feasibility, reliability and validity of the ACMEplus instrument translated into the languages of the participating centres.

### **Relationship between ACMEplus and other European projects**

Many of the partners in the ACMEplus project have previously worked together in the EASYcare project which was also financed by the European Union. EASYcare is concerned with measuring functional status and quality of life in primary care whereas ACMEplus focuses on casemix and outcome in secondary care. The two instruments will therefore be complementary to one another, forming part of a growing family of instruments designed to look at health, social, and functional status of older Europeans both in the community and in hospital settings.

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\* A range of statistical techniques will be used, but previous experience has indicated that a mixture of regression techniques and recursive partitioning will be the most efficient method of obtaining case-mix groups which will be homogeneous in respect to various measures of hospital outcome.

Project number:	QLK6-CT-1999-02182
EC contribution:	€1,288,350
Duration:	36 months
Type:	RS
Starting date:	01/03/2000

## ***OLD AGE AND AUTONOMY – THE ROLE OF SERVICE SYSTEMS AND INTERGENERATIONAL FAMILY SOLIDARITY***

### **Objectives:**

The main objective is to enhance cross-cultural knowledge about the interplay between personal, familial and social service factors as impacting on quality of life of aging European population. Specifically, analyzing the evaluated and used mixes of informal and formal support by elders and family carers, and the way different family cultures and welfare systems promote quality of life and delay dependency in old age.

### **Brief Description:**

The research focuses on 3 prominent dimensions that impact healthy aging and coping of family caregivers: mixes of informal (family) and formal (service systems) care, family norms and intergenerational transfers and family coping with beginning dependency of an older member. A cross-cultural approach is used, comparing five nations and different welfare regimes – more traditional societies like Spain and Israel, to more modern countries like UK, Norway and Germany. The study adopts a cross-national, cross-generational perspective using a multi-method design of quantitative and qualitative methods, and cross-sectional and a longitudinal approach. Survey (cross-sectional): The baseline data collection was performed through standardised survey in all 5 countries. Measures: A basic research protocol (in English), was translated and adopted to target languages, including: Quality of life (WHOQOL-Bref); Intergenerational solidarity and ambivalence measures; Values and preferences; Coping; Use of and satisfaction with formal health and welfare systems; Background and health variables. Representative samples were selected based on age groups (N = 800 ages 25-74 and 400 aged 75+, totaling 1,200 in each country) and interviewed at their homes. Interview and Panel (longitudinal): The in-depth interviews are partly geared to validate the survey data, and partly to uncover interpersonal obligations and emotions focusing on caregiving demands, dependence, coping and quality of life. 10 dyads in each country were selected from the 75+ and their child caregivers They represent the group of ‘elders at risk’ and were interviewed by in-depth measures using an interview guide that was pretested, translated and retranslated into the target languages.

The study results were presented in many national and international conferences as well as discussed with policy makers and service providers in the five countries. Two monographs were published: The first – Daatland, S.O. & Herlofson, K. (Eds.) (2001), Ageing, intergenerational relations, care systems and quality of life – an introduction to the Oasis project. Norway: Norwegian Social Research, Rapport 14/01. This monograph outlines the theoretical bases of the study. The second – Lowenstein, A., Katz, R., Mehlhausen-Hassoen, D. & Prilutzky, D. (2002), The research instruments in the Oasis project. Haifa, Israel: The Center for Research and Study of Aging, University of Haifa. This monograph relates to the quantitative measures used in the study. Additionally, two chapters written by team members will be published next year in the book: Bengtson, V.L. and Lowenstein, A. (Eds.), Families and global ageing. New York: Aldine de Gruyther.

Meetings were also conducted with international experts in quantitative and qualitative research to discuss the findings, funded by Accompanied Measures for Oasis.

### **Website**

More information about the Oasis project can be found at the project's homepage:  
<http://oasis.haifa.ac.il>

### **Keywords:**

Quality of life of elders and family caregivers; mixes of health and welfare service use;  
intergenerational family solidarity; conflict and ambivalence in family relations;  
Elders at risk of dependency; promotion of autonomy in old age

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Type:	RS
Starting date:	01/02/2000

## ***Disability Prevention In The Older Population : Use Of Information Technology For Health Risk Appraisal And Prevention Of Functional Decline***

### **Introduction:**

More effective preventive care for older persons might be achieved by multidimensional evaluation for potentially modifiable risk factors of disability and seeking to minimise their adverse impact. In collaboration with U.S. university colleagues, the Bern (Switzerland) geriatrics group has developed an adapted version of Health Risk Appraisal for the Elderly (HRA-E). The HRA-E products to date include: a self-administered questionnaire for comprehensive risk assessment (English and German language), software for processing computer-generated reports to older persons and to their health care providers, and favourable findings from field tests in older subjects.

The six country consortium proposes to adapt the HRA-E for the use in Europe, and to conduct three randomised controlled field trials in Hamburg with over 60-years old persons, in London and Switzerland with over 65-years old persons to test the effects of the HRA-E on health behaviours and process of care. The mid-to-long term goal is the prevention of disability. In collaboration with the partners from other European countries (Denmark, Netherlands, Austria) the results will be disseminated and efforts will be made to promote translations into other languages and to integrate the system into European primary care systems.

### **Objectives:**

The goal of the project is to maintain function and in the mid-to-long term prevent disability and minimise unnecessary service utilisation among persons 65 years of age and older. (6.5.) Health care services: the development and testing of a new intervention that could be integrated into primary care at relatively low costs; the project addresses all categories of older persons, including older persons at the transition after retirement. (6.4) Technology: Health Risk Appraisal for the Elderly (HRA-E) uses information technology for identifying modifiable risk factors for disease and disability and generating feed-back statements to older persons and health care providers. (6.3) Epidemiology: HRA-E creates a basis for identifying preventive health care needs. (6.2) Healthy ageing: HRA-E creates a common database for future cross-national comparative evaluation on determinants of healthy ageing.

### **Description of the work:**

Pilot phase: Regional adaptation of the questions and feed-back statements of the HRA-E based on expert knowledge, focus group meetings, and pilot testing; conducting of pilot field tests in Germany (N=164) and England (N=348); updating the software; preparing the approach for integrating the system into the regional primary care systems; and preparing the logistics of the randomised studies.

Field phase: To conduct three randomised controlled trials in Hamburg (N=3.326), Bern (N=4.046), and London (N=3.139). Study population: Community-dwelling persons aged 60 years and older, registered in selected primary care practices. Pre-randomisation postal questionnaire will be used for base-line data collection. Randomisation: Two thirds of practices will be allocated to additional physician training. Older persons of these practices will be randomised to intervention group and

control (usual care) groups. Older persons of the remaining one third of practices (no additional physician training) will serve as a second control group.

Intervention: Persons in the intervention group will get the HRA-E intervention (written feed-back with reinforcement in collaboration with primary care practitioners over a one-year period).

Outcomes: At one-year follow-up, HRA-E questionnaire and telephone follow-up will be administered to all subjects to evaluate the effects on health behaviour. Electronic chart information and health insurance data will be collected for measuring health care use if possible.

#### Synthesis and dissemination:

The synthesis will be based on site-specific and comparative pooled statistical analyses according to an intention-to-treat analytic plan. Dissemination of the intervention method and the results will be targeted towards European health care professionals (emphasis primary care physicians) and health and social authorities. Participants from Denmark, the Netherlands and Austria will be involved for developing and disseminating scenarios for practice implementation in participating and non-participating European countries.

#### **Milestones and expected results:**

9 months: Beta -tested software version of region/ nation adapted HRA-E;

18 months: Recruitment of subjects for randomised studies completed;

30 months: Mailing of follow-up HRA-E completed in all 10,511 subjects;

33 months: Final database with follow-up data from each study site;

36 months: Final report with synthesis and scenarios for implementation;

We anticipate a favourable impact of the HRA-E on health behaviours and a high interest of health professionals and health authorities for implementing the system in practice.

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EC contribution:	€1,274,385
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Type:	RS
Starting date:	01/03/2001

## *The Aged In Home Care Project*

### **Objectives:**

Analyze the structural and organizational characteristics of Home Care (HC) services for the elderly in 10 European countries, along with their client characteristics, outcomes and resources utilization. Design the first evidence-based HC Service model. Describe and compare the characteristics of patients receiving HC and of HC systems in each country.

### **Brief Description:**

The AD HOC project aims to identify and propose a model of Home Care (HC) for the elderly through the analysis of the structural and organisational characteristics of HC Services in 10 European countries, along with the clinical and functional characteristics of their clients, and will cover a 30 months period from the initial activities to the definition of a reference HC Service model. For each site, the sample will be obtained by a computer driven randomisation of all subjects aged 65 years or older who are already receiving HC services at the beginning of the project. All the information collected will contribute to the creation of the first cross-national database on HC in Europe (the Community Care Data Centre) containing the characteristics of HC patients and the structural and organisational characteristics of the HC Services of each national site. Comparative and survival analysis will be used to describe and monitor patients receiving HC, as well as to identify the characteristics of patients and services associated with better outcomes.

To describe the HC patient characteristics, a random sample of 405 recipients of HC services in each country will be assessed at baseline, and at six and twelve months thereafter. The resident Assessment Instrument for Home Care (RAI-HC), a validated second generation assessment tool, will be used in order to provide information on several domains: personal and demographic information; cognition, communication/hearing; vision; mood and behaviour; social functioning; informal support; physical functioning (self performance of instrumental – IADL – and personal – ADL- activities of daily living). A specifically designed form, the European Home Care Services (EU-HCS) assessment form, will be used to collect information on the specific characteristics of HC Services in each sites. The variable of interest will include the setting, the financial and management structure, the range and organisation of the service, and the service delivery.

Finally, the project will lead to the definition of a reference model of HC – not available at the present time – which might best respond to the needs of elderly in Europe.

### **Keywords:**

Home care - geriatric assessment - functional outcomes - resources consumption - services characteristics - services organization - patients characteristics - database.

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Project number:	QLK6-CT-2000-00303
EC contribution:	€1,029,984
Duration:	39 months
Type:	RS
Starting date:	01/03/2001

## ***Information, Health And Social Needs Of Older Disabled People (Parkinson's Disease) And Their Carers***

### **Objectives:**

The project aims to (1) classify information needs of older disabled people (with Parkinson's disease) & their carers & compare with professionals' perceptions of them, (2) explore factors that motivate professionals to involve individuals in care decisions, (3) identify cross-national education strategies to enhance functional independence & well-being of patients & carers & (4) make recommendations for service and policy development for care of older infirm people.

### **Brief Description:**

The information, health and social needs of older people with disabling conditions often differ from those perceived by professionals and therefore may go unmet. Knowledge and understanding of their illness empowers the individual, maximizes independence and improves quality of life. Over the 3 years of the project, 500 disabled older people with Parkinson's disease and their carers, together with 700 professionals in 7 European countries will be interviewed about their information needs and how they may best be addressed. In addition an extensive database will be developed of international literature, information sources and good practice in relation to meeting the health and social care needs of older disabled people and their carers. This will be used together with the views and experiences of an expert roundtable of users and professionals to create a critical mass of knowledge. Recommendations for policy and service development for the health and social care of older infirm people will then be made & comprehensive cross-national traditional and internet-based education materials for patients, their carers and professionals will be developed, piloted and evaluated. A final scientific conference will be held to disseminate the findings and materials and to ensure continuing development, collaboration, monitoring and modification of project materials. This should help to ensure more appropriate standards of future support, services and care for older disabled people.

### **Keywords:**

Disability and ageing - Parkinson's disease - Patient information needs - Carer information needs - Inter-professional education - Service development.

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EC contribution:	€1,420,752
Duration:	36 months
Type:	TN
Starting date:	01/03/2001

## ***THE CARE AND MANAGEMENT OF SERVICES FOR OLDER PEOPLE IN EUROPE NETWORK***

### **Objectives:**

To establish a wide-ranging European network of organisations involved in managing services for older people focusing on the efficient integration of services between the main interfaces involved (primary/ home care; acute care; residential care). To develop concepts/ tools related to factors that promote or inhibit effective and efficient integration.

### **Brief description:**

This project is based on a matrix structure which will provide a remarkable degree of cross-fertilization between eleven countries (Netherlands, UK, Belgium, Finland, Swede, Greece, Italy, Ireland, Denmark, Spain, Germany) and nine categories of partners (R & D organisations, care homes, social care providers, sickness funds/purchasing organisations, carers, users, primary care, acute hospitals, management consultants). The matrix structure is intended to maximise opportunities for networking and interchange between similar agencies from different countries, between the various agencies from the same country, and between different agencies from different countries. The network will focus on the three key interfaces and intrafaces of the cure/ care triangle (primary/ home care-acute care; acute care-residential care; residential care-primary/ home care). This network will be client-centred. Users, purchasers and providers of health and social care will be regarded as clients for the purposes of the network.

The project will have three phases: Sharing and exchanging information; exploring the interface and intraface issues; and analysing the policy and planning implications of integrated care for older people.

Outputs will include a website and database of both research and innovative activities and projects in the field of integrated care for older people, including both examples of best practice and factors promoting and inhibiting integration of services; either a handbook on the management of integrated care for older people, or a series of reports from each of the working groups, identifying the principles issues emerging from the working groups; and recommendations for new or refocused research.

### **Keywords:**

Management of services - integrated care - primary care - acute care - residential care.

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EC contribution:	€1,300,000
Duration:	36 months
Type:	RS
Starting date:	01/02/2001

## *Cross-national determinants of quality of life and health services for the elderly*

### **Objectives:**

The project studies the determinants of quality of life in older people in 6 European countries.

1<sup>st</sup> objective: assessment of the predictors of major health outcomes.

2<sup>nd</sup> objective: assessment of the impact of differences in health services provision.

3<sup>rd</sup> objective: assessment of the relation between functional status and health services use.

4<sup>th</sup> objective: assessment of the impact of the social networks on the health status.

### **Brief description:**

The first step is the creation of linkages between the data set of the six longitudinal studies: ILSA (Italy), LASA (The Netherlands), CALAS (Israel), Aging in Leganes (Spain), TamELSA (Finland), SATSA (Sweden) and local/ regional death registries, using a combination of information such as health care codes of participants, birth-date and home address.

Data on hospitalisation rates in the last 5 years will be obtained by linking the data set to hospital discharge records from the hospitals in the geographic areas of the studies.

Municipal registries will be checked for all changes of address since the inception of the study, in particular changes from community homes to institutions, for both living and deceased subjects.

The second step will be the creation of a common database to be used to calculate the following indexes:

Age, sex, and cause-specific mortality rates

Age, sex, and cause-specific hospitalisation rates

Age and sex specific institutionalisation rates

Relative Risks of socio-demographic, behavioural and health factors for hospitalisation, institutionalisation and mortality

The third step will be the preparation of a standardised instrument, to be administered to referents in the local health units, to conduct a survey on the state of art of health services.

Finally, we will create a linkage between the common database of the longitudinal studies and the data collected on the surveys of health services, to assess the impact of health services on the major health outcomes of the study. Moreover, a cross-national comparison of the impact of social networks on the health status of the elderly, controlling for other known risk factors, will be evaluated.

### **Addendum**

The CLESA has proposed an extension of the consortium to Newly Associates States (call for proposals launched on May 31<sup>st</sup>, 2001) to Czech Republic, Lithuania, Poland. The proposal was accepted with a budget of 173,892 Euro for completing WP2, which is the workpackage aiming at evaluating the health services for the elderly. In these new countries, we could not rely on the availability of longitudinal studies, so we have limited their inclusion for the assessment of the health services availability and access. The main objective is, therefore, to develop a European multinational working core of information on the state and evolution of the countries health- and social-services for the old population. In this new shape, the CLESA Health Care Services component will compare 3 north, 3 south and 3 east European countries, during the years 1990-

2000. The newly re-planned study will now deal with issues of evolution and revolution in the health services, and will provide relevant information on the profile of care for the elderly in different european countries.

**Keywords:**

Determinants of quality of life – disability - longitudinal studies - health services

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Type:	RS
Starting date:	01/05/2001

## *MINORITY ELDERLY CARE*

### **Objectives:**

To propose the 'best' way to manage the delivery of health and social care to ethnic minority elderly regarding quality, efficiency and user acceptability by establishing their expectations, needs met, gaps in services and their assessment of this.

Minority ethnic elderly, minority organisations and mainstream providers 'perceptions' and effectiveness of the actual delivery of health and social care.

### **Brief Description:**

The Objectives are constructed as research elements from which a systematic assessment in terms of quality, efficiency and user acceptability can be made. In each element, gaps in actual delivery of care and experiences of services will be identified by interviews with three target groups: the minority elderly, mainstream and minority service providers. In turn it will examine anecdotal presumptions held by the three groupings, e.g. 'they will return home', 'families look after their own'. After 6 months of preparation, the data will be collected sequentially over the next 20 months of the study and analyses completed in parallel. The minority elderly will be surveyed first, followed by mainstream providers and then minority organisations. The sampling methods will try to capture various factors in a quantifiable way, making them amenable to direct statistical tests of the data, as well as any future meta-analyses or retrospective comparisons. The key factors are: Factor 1 - minority groups; Factor 2 - geographical spread; and Factor 3 - international differences.

### **Data Analysis:**

The data and information generated from the interviews of minority elders, mainstream providers and minority organisation will be analysed using both descriptive statistics (measures of central tendency, frequency, standard deviation etc.) and inferential statistics (in order to generalise from the samples). The particular techniques used will depend on the size of the sample. A final decision on the technique(s) to be used will be made after further discussion between the partners, but a likely approach to be used is Factor Analysis.

The dissemination strategy will be designed with the aim that the MEC study will help contribute significantly to policy planning to improve care and quality of life of minority elderly in Europe. The MEC study is led by University of Bradford in the UK and the 10 country focus comprise of the UK, F, D, E, NL, FIN, CH, BA, HU, HR.

### **Keywords:**

Comparative research project in ten European countries to investigate the quality and effectiveness of health and social care services to minority elderly by researching three target groups: the minority elderly - mainstream and minority.

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EC contribution:	€702,912
Duration:	30 months
Type:	RS
Starting date:	01/04/2002

## ***Providing Integrated Health And Social Care For Older Persons Issues, Problems And Solutions***

### **Aims and expected achievements:**

PROCARE is to help in defining the new concept of an integrated health and social care for older persons in need of care by comparing and evaluating different modes of care delivery. The project will identify structural, organisational, economic and social-cultural factors and actors that constitute an integrated and sustainable care system with enhanced outcomes for all actors involved. The key objectives and expected achievements thus read as follows:

- to confirm the thesis that a new model of community health and social care is needed to enhance the care for older persons (confronting “models of good practice” vs. critical arguments),
- to provide an integrated literature review and a cross-national comparison of participating EU countries,
- to create a data base collecting data (models of “good practice”, quality indicators, outcome indicators etc.) that are comparable across the range of countries studied,
- to provide valid research methods to evaluate long-term care services for older persons, in particular at the interface between health and social care, and between institutional and community care,
- to contribute to the development of research methods for evaluating successful integration of health and care systems,
- to assess models of integrated care with respect to their efficiency, quality and user-acceptability,
- to identify structural, organisational, economic and cultural factors, and actors that constitute an integrated care system with enhanced outcomes for all actors involved,
- to develop performance indicators for use in evidence-based policy making, planning, quality assurance and controlling social and health services,
- to list and analyse the most important factors for a successful integration of health and care service delivery,
- to involve and bring together the most important actors for integrated care delivery (health and social care professionals, care recipients and informal or family carers etc.) in this project by means of focus group discussions, participation in project meetings and dissemination activities,
- to promote the dissemination of best practice by involving professionals at different levels.
- to provide evidence-based policy recommendations, and
- to publish results and policy recommendations in a series of reports and on the internet (electronic newsletter, links to similar data-bases); in addition, the data base will be constantly developed and cured for an ongoing publicly accessible use,
- to organise an international conference open to the public.

### **Methods:**

The literature overview will focus on the following research question: “Which of the variety of innovations in modes of organisation, finance and professional collaboration observed in Europe over the last decade have been the most successful and long lasting?”. National reports will be compiled to a European overview.

The development of performance and quality indicators will be based on individual interviews with clients and their carers, and focus on group discussions with all stakeholders involved in selected models of “good practice” in integrated care delivery. National analysis will be undertaken with a

comparative approach to facilitate a European overview with respective policy recommendations for local, national and European levels.

The dissemination of good practice by involving professionals and various organisations from 9 EU Member States will promote the development of a European understanding of integrated care, and shared views of definitions and approaches. “National Project Committees” with representatives of all relevant stakeholders will be established to guide and support the national project teams.

Regular project meetings and the final international conference will be to co-ordinate the national and comparative research and, occasionally, to involve policy-makers and representatives of the “National Project Committees”.

All results, data and reports will be published on the Web and, where appropriate, in brochures and scientific publications.

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## *Triage Decision Making For The Elderly In European Intensive Care Units*

### **Objectives:**

The project aims to

- make triage decisions for the elderly in Europe more transparent, beneficial and fair
- make triage decisions for the elderly more cost-effective
- facilitate European harmonization of standards for ICU triage in the elderly

### **Brief Description:**

The project consists of 3 interdependent clusters of work packages: 1. The acquisition of empirical data about triage decisions in the elderly. 2. A triple analysis of the context of triage decisions in the elderly. 3. Valorisation of the results. The work will be carried out by a European-wide consortium of a) ICUs whose researchers have a proven interest in intensive care, socio-economics and ethics and b) analysts specialised in geriatrics, economics, public health, philosophy and ethics with high level expertise in studying medical practice. The ICUs will coordinate the acquisition of data which, the analysts will analyse. All work is carried out in close interaction.

The consortium will first identify the important definitions that must be defined prospectively to perform the empirical studies (WP 1) and then perform the empiric triage study (WP 2). 2. The analytic core activities are organised in 3 work-packages. WP3 will produce a social map of the ethical values of the actors involved in or concerned with ICU triage decisions in the elderly, including policy makers. This analysis will be performed utilising the new empirical data provided by WP2, and the results of the analysis of WP4 (ICU costs) and WP5 (benefit analysis), as well as standard ethical and sociological literature. WP4 will make a cost-effectiveness analysis of ICU costs in the elderly, while WP5 will make a statistical analysis of benefit parameters, resulting in a benefit predictor. 3. The project results will be put to work and deepen quality for the standards used by ICUs for the elderly in Europe. This will be done preparing a) standardised triage instrument for ICU staff use b) a consensus statement amongst ICU professionals to explain their position to other social actors, c) guidelines for public policy. Patients, families and public policy officials will be involved in this preparation (WP6). The final report will be presented in a technical and popular version (WP7).

### **Keywords:**

Elderly – triage - socio-economics

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Duration:	36 months
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Starting date :	01/01/2003

## ***Care for the Aged at Risk of Marginalization***

### **Abstract**

CARMA aims to enhance the well-being of the growing aged population in Europe. CARMA will pool the resources of academic research institutions, social service providers and educational institutions to analyse current social care services for the aged from a multitude of angles: Among others, with longitudinal studies on coping skills of the aged, a comparative study of care arrangements, and a comprehensive literature review.

The findings of all these studies will be discussed and developed further in conferences with the partners and external experts, and will be integrated into Guidelines and Protocols for Policy Makers, Social Service Providers, and Private Networks.

### **Objectives:**

CARMA's main objective is to provide guidelines and protocols for improving health and social care services for the aged that are addressed to all levels:

- 1 - Macro: Guidelines for Policy Makers and Social Service Providers
- 2 - Meso: Guidelines for the Training of Staff in Social Services
- 3 - Micro: Guidelines for Private Networks

### **Brief Description:**

CARMA is based on a multi-national, multi-level and multi-method research approach. It combines the practice of service providers with scientific research, training of health and social care professionals, and the consultation of policy makers. CARMA will create an overview on the various measures taken by different types of European welfare states to prevent marginalization of the aged. This will be the first scientifically evaluated compendium of available measures against marginalization of the aged. CARMA will focus on concepts that empower older people and support their independence. Thus mobile health and social care services, day care centres, assisted living complexes and other innovative approaches will be documented in Southern, Central, Northern, Eastern and Western European countries.

CARMA will also do a longitudinal survey on aged people who use health care services, based on personal interviews. The aim is to gain a deeper understanding what services are most important for helping individual clients to continue living independently. This study will be done in parallel in several countries for more culture-independent findings. CARMA will analyse informal social care to give indications for the development of adequate support systems for this form of care. The results in different countries show different welfare state approaches and their consequences embedded in specific preconditions. Thus, CARMA will help social service providers and their staff to actually provide exactly what their clients need, and to build on the resources they already have. By co-evaluating the results of these multiple approaches, CARMA will fill in concrete knowledge gaps about the well-being of old people, in order to generate results which will be directly applicable as practical feedback for improving social services and thus the living conditions of old people in Europe.

**Keywords:**

Care Services and Informal Care for the Aged - Coping Resources of the Aged - Marginalization of the Aged

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Duration:	36 months
Type:	RS
Starting date :	01/01/2003

## ***Keys for quality performance management of the care of older persons in Europe***

### **Objectives:**

The objective is to develop an effective tool for the management and performance evaluation of care services for older persons. The project uses and further develops models such as the Target Efficiency Measure and the 3 D Quality Matrix. The aim is to test and validate the methods by empirical research in six European countries, and to disseminate the results as a Handbook of CareKeys 3DQ-Model.

### **Brief Description:**

Special focus is on linking client preferences and quality of life objectives to the professional and managerial objectives of good quality care, and on establishing the validity of the indicators and models being developed. Social and Health Economics research, Best Practise modelling and user trials are used to achieve the project goals. The work is organised in 7 work packages and 8 research stages, each addressing a primary theme. The end of each stage represents a significant milestone with a testable piece of the CareKeys 3DQ-Model. The milestones are: evaluation of existing measures and business practices, exploration and specification of new measures and practices, specification, testing and validation of the final model, and consolidating the results in a Handbook with support materials. Critical to the success of CareKeys will be its ability to integrate with existing care management systems. This is explored in relation to the assessment instruments currently employed in the project countries (e.g. Resident Assessment Instrument). A Minimum dataset specification will be provided for those users without advanced care planning systems. A key objective of the CareKeys project is the broadest possible dissemination of best practice and supporting tools. Dissemination of the results is an ongoing task together with the project work. Hence, the CareKeys research and development is an iterative process, involving care managers and researchers in an active process of user involvement, stakeholder empowerment, and stakeholder co-operation. The final, validated model will be documented for further possible IT-development. The project initiation phase will cover detailed planning and standardisation of the work, and a project conclusion phase covers dissemination and exploitation.

### **Keywords:**

Care management, performance evaluation, quality of life, quality of care, client quality, professional quality, management quality, Target efficiency, equity of care, integration of care

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EC contribution:	€2,417,122
Duration:	36 months
Type:	RS
Starting date:	01/01/2003

## ***Services for Supporting Family Carers of Elderly People in Europe: Characteristics, Coverage and Usage***

### **Objectives:**

EUROFAMCARE will provide a European review of the situation of family carers of elderly people in relation to the existence, familiarity, availability, use and acceptability of supporting services. EUROFAMCARE will push a change management process at various policy levels to promote social policies towards a partnership approach between family carers, professional providers and cared-for.

### **Brief Description:**

Six countries (Germany, Greece, Italy, Poland, Sweden, United Kingdom) will form a trans-European group, systematically representing the different types of welfare-states in Europe. In a comparative study each of the six core countries will collect data from about 1,000 family carers and their dependent elderly family members in different regional sites. The families will be interviewed face-to-face at home using a joint family care assessment. The views of potential service providers involved will be obtained by telephone. Quantitative and qualitative data of these interviews will be entered in National Data Sets and a European data base for cross-national analysis. A typology of care settings will be developed considering examples of good practice and beneficial and obstructive circumstances.

Pan-European expertise, knowledge and background information about the support, relief and expertise of family carers recognising the variety of the different social-, health- and welfare systems in a future Europe will be achieved by reviews and expert interviews in the six project countries plus 17 further European countries.

A representative of the WHO/ EURO as a member of the project group will conduct interviews with European decision makers to gather their views about strengths, weaknesses and opportunities in their responsibilities to support family carers.

A socio-economic evaluation on the basis of the National Surveys and the pan-European background information will calculate the economic consequences from perceived quality of life to European-wide politico-economic implications.

The last step will be a feedback research action phase based both on the study results and on the pan-European expertise. The partners will push a change management process at the level of local authorities and service providers as well as at the level of national and European policies.

### **Keywords:**

long-term (home) care, quality of life of family caregivers and their dependent elderly, professional care providers, partnership approach in family care, change management, typology of care settings

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SME-specific Projects

**CRAFT**



Project number:	QLRT-1999-70549
EC contribution:	€409.686
Duration:	24 months
Type:	CRAFT
Starting date:	01/03/2001

## *Ultrahigh resolution ophthalmologic optical coherence tomography*

### **Objectives:**

The *objective* of this project is to develop a new generation of an ophthalmologic technology which should allow early diagnosis and monitoring of retinal diseases the worldwide leading causes of blindness in the aging population. This technique is called ultrahigh resolution optical coherence tomography (UROCT) and will be based on newly developed compact and reliable components suitable for clinical use.

### **Brief description:**

New medical imaging technologies can improve both the diagnosis and the clinical management of a disease and therefore have a significant, challenging impact in medical research and clinical practice. *State-of-the-art*, minimally invasive *imaging techniques* have revolutionized diagnostic medicine during the last decades. In the last decade, advances in optics, fibre as well as laser technology have enabled the development of a novel non-invasive optical biomedical imaging technology, called optical coherence tomography (OCT). It is analogous to conventional ultrasonic pulse-echo imaging, except that OCT does not require direct contact with the tissue being investigated and that it measures echo delay and intensity of back reflected infrared light rather than acoustic waves from internal tissue structures. The eye is essentially transparent, transmitting light with only minimal optical attenuation and scattering and also provides easy optical access to the anterior segment as well as the retina. Hence, optical ranging measurements, the optical analogue of ultrasound A scans, were first demonstrated in 1986 using femtosecond light pulses as well as low coherence interferometry. Since then, numerous clinical as well as basic studies demonstrate the potential of OCT for routine clinical ophthalmic diagnosis.

Despite the promising and clinically valuable results of these studies, the resolution and performance is the main technical limitation of the existing clinical ophthalmic OCT technology and is significantly below what can be achieved theoretically and what has been demonstrated in the laboratory recently. The main innovation of the proposed UROCT instrument will be improved axial resolution of the cross-sectional tomograms, that should achieve significantly enhanced visualization and quantification of intraretinal structures for more sensitive and earlier diagnosis of ocular pathologies. The scope for development will include: ultrabroad bandwidth optics and light sources, respectively and a compact clinically feasible, reliable set-up that is optically, electronically and mechanically optimised to accommodate the ultra broad bandwidth and that can be used for clinical practise. With recent advances in technology, including the emergence of state of the art ultrahigh bandwidth femtosecond laser technology, a third generation ophthalmologic OCT technology is being developed in the proposed project. This new OCT technology represents an advance in performance, achieving in vivo retinal imaging with axial resolution close to that of conventional histopathology possibly enabling diagnosis of ocular pathology in unprecedented early stages.

### **Keywords:**

Retinal disease – femtosecond laser – optical coherence tomography - ophthalmology

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EC contribution:	€481,340
Duration:	24 months
Type:	CRAFT
Starting date:	01/06/2002

***Development of a process for the manufacture of high performance  
near net shape orthopaedic prostheses***

**Objectives:**

The objective of this project is to develop a novel manufacturing process to produce customised, truly porous, hydroxyapatite-coated cement-less orthopaedic prostheses. The project will create a prosthesis implant that will integrate with the surrounding bone in such a way as to prevent movement of the prosthesis during normal operating conditions. The improved osteo-integration of the prosthesis will reduce the need for remedial surgery due to loosening after years of service.

**Brief description:**

This work requires the development of processes to create the optimum implant from bio-compatible alloys in the form of a high-strength, NON RANDOM micro-porous structures. This technical objective is to be achieved by developing 'state-of-the-art' medical imaging, 3D CAD, Selective Laser Sintering (SLS) Direct Metal Melting (DMM) of bio-metals and Hydroxyapatite deposition, to produce a new, clinically-proven technology. The resulting implants will have a novel, bone like surface structures, which allow the effective transfer of load from the implant to the surrounding skeleton and vice versa. These forms will be manufactured using layered fabrication technology, which allows the inclusion of re-entrant features, and will permit the full interlock of bone within the implant. Additionally these structures will act as multi-directional stabilisers to resist everyday forces associated with patient locomotion. To achieve this, it is intended to use two manufacturing routes to produce the cobalt chrome parts. The first will use investment casting combined with Rapid Prototyping as an established route to demonstrate the validity of the new surface forms in relation to existing designs. The second uses DMM derived powder metallurgy techniques to generate the macro features while maintaining the highly beneficial, fully interconnected, micro-porous structure.

**Keywords:**

Prosthesis implant – Direct Metal Melting – micro-porous structure – Rapid Prototyping – remedial surgery.

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EC contribution:	€507,314
Duration:	24 months
Type:	CRAFT
Starting date:	01/06/2002

## ***An Affordable & More Effective Closure Treatment for Chronic Ulcers to Improve Patient Mobility and Quality of Life – ‘Rapi-Heal’***

### **Objectives:**

2 Million people in Europe suffer from chronic external ulcers every year. In Europe due to our dietary trends and ageing population, this situation is exacerbated by the links between the onset of external ulcers caused by either diabetes melitus or pressure sores amongst hospitalised or immobile elderly people. It is estimated that 3% p.a. of all diabetics will develop chronic foot ulcers and that around 75% of pressure and venous ulcers occur in the age group 55 to 85. These trends combined, are predicted to increase the number of external ulcer sufferers by 25% by 2010 to 2.5 Million, with 24,000 likely to result in amputation of a limb. It is estimated that the total cost of treatment of all chronic ulcers in the region of € Bn p.a. with typical healing times of between 12 and 24 weeks.

This project aims to develop a topical treatment device that will accelerate healing rates of typically difficult-to-heal ulcers in the lower limb. The device will remove the majority of harmful bacteria containing wound fluids and stimulate the growth of healthy tissue to replace that damaged by the ulcer. Our aim is to develop a device that can be manufactured and operated cost effectively in order that an increased number of patients across the EU and beyond will benefit from reduced healing times. Furthermore, the device will be made mobile so that the majority of patients can continue with normal life whilst undergoing treatment.

### **Brief description:**

Initial studies will focus on a range of ulcers of the leg and especially the lower limb and data will be collected from a number of patients. Metrics will include size, anatomical location, wound fluid characteristics and production rate and surrounding skin condition. Furthermore, phases of healing will be observed and data recorded relating to transition to closure of the wound. Data collected will be input into the design phase of the wound closure composite. From the data collected and analysed, a detailed design will be developed for the wound abstraction element together with the system of channels that will be used within this. Development and subsequently prototype injection moulds will be designed, manufactured and trialled. These moulds will be used to produce functional parts of the abstraction system. A portable unit for the purpose of abstraction of the wound fluids will be designed and developed. This unit will be self powered and therefore will not require the use of mains electricity or battery power. Prototype parts will be moulded and a working prototype unit produced. A number of trials will take place to verify the correct function of each element of the system prior to them being combined to form a complete working prototype device. Healthcare professional, carers and other relevant personnel will review the system in operation and provide feedback which will be used as input into design and functional iterations.

### **Keywords:**

Diabetic ulcer, venous leg ulcer, pressure ulcer, accelerated healing

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EC contribution:	€690220
Duration:	24 months
Type:	CRAFT
Starting date:	01/08/02

*Seaweed gels as fillings in pads and mattresses for therapeutic use and care of the elderly*

**ACROMYM : SCAFTCOE**

**Objectives:**

The project addresses the problem of pressure ulcers in the elderly and infirm. The work proposes an innovative approach to the need for effective prevention and treatment, by use of the particular properties of seaweed allied to new technologies in materials and electronics.

Prototypes will be developed for both standard (preventative) use and acute care purposes. Many other applications will be possible for these products in wound care and orthopaedics.

The research supports the EU programmes of 'Integrated Production of Biological Materials' and 'The Ageing Population and Disabilities'

**Brief description:**

The research consists of 5 interdependent, technical, workpackages:

The formulation of the seaweed gels and investigation of properties – experiments will be carried out to determine the optimum thermal, viscosity and mechanical properties of the gels.

Materials & Construction of the Envelope – includes the process of selection of materials for the envelope and cover, and the best way of welding the materials. The envelope will be capable of being reactive to pressure and temperature. Prototypes will emerge from this phase.

Investigation of Interfaces – will focus on the interface between the gel/cover and body of the user. The criteria will include – ability to reduce pressure and shearing forces to the body, and to achieve patient comfort.

Production Safety Testing – will investigate all aspects of product safety

Field Testing of Prototypes – will encompass a comprehensive testing regime using volunteer patients according to strict scientifically rigorous conditions.

The SME participants will set the specifications, provide raw materials, evaluate the development pathway of the prototypes and assist in the distribution of the prototypes for testing.

**Keywords:**

Pressure Ulcers – Seaweed – Products for Wound care - Orthopaedics

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Duration:	24 months
Type:	CRAFT
Starting date:	01/01/2003

**DOPARTAGO : Dopaminergic Partial Agonist with Potential  
against both Parkinson's Disease and Psychoses.**

**Objectives:**

Greater understanding of Parkinson's Disease (PD) and Psychoses will constitute a major contribution to the quality of life in Europe. Geriatric and other chronic diseases have become a real threat to the economy in the western world today. The proposed research of the Dopaminergic Partial Agonist concept (DOPARTAGO) is likely to deliver new atypical anti-psychotics with an improved side-effect profile, as well as a new and long-acting drug for improving the pharmacotherapy of PD.

**Brief description:**

GMC1111 represents a new therapeutic approach, based on prof. Arvid Carlsson's DA autoreceptor concept. There is one competing drug, Aripiprazole, which was recently approved for marketing in the US against schizophrenia. Among the compounds claimed in the patent application covering GMC1111, there are likely also compounds useful to treat PD.

Research is needed to bring GMC1111 to the stage of "proof of principle". Part of this development program is covered by the DOPARTAGO CRAFT project (up till, but not including, Phase I studies). A synthesis program integrated with pharmacological testing, a so-called SAR Project, will be necessary to identify one or two drug candidates out of the compounds covered by the GMC 1111 patent application. A large scale synthesis (20-100 g of GMC 1111) and a toxicological study in two different species are included in the development program.

**Keywords:**

Schizophrenia, Parkinson's disease, D2, D3, partial agonist, dopamine stabilizer

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EC contribution:	€808,600
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Type:	CRAFT
Starting date:	01/01/2002

The potential of oligonucleotide submicron positively charged emulsion ocular delivery system for age related macular degeneration

### **Objectives:**

Age-related macular degeneration (ARMD) is a common eye disorder which is becoming the leading cause of blindness in industrialized world. The wet form is the more severe type of ARMD. Although the wet form affects only 10% of patients, it accounts for 90% of the blindness caused by ARMD. No effective therapeutic treatment is available to date. The objective of the present research proposal therefore is to develop a product to treat and cure ARMD, by using the combination of two novel technologies, Cationic emulsion and Ocular Electroporation to deliver anti-angiogenic oligonucleotides (ODN) in order to inhibit the neovascularization responsible for the disease. To demonstrate the efficacy of the combination, ocular pharmacokinetic studies and animal models of the disease will be used. Scale-up, stability studies and set up of specification will then be performed in order to have a final product which will be ready for Phase I clinical trials in human.

### **Brief description:**

Extensive physico-chemical investigation and optimization of the ODNs association with cationic emulsion will be performed by the group of Prof. Simon Benita (inventor of the Cationic Emulsion technology) at the University of Jerusalem in collaboration with Novagali SAS (exclusive owner of the Cationic Emulsion technology). Novagali will develop the assay methods and perform the pre-stability testing. This will be followed by an ocular tissue distribution study in animal eyes (rabbits, rats). The proof-of-concept of cellular ODN uptake, using the association of the Cationic Emulsion with Ocular Electroporation, will be performed in rat models developed by the INSERM 450 group. The rat corneal neo-vascularization model will be used to determine the optimal parameters of the combination of the Cationic Emulsion with the Electroporation in order to enhance ODN ocular penetration and to allow ODN to reach the target site. The new product will then be tested in the rat choroidal neo-vascularization model, according to Cationic Emulsion and Electroporation parameters determined in the corneal model. An animal ocular tolerance and safety study will then be performed. The manufacturing process of the Cationic Emulsion will be optimized and scaled-up by Octoplus BV. Both Novagali SAS and Octoplus BV will perform ICH Stability studies and define the specifications of the final product. The new ocular delivery system can be a treatment kit consisting of the ODN Cationic Emulsion and the Electroporation device. During the course of the last part of this development Novagali SAS and Coraltis Ltd. will perform market analysis studies, select an appropriate partner (by preference European) and prepare for market implementation.

### **Keywords:**

ARMD – Oligonucleotide – Antisense – Cationic – Emulsion - Electroporation

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Type :	RS
Starting date :	01/12/2002

## ***TELEDOC: Telerehabilitation system using haptic interfaces and virtual reality techniques***

### **Objectives:**

This project intends the development of a complete system for telerehabilitation making also use of VR techniques. The use of VR applications provides the capability to create an environment in where the intensity of feedback and training can be systematically manipulated and enhanced in order to create the most appropriate, individualized motor learning paradigm.

### **Brief description:**

This project presents a solution to rehabilitation needs by creating a technology to provide rehabilitation therapy at the patient's home, or in satellite facilities, using a networked computerized system (telerehabilitation) bridging the gap between the rehabilitation hospital and the community. Such remote therapeutic intervention will clearly increase the disabled individual's self-sufficiency, as well as family support and involvement in the therapy. For disabled individuals that are self-employed, or perform home-based employment on a regular basis, telerehabilitation will be beneficial through the elimination of the time needed to travel to and from the clinic. For individuals on temporary disability, such a system would also shorten time lost from work, because of an intensive and monitored home-based therapeutic intervention. In the case of orthopedic patients, special force feedback interfaces need to be developed to allow on-line rehabilitation at home.

Similar to computer games, VR rehabilitation exercises can be made to be engaging, which is important in terms of the patient motivation. VR sensor technology can also be used to fully quantify any progress made by the patient, especially in terms of motor control improvement.

The project will end with a fully operative system demonstrator of the technology developed. This system will include:

- Haptic interfaces developed for some specific therapies: knee, ankle, wrist, etc.
- VR-based rehabilitation routines to make sessions funnier and increase patient motivation.
- A Clinical database for information management
- Communication links among the different subsystems.
- System software to control overall activity.

### **Keywords :**

Telerehabilitation, Virtual Reality in medicine, traumatology.

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