

3.3 Cancer

3.3.1 Summary

More than two million new cases of cancer will be diagnosed in the EU over the next year. This represents a huge healthcare and financial burden to the Member States. The treatment of many cancers is inadequate, and represents an important area of unmet need in healthcare provision. There are multiple research and clinical networks in Europe, and the success of this proposal is dependent on close working relationships with major cancer organisations such as the EORTC, other national cancer bodies and the major cancer charities.

Our rapidly expanding understanding of the genetics and molecular pathology of cancer development and progression offers a tremendous opportunity for exploiting the underlying science into safe and effective new therapies. Increased understanding of the molecular genetics of cancer development and progression has unearthed a wide array of genetic abnormalities in many cancers. These are potential novel targets, although relatively few of these may be critical to the cancer's growth and survival. Therefore, greater understanding and validation of these targets is urgently required.

This proposal does not specifically address the identification of novel targets, but stem cell research may be valuable in this regard. Improving our understanding of the validity of the multitude of novel targets will enable us to focus rapidly on leads where there is a higher chance of success. Approximately 45% of all new chemical entities (NCEs) in development are being aimed at the cancer market, but the development of these NCEs is slow and economically high risk. Although cancer drug development presents particular problems such as tumour heterogeneity, the main bottlenecks affecting the rapid delivery of new therapies are similar to other therapeutic areas. The predominant issues centre on the identification and validation of biomarkers, together with development of more relevant pre-clinical disease models that better predict clinical outcome. Specific proposals for each of the main bottlenecks are summarised below.

Identification and Validation of Biomarkers

- Establishing a core Cancer Biomarker Community of Experts(CoE) with responsibility for the definition of standards, and to outline the plan for the Regional Biomarker Centres;
- The creation of Regional Biomarker Centres (4-6 required) to service populations of 50-60 mn, handling and processing in the region of 50,000 samples annually, using a broad range of technologies, to defined protocols and standards;
- The development of databases of genetics and cancer biomarkers to collect and collate all scientific and clinical data from relevant trials, to underpin the validation process;
- Establishing an expert panel focussed on the paradigm of biomarker development and evaluation;
- Molecular pathology CoE to underpin the biomarker programme and to develop standards for molecular pathology biomarkers linked to clinical and laboratory best practice standards;
- Establishing a Clinical Imaging CoE to link with ongoing FP6 activities in the area of imaging biomarkers;
- Linking of industry, SMEs and academic centres for the development of translational research programmes through an extended Community of Experts in Translational Science.

Pre-Clinical Pharmacology

- The development of novel predictive *in vitro* and *in vivo* models focused on targeted approaches and biopharmaceuticals;
- Establishing a Cancer Stem Cell CoE and research programmes in various cancer types;
- The development of a web-based Clinical Pharmacology CoE, and also research programmes to exploit microdosing approaches, and modelling and simulation techniques;
- Establishing a Systems Biology Cancer Specific CoE, and research programmes focused on cancer prevention, invasion and metastasis, and pulmonary diseases.

Patient Recruitment and Risk Assessment

- The development of a pan-European Cancer Trials Website linked to the WHO-led International Clinical Trials Registry Platform (ICTRP);
- The creation of a European Research Centre for Uncommon Cancers;

- Establishing a European Stakeholder Consortium to enhance our understanding of Value Demonstration in evaluation of novel anti-cancer therapies;
- The formation of a forum with regulatory authorities to discuss such issues as innovative adaptive trial designs, the use of biomarkers, and the review of clinical end-points for regulatory approval.

The proposed programme will generate large quantities of data from a variety of sources. Creating the capacity to search, query, extract, integrate and share data in a scientifically consistent manner across these sources (clinical and scientific datasets) will be challenging. Illustrative proposals are given in the Knowledge Management section.

This programme's chances of success will be significantly increased if it is supported by a strong educational programme, such as the one described within the Education section. Establishing a European Medicines Research Academy (EMRA) would support the delivery of a translational, trans-disciplinary educational programme to support all clinical and scientific staff. In addition, an educational programme to support patients careers and patient groups would be essential.

3.3.2 Introduction

The treatment of cancer represents a major area of unmet need across Europe and all other areas of the world. Although the aetiology of different cancers varies, all are associated with a loss of cellular growth control. It is a major cause of morbidity and mortality across the world, with more than 1.4 million cases in the US in 2005, with a similar incidence across the EU-15, with almost two mn cases. In Western society, approximately one in every four deaths is from cancer. Unfortunately, survival rates in Europe for the common cancers remain inferior to the US, with almost one million deaths per year (Figure 23). These figures do not include diagnoses of *in situ* (preinvasive) cancer, or the estimated one million cases of non-melanomatous skin cancer that will be diagnosed in 2005.

Cancer	Cases	Crude	ASR (E)	ASR (W)	Deaths	Crude	ASR (E)	ASR (W)
Oral cavity and pharynx	53,556	14.29	12.71	9.28	20,178	5.38	4.64	3.31
Oesophagus	24,812	6.62	5.38	3.71	22,917	6.11	4.85	3.29
Stomach	70,798	18.89	14.13	9.35	54,919	14.65	10.58	6.81
Colon/Rectum	217,526	58.04	44.04	29.36	111,781	29.82	21.38	13.63
Liver	31,057	8.29	6.41	4.37	34,132	9.11	6.81	4.51
Pancreas	41,340	11.03	8.35	5.53	45,599	12.17	9.02	5.88
Larynx	23,304	6.22	5.45	3.92	10,326	2.75	2.28	1.59
Lung	196,836	52.52	42.16	29.12	183,653	49	38.27	25.96
Melanoma of skin	38,213	10.2	8.89	6.81	9,010	2.4	1.94	1.37
Breast	210,631	56.2	48.84	35.38	73,592	19.63	15.57	10.61
Cervix uteri	22,618	6.03	5.35	4.15	10,098	2.69	2.17	1.52
Corpus uteri	37,411	9.98	8.31	5.81	8,998	2.4	1.7	1.08
Ovary etc.	34,468	9.2	7.74	5.6	22,999	6.14	4.78	3.23
Prostate	144,504	38.55	27.77	17.97	56,035	14.95	9.73	5.72
Testis	8,810	2.35	2.25	2.13	641	0.17	0.15	0.13
Bladder	73,132	19.51	14.7	9.78	29,773	7.94	5.44	3.35
Kidney etc.	46,228	12.33	10.1	7.21	22,418	5.98	4.54	3.03
Brain, nervous system	28,866	7.7	6.91	5.66	21,681	5.78	4.97	3.77
Thyroid	16,311	4.35	3.99	3.22	3,245	0.87	0.63	0.41
Non-Hodgkin lymphoma	52,440	13.99	11.5	8.46	25,906	6.91	5.24	3.55
Hodgkin's disease	8,407	2.24	2.13	2.01	2,251	0.6	0.49	0.36
Multiple myeloma	21,426	5.72	4.36	2.92	15,259	4.07	2.93	1.88
Leukaemia	43,518	11.61	9.55	7.52	29,714	7.93	5.97	4.2
All sites but skin	1580,096	421.57	338.83	238.85	<u>929,992</u>	248.12	186.54	123.93

Figure 23 : Cancer Mortality in the EU15

Importantly, cancer does not affect all races equally, either in terms of incidence or outcome. US statistics suggest that African-Americans are more likely to die of cancer than people of any other racial or ethnic group. From 1997 to 2001, the average annual death rate for all cancers combined was greatest for African-Americans, followed by white Americans, Hispanics, American Indians/Alaska Natives, and Asians/Pacific Islanders. Many countries, including the US (*Healthy People (HP) 2010*) and the UK are aiming to reduce the incidence of cancer and the associated mortality by public health initiatives such as those designed to improve lifestyles.

The incidence of cancer varies widely in the EU, both between and within tumour types, as a result of factors such as variations in environmental exposure to carcinogens. Figure 24 contains incidence and prevalence figures for cancer across the 'old' EU. The incidence and prevalence of different cancers at five years varies widely between countries, even allowing for the differences in population size. These figures are an important indication of the overall cancer burden on EU society, which is a function of both the incidence and prevalence of the diseases, with many prolonged systemic treatments. We are now witnessing significant improvements in cancer outcomes, initially childhood and haematological malignancies. However, more importantly, the cancer burden of the common cancers such as breast and colorectal has increased significantly in EU populations in recent years. Prevalence figures at five years indicate that more than four million people are affected, with this number likely to increase substantially with the increase in size of the EU, and with improvements in treatment.

Population	Cases	1-year prevalence	5-year prevalence
European Union	1,571,351	1,108,845	4,383,216
Austria	32,828	23,349	93,377
Belgium	47,575	35,107	136,267
Denmark	23,666	15,733	61,252
Finland	20,473	15,068	59,867
France	245,662	189,262	760,295
Germany	346,558	243,658	960,318
Greece	36,505	24,139	95,236
Ireland	12,461	8,025	31,216
Italy	264,551	190,746	750,540
Luxembourg	1,683	1,196	4,624
The Netherlands	62,647	47,170	187,560
Portugal	36,588	26,066	104,738
Spain	151,046	106,444	430,202
Sweden	40,066	30,079	121,628
United Kingdom	249,042	152,804	586,096

Figure 24 : Incidence and Prevalence of Cancer Across EU Countries

The results of cancer treatment have improved dramatically over the past two decades. These improvements include better organisation of services, greater investment in support services such as X-rays and pathology, and improved screening services enabling prevention and earlier diagnoses. This is in addition to advances in cancer treatments.

3.3.3 Present Status of the Disease Area

The treatment of cancer has improved dramatically over the past 10 years, with better outcomes now being observed in many tumour types. The first improvements in survival were seen in childhood cancers and haematological malignancies, but we are now seeing significant improvements in many adult solid tumours, where prevention and early diagnosis are vitally important.

Many factors have influenced the recent improvement in survival rates that has been seen with acute cancer treatment. Better health facilities, improvements in organisation of treatment delivery such as the establishment of multidisciplinary care and the introduction of screening programmes, together with an increased public awareness of cancer, have all had an impact. In addition, improvements in surgery, radiotherapy and systemic treatments have also had an impact on outcomes, as follows:

- Improved quality of local treatment (surgery and radiotherapy) and supportive care, and the use of effective systemic adjuvant therapies, for example in breast and colorectal cancers;
- Introduction of new chemotherapy medicines;
- Development of novel targeted therapies. These include growth factors such as imatinib, trastuzumab, erlotinib, cetuximab and gefitinib, and anti-angiogenesis agents like bevacizumab.

The challenges for cancer drug discovery are commonly addressed from an organ-specific standpoint, with significant differences in pathophysiology between different tumour types. However, there are also generic cancer-specific issues, which are peculiar to the malignant phenotype, such as invasion and metastases.

Despite this, the major problem facing cancer treatment remains the lack of quality systemic treatments. It is interesting to note that, at present, almost half of the new chemical entities in clinical development are being developed against cancer targets. Many of these projects are high-risk, however, as there is a general lack of disease-related biomarkers to support early decision-making on these products.

Overall, the drug development process in this field remains extremely slow, inefficient and costly. We urgently need to be able to accelerate the progress of new potential cancer therapies into the clinic. The bottlenecks to the drug development process in cancer are, in general, similar to other disease areas, with the major problem areas being pre-clinical pharmacology, the identification and validation of biomarkers and patient access issues. However, there are specific issues that are particular to cancer:

- Cancer represents wide range of diseases each with individual biologies and issues;
- Greater understanding of genetics required for all cancers;
- Inter- and intra-tumour heterogeneity is major problem;
- Greater understanding of pathophysiology required for all cancers;
- Improved therapy is considered an unmet need for the majority of adult cancers, particularly for common solid tumours;
- Lack of efficacy is the predominant issue;
- Safety is important, but is currently a secondary issue;
- Drug resistance to targeted therapies;
- Lack of validated biomarkers;
- Inadequate surrogates of long term survival;
- Need for complex biomarkers;
- Mechanistic markers for proof of mechanism are less of a problem;
- Lack of appropriate pre-clinical models predictive of efficacy;
- Targeted treatments;
- Biopharmaceuticals;
- Stem cell models.

There remain limitations to how we work in the cancer community. With several notable exceptions, such as the European Organisation for Research and Treatment of Cancer (EORTC), we tend to work in relatively small groups or networks, frequently limited by national boundaries. However, for particular cancers there are very successful tumour-specific groups, such as the Breast International Group (BIG). A Network of Excellence, CONTICANET, has also been established as part of FP6 to co-ordinate the research and treatment of connective tissue cancers across the EU.

The links between industry and academia are currently sporadic and uncoordinated and, as a result, full exploitation of the potential synergies has not been achieved. This has resulted in slower, more costly and generally over-regulated processes. The relationship between industry and European regulatory bodies differs to that in the US, and more interaction is needed. Although the scientific-clinical interface in the cancer field is more successful than some other therapeutic areas, development of the translational interface is urgently required. Links with patients, their carers and patient support groups is fundamental to all clinical/scientific groups, whether in academia or industry, and we urgently need to involve them more consistently and effectively in all our scientific and clinical programme designs. The oncology community will significantly benefit from the education and training together with a robust knowledge management approach, for patients and their carers as well as the physician/scientist community.

The EU has, rightly, judged that it is important for patient groups to be actively involved with the planning and operation of research programmes. This will be strongly supported in the cancer arena, where there are many emerging patient groups. This is fundamental to this proposal.

Cancer research and treatment is functionally multi-disciplinary at all stages. This proposal builds on this strength, through the involvement of a broad range of health care professionals, established industrial partners and SMEs. This aspect of the programme will strongly link with the training and education packages.

Within the EU, both the major industrial partners and the SMEs have a substantial potential for growth. The opportunities are enormous, particularly in the cancer field. These developments, however, would also offer significant collateral benefits for many other therapeutic areas.

The opportunities include, but are not limited, to the following areas:

- Identification and development of biomarkers;
- Identification and development of diagnostics and stratification tools;
- Imaging hardware and software for the digital integration of data.

3.3.4 Bottlenecks

3.3.4.1 Identification and Validation of Biomarkers

The use of biomarkers in early drug development has been identified as a major route by which we can improve the efficiency of the drug development process for cancer prevention and therapy by enabling rational early go-no go decision-making and reduced risk of attrition at proof-of-concept. This should focus Phase III accrual on agents with a higher chance of success, and reduce patient exposure to ineffective medicines. This will require access to a wide range of normal human and cancerous tissues, which will need strong links with existing biobanks. The development of validated efficacy and safety biomarkers will significantly improve our decision making process in early development by:

- Early identification of proof-of-mechanism and proof-of-principle/concept;
- Identification of sensitive sub-populations, leading to personalised medicine approaches;
- Efficient early identification of unexpected side-effects;
- Early identification of inactive drugs and a reduction in the risk of late stage attrition.

The focus of cancer biomarker research in the past has been on 'simple' or mechanistic biomarkers using standard biochemical and pathological techniques. Increasingly, biomarkers are being developed that use a variety of evolving platform technologies, including genetics, omics, molecular pathology and imaging. This raises many interesting challenges. The identification, standardisation and validation of these biomarkers is fundamental if they are to be effective in drug development and the regulatory process.

These biomarkers can be used at various stages during drug development, including:

- Diagnostic and prognostic markers (cancer specific);
- Patient stratification by genotyping;
- Predictive markers for efficacy;
- Surrogate 'markers' (end-points) for long-term drug efficacy;
- Predictive tumour genotyping for efficacy (responders/non-responders and safety).

The identification, standardisation and validation of effective biomarkers would dramatically impact on the quality of decision making in cancer drug development and, therefore, is pivotal to this submission, with a number of core proposals:

- Establishing a core Biomarker Community of Experts, with responsibility for the definition of standards and to outline the plan for the Regional Biomarker Centre:
 - The development of common European standards for validation of biomarkers;
 - The co-ordination of national networks, tissue banks, clinical expertise, SMEs and the pharmaceutical industry;
 - Regulatory standards and dialogue/ acceptance of validation.
- The creation of a Regional Biomarker Centre to act as reference centre for biomarker measurement, and to act as the central hub responsible for the system of accreditation for all laboratories performing biomarker assays. This is to ensure common standards and methodologies to service the EU population. The network would be responsible for handling and processing all approved clinical trial samples, using a broad range of technologies, to defined protocols and standards:
 - Genotyping: personalised medicine;
 - Pharmacogenetics;
 - omics;
 - Novel technologies.
- The development of a Cancer Biomarker database to collect and collate all scientific and clinical data from relevant trials by pulling and pooling information from existing sources, to underpin the biomarker validation process and to facilitate learning across tumour types;
- An integrated research programme using Systems Biological platforms to assist in the identification and prioritisation of potential biomarkers. This would include the use of modelling and the si-

mulation of cellular and extra-cellular pathways/networks to select from, amongst a variety of options through sensitivity analysis and similar approaches. Other approaches would include analysis of tissues and body fluids to assemble a profile of gene expression, protein and metabolite distribution. Such triomic signatures would be associated with specific biological processes, such as metastasis and invasion, supported and validated by appropriate multivariate statistical analysis;

- The development of a pathology Community of Experts to support the biomarker programme with quality molecular pathology, including digital telepathology, to enable pathology QC/review, along with standardisation for molecular pathology biomarkers;
- Development of a Translational Science Community of Experts to promote standards of translational research and to develop an integrated programme of research;
- Establishment of a Clinical Imaging Community of Experts Programme to link with the pre-clinical EU CoE established via FP6. The aim of this group would be to establish imaging standards, approve Imaging Centres in whole body *in vivo* imaging techniques such as MRI, microPET and microCT, and to develop image analysis and informatics processing solutions. This network will also be responsible for the identification of imaging biomarkers, in the following prioritised areas in particular:
 1. Angiogenesis;
 2. Invasion;
 3. Apoptosis and proliferation;
 4. Correlation of pre-clinical imaging with clinical outcome.

High-throughput technologies such as genomics, proteomics and metabonomics will result in data generation on a massive scale, both in companies and regulatory bodies, on all products, covering R&D across all therapeutic areas. These pre-competitive data can be used to increase the predictive power of current models. The emerging systems biology approach, for instance, requires both data integration at the molecular level (for example, omics) and the availability of sophisticated mathematical or computational models at the pathway, cellular, organ or disease physiology levels (so-called multiscale models). Although such modelling efforts are still in their infancy, they are rapidly coming of age, and some integrated computational models are already in use. The Knowledge Management Pillar, as outlined in this document, is intended to exploit the data generated from these proposals to the full. It is fundamental to both this and the following sub-sections.

3.3.4.2 Predictive Pharmacology

There is an urgent need for better and more informative pre-clinical models predictive of clinical outcome. These will be used to facilitate a better understanding of disease, identify new targets and predict responses to therapy using novel candidate medicines. Major areas for development include:

- Establishing a Community of Experts for Predictive Pre-Clinical Models:
 - These models will include *in vitro* stem cell and engineered cell lines, and models of invasion and metastases. These models will include *in vivo* approaches to evaluate novel biopharmaceuticals. Techniques will be developed to purify stem cell populations from common cancers. These could be used to identify novel cancer-specific targets, to understand cancer biology, and to evaluate the efficacy of established and novel agents against these populations.
- The development of a web-based European Clinical Pharmacology Modelling and Simulation Community of Experts:
 - Use of *in silico* modelling and simulation in all stages of drug development;
 - Improved study design to address regulatory questions that would minimise patient numbers while protecting safety and ensuring an improved benefit to cost ratio;
 - Increased use of modelling and simulation will aid the understanding of exposure–response relationships with regard to both safety and efficacy. It will also help the understanding of drug metabolism, and also the target biology in humans. Modelling can also be applied in the context of a disease biomarker, helping to understand the variability, signal-to-noise ratio and linkage (causative vs. co-incidental) of a biomarker or a pattern of markers to different disease stages. Clinical trial simulation is a valuable tool to test trial design factors, identifying non-robust co-variables likely to confound a trial's outcome. The resulting study designs will be more robust, executed more quickly with fewer

subjects, and also lower numbers of non-responders or adverse events. The resulting clinical programmes will be cheaper, and result in decisions being better informed.

- **Systems Biology: Establishing Cancer Specific Community of Experts:**
 - To develop European expertise in Systems Biology further, with a particular focus on cancer. This will be achieved by building on understanding from the Systems Biology programmes established in FP6 to capture learning and share experience. Furthermore, there is a need to collate the wealth of information, knowledge and technologies from Systems Biology approaches that have been used widely to study signal transduction, and to validate the approach in the context of cancer biology. To do this, we recommend the establishment of a Community of Experts in Systems Biology. This CoE will facilitate the co-ordination of research between academia and industry, building on existing relationships with the academic centres of excellence active in the field, many of which already focus on aspects of cancer biology. It will also co-ordinate information exchange with other European and national initiatives in this emerging discipline. The CoE would be responsible for outlining research programmes where systems biology approaches would enhance our understanding of disease mechanisms and target function, for example in the field of invasion and metastases, specific to cancer and/or lung disease, spanning cross-disease interests in cancer, respiratory physiology and inflammation.

3.3.4.3 Patient Recruitment: Dedicated Contact Networks (Patients, Clinicians, Academia, Industry)

Patient recruitment is often the time-limiting factor for clinical trials. The objective of these proposals is to speed up the recruitment of appropriate patients, and to involve patient groups throughout the clinical trial process. Specific proposals are as follows:

- Establishing a pan-European Cancer Trials Information Website to provide information to the public about the value of cancer trials and treatments. This website will also provide access to existing databases of on-going and planned trials and databases of results;
- The creation of a Clinical Community of Experts (European Research Centre for Uncommon Cancers) focused on the treatment of uncommon cancers. The aim of this group is to identify rare patient populations in order to facilitate clinical research, to provide information to patients and patient groups about these cancers, and to facilitate the development of an integrated translational research programme. This would stimulate the development of novel therapies for commercially non-attractive indications;
- Establishing a European 'Value Demonstration' Consortium to integrate patient-focused quality of life data, patient reported outcomes and burden of disease.

As outlined in the summary, the Cancer Efficacy proposal will be supported by the developments that are proposed in the Education section. Training programmes for health professionals will address the issues of key skills availability and CME. In addition, the availability of training programmes for patient and related groups, in addition to the new Clinical Trials Website, will significantly improve patient recruitment.

3.3.4.4 Risk Activity and Outcome Assessment with Authorities

Adaptive or innovative trial designs for Phase I, II & III, with Phase IV risk management activities for post-marketing activity:

- Establishing a discussion forum with the regulatory authorities. This will include representation from patient groups, academia and industry, and will discuss issues relating to patient access and trial design, including a review of regulations on the use of novel therapies in exploratory clinical research programmes.

3.3.5 Resources

In this section, the estimates of the costs of these recommendations are displayed by project proposal for each bottleneck. The duration of most of the research topics proposed is between five and seven years, and all figures are expressed in millions of euros per year. As many of these proposals are in outline format, the costs represent a best guess by the participant group. These figures will be updated as the proposals are developed and approved.

Activities	Costs (€mn)
Identification and Validation of Biomarkers	42.2
Establishment of Biomarker CoE	0.8
Regional Biomarker Centre including biomarker assays and Informatics	20.0
Cancer Biomarker Database	1.5
Integrated Research Programmes Systems Biology	3.0
Pathology Biomarker CoE	2.4
Translational Science CoE and Research Programme	2.5
Clinical Imaging CoE and Research Programme (clinical costs)	12.0
Predictive Pharmacology	9.8
Predictive Pharmacology pre-clinical models CoE and Research programmes	2.5
Cancer Stem Cell Programme	5.0
Web based Clin Pharm Mod & Simulation CoE and research programme	1.5
Establishment of Systems Biology (Cancer) CoE	0.8
Patient recruitment and Risk Assessment	14.7
Pan European Cancer Trials Website	1.5
European Research Centre for Uncommon Cancers and research prg.	4.2
Quality-of-Life and Outcomes demonstrating consortium	9.0
TOTAL CANCER (€mn per year)	66.7

3.3.6 List of Contributors

Improved Predictivity of Efficacy Evaluation: Cancer			
Stakeholders Group	Last Name	First Name	Institution
European Commission	Kelm	Olaf	DG Research
Academia	Cassidy	Jim	University of Glasgow
	Grivell	Les	EMBO
	Harris	Adrian	University of Oxford
	Kaye	Stan	Institute of Cancer Research
	Marty	Michel	Institut Gustave Roussy
	Newell	Herbie	University of Newcastle
	Verweij	Jaap	University of Rotterdam
Regulatory Authorities	Pignatti	Francesco	EMA
Companies, Pharma & SME	Carmichael (Chair)	James	AstraZeneca
	Tambuyzer	Erik	Genzyme Europe
Patient Organisations	Baird	Jesme	European Cancer Patient Coalition
	Schöffski	Patrick	European Cancer Patient Coalition
	Van der Streichel	Didier	European Cancer League