A Platform for Translational Cancer Research

1. The patient at the centre of cancer research
Cancer affects everybody. According to a recent WHO study, 3.2 million people are diagnosed with cancer each year in Europe with 1.7 million annual casualties and the situation is set to worsen in general terms as the European population ages. There is not a single person who hasn’t been touched by cancer or has had or will have a friend or family member diagnosed with the disease. This dismal state of affairs underpins the need for developing strategies as well as novel approaches to reduce cancer incidence, morbidity and mortality.

Today, despite the spectacular progress in cancer biology we have experienced in the last decades there still remain many unsettled questions regarding cancer prevention, diagnosis, recurrence, treatment, and resistance to treatment. The advent of novel and powerful technologies derived from functional genomics, proteomics, bioinformatics and functional imaging has provided new opportunities to improve diagnostic methods and treatment, but we still lack the coordination and critical mass required to rapidly implement new discoveries in a clinical setting.

Cancer research in Europe has the potential for making a difference as it has a number of unique strengths such as a strong foundation in biomedical science, good patient registries, infrastructures that span from repositories to bioinformatics as well as thriving comprehensive cancer centers (CCCs) and basic/preclinical cancer research institutions of high international standing. Research, however, is fragmented and lacks coordination, and as a consequence Europe has been unable to harness its potential for translating basic research discoveries into a clinical setting for the benefit of the patient. What is needed is a paradigm shift in cancer research that addresses the translational research continuum.

2. The translational research continuum: Need for a comprehensive platform for translational cancer research
“Translational research can be briefly defined as the action, process or method which converts scientific discoveries into clinically useful applications that benefit patients”. In this broad operational definition are included all types of discoveries from basic research to epidemiological and early clinical studies and the recognition that application of a discovery into clinical goals can lead to improvements in many diverse aspects, such as diagnostic, therapeutic, prevention, or quality of life, among others. Translational research is thus not limited to a strict interface between basic and clinical research, but should be seen as a conceptual change in how we view and organise the entire research process and where all aspects of the cancer research continuum from basic to clinical to outcome research and epidemiology, are integrated and properly articulated to implement new treatments and technologies. Given the increasing multidisciplinary nature of translational research, there is today no single European cancer institution or even country with the critical mass required to deliver in all cancer areas. Consequently, it is becoming crucial to have access to a European research infrastructure in which care and prevention is integrated with research and education.

3. CANCER RESEARCH – STATE OF THE ART
The spectacular development of knowledge in basic biology and physics provides the preclinical and clinical research with expanding new information possible to use for diagnostics, treatments and prevention.

Prevention and early detection are necessary for reducing the overall cancer burden in a population. Combining research in this area with risk assessment and prevention will help to reduce the strain on the health care. Cancer biology research will sort out information of relevance for aetiology and precursor lesions as well as risk assessment based on molecular genetics for new preventive strategies. This type of research will not only be linked to epidemiology but also to health economy and behavioural sciences.

Knowledge from cancer biology research continuously makes tumour classification more detailed. The development of molecular pathology/cytology will completely change the tumour classification and increase the number of disease entities. Research on the metastatic phenotype will sort out which patients suffer from microscopic dissemination of disease and which patients have only a local tumour. Molecular pathology provides one important step towards personalized cancer medicine.

Development of new therapies, medical oncology as well as radiation therapy, includes identification of new targets for therapy and new agents or ways to deliver radiation therapy. This is a expanding research area which also reflects the activities of the pharmaceutical industries, investing more research money in oncology than all other main research areas together. An effective development requires integration of basic, preclinical (relevant animal models) and clinical cancer research with strong infrastructures not possible to establish in one single center.

Identification of new targets for therapy involves not only the tumour cells but the whole infrastructure of the tumour with the view of the tumour being more or less an organ. Components of the vasculature are already targets for anticancer therapy. Targets in the tumour cells may be hampered by the problem of heterogeneity in the cell population. Therefore research on tumour stem cells or progenitor cells should be another prioritized research area.

A key to develop personalized cancer medicine is methodologies to predict response to therapy. By biomics advanced studies of DNA alterations and expressions of RNAs and proteins are possible on human tumour and normal tissues. This opens up new possibilities to identify and validate biomarkers for tumour response and normal tissue reactions related to treatments. The high complexity in this research area makes bioinformatics and the development of systems biology necessary. Apart from technical platforms biobanks and patient data registries are necessary structures.

The clinical trials successively change in character due to two principal phenomena: the need to include biological questions in the trial design and the more complex multidisciplinarity needed for the patient care. The biological driven clinical trials should be designed to identify characteristics in tumours or normal tissue linked to positive or negative effects of the treatment. Multidisciplinarity aims at optimizing treatment of the patients. The clinical research will in future to a larger extent study interaction of innovative methods in different diagnostic and treatment modalities making the clinical trials still more complex.
The goal for translational cancer research is to innovate care and prevention. For estimation of innovative effects of new diagnostics and treatments structures for observational studies of detailed, population based patients registries are required. Such structures are unique for some countries in Europe and should be used for development of the observational study technique to continuously follow the effects of new innovative technologies introduced in the cancer care.

Patient stratification, diagnostics, treatment and follow/up treatment is set to change dramatically within the next ten years, as medicine will increasingly move towards personalized treatment. Our knowledge of the complexity of cancer will expand exponentially during the same time-period and as a result we will need new ways (1) to handle the complexity of information available and (2) to organise the way in which we carry out research. This will include developing criteria for classification of patients so that each will receive the best available treatment based on current state-of-the-art research. Today, for example, we know that breast cancer may consists of as many as ten different types of cancer, each responding differently to treatment, and we have yet to find out if the same is true for other cancer forms.

Standard operating procedures will need to be harmonized among clinical research centres, and infrastructures such as patient registries, biobanks, structural biology, bioinformatics, as well as others should also be brought into line. Tomorrows cancer research must be coordinated between clinical research to integrate all the diagnostic and treatment discipline used in a concerted action to solve important patient problems

4. Challenges and limitations of European translational research
Oncology is a unique discipline that is increasingly depending on multidisciplinarity. The concept was progressively defined during the 20th century and developed around clinical considerations in order to have surgeons, radiologists, pathologists, radiation- and medical oncologists working together in concord.

Oncologists, internal medicinists and organ specialists have argued for sometimes as to with whom should treatment reside. Moreover, cancer centres have quarrelled with university hospitals as to who is best suited to treat patients. As if these clinical problems were not enough, there is an even a bigger gap between basic and clinical cancer researches, making it next to impossible today, with the exception of a few dedicated comprehensive cancer centres, to systematically translate discoveries into inventions in therapy and diagnosis and to implement the results in routine care. The intrinsic complexity and heterogeneity of oncology, which encompasses many different diseases, research areas and specialties, has been made more difficult by the competition for patient support between the stakeholders.

5. The Comprehensive Cancer Centre
A Comprehensive Cancer Center (CCC) is a facility in which care and prevention are integrated with research and education. The National Cancer Institute in USA sets very high standards of excellence for US CCCs. Criteria for European CCCs are currently being identified by the Organisation of European Cancer Institutes (OECI) as part of the accreditation/labelisation program. The concept of a CCC arose as a consequence of the increasing complexity of cancer activities and increasing need for innovation. The translational cancer research continuum, in which the patients are always in focus, stands at the heart of a CCC where all components of the research process, from basic to clinical to
outcome research and epidemiology, are fully integrated with each other. This structure should ensure that research and implementation of new technologies are adapted to patient care and evaluated in response to research results. Innovation requires a health care of high quality with the latest knowledge implemented in the routine care.

6. The need for critical mass in translational research: Added value of forging a platform of European Cancer Centres

Although we have remarkable resources in Europe no single cancer institution or even country has the critical mass to deliver in all cancer areas. In order to conduct truly innovative science we need proficient sustainable mass in both cutting-edge knowledge and technological platforms. Multidisciplinary science requires multinational collaborations. An example of this is the BIRTH project, which is a truly inter-centre collaboration in translational breast cancer research. This project was unfortunately not eligible for EU funding, since the Commission lacked an appropriate instrument. Today, the complexity in care and research is rapidly increasing and new and expensive infrastructures are being required for modern discovery-driven translational cancer research. Bringing together CCCs and basic/preclinical cancer centres in an integrated network to collaborate and share resources is the only realistic solution to solve the problem of suboptimal critical mass in translational research.

It is the clear wish and intent of the CCCs/ basic and preclinical cancer research centres of Europe to work more closely together in a platform for translational cancer research to optimize the translational cancer research process and increase the global competitiveness.

This fact that has been recently been made clear by the “Stockholm Declaration” (Molecular Oncology), which has been signed by major basic and comprehensive cancer centres form all over Europe. Such an interlinked and articulated platform of cancer centres is expected to provide the following benefits:

It will have the necessary resources and know-how throughout the entire research continuum, e.g. basic/laboratory research, early and late translational research, clinical research, epidemiology, as well as implementation both in care and outcome (population based) research. The platform will provide an essential infrastructure to facilitate rapid advances in knowledge, communication, as well as effective translation of discoveries and programs into practice. Moreover, it will host pilot or developmental research projects and processes, it will standardise treatments and protocols, and will stimulate career development. The latter is fundamental to attract and retain the best scientists in Europe.

It will provide the stability needed to carry out multidisciplinary projects that require flexibility and long-term commitment. The top down structure of the platform will facilitate rapid trans-centre (transnational) communication and sharing of innovation.

It will stimulate the setting-up of joint databases that conform to harmonized clinical informatics infrastructure; support the development and expansion of population databases and other resources such as data safety and monitoring of human subjects. Sharing protocols, and maximize collaborative research opportunities will avoid duplication and fragmentation of resources. The participants will work together to develop a methodology to implement and evaluate innovations by observational studies by means of quality assured, detailed, population based patient registers.
The large number of potential patients available in the entire platform will make possible to implement laboratory and clinical research and early detection technologies into clinical routine care as well as to evaluate the effect of new treatments. The platform may also provide patient access to trials and tumour samples for studies and clinical trials involving rare diseases given the large uptake area (20 x 2-4 million people).

By pooling resources it will be possible to perform validation studies (evidence-based medicine) in research areas which are uncoordinated or too expensive for stand-alone research (molecular pathology or imaging). A platform will have the capacity to host major biomedical research programs in tumour markers as well as to cross reference with population databases (i.e. linking patient subgroups to genetic profiling). It will also harmonize tools, reagents, technologies, protocols, and treatments.

It will be the main cancer research actor for communication with the Commission, with governments of the Member States and other stakeholders. It will provide with a natural partner for the pharmaceutical and biotechnology industry. The Innovative Medicine Imitative (IMI), which is a joint effort by the pharmaceutical industry and the Commission, clearly states that it looks to the scientific community to provide panels of experts in various cancer/related fields. A platform can identify and provide these experts and can orchestrate discussions with multiple national ethical review boards for transnational research projects as required by industry. To foster a long term culture of collaboration between industry and academia.

The platform may be a target for other funders, who wish to increase competition for cancer research money and decrease the fragmentation in funding.

Since each centre within the platform will have a local/regional role it will be possible to take advantage of these existing networks to disseminate new therapies as well as knowledge and technology.

It will speed-up the dissemination of knowledge and information to less developed areas in Europe. It will also stimulate global cancer research collaboration.

It will provide the opportunity of establishing the first pan-European masters program in translational medicine.

It will identify and promote excellence in any given research area or discipline by engaging the best scientists all over Europe.

It will represent a flagship for cancer research in Europe and a pillar of ERA and is expected to have a substantial impact on global collaboration.

7. Measuring innovation: are we on the right path?

Innovation is created in a multidisciplinary culture with enough sustainable critical mass in personal and technological resources through the translational pathway. But creating innovation is not enough; one must also validate the outcome of such research with regards to patient benefit. To create requisites for measuring innovation one need strong population based patient registers. By following patients advanced studies can be performed in outcome research to validate new treatments in care.
8. Sharing innovation: international training and mobility in translational cancer science

Many countries do not have sufficient resources to train cancer researchers and support a high level of preclinical and clinical research. The situation will steadily change for the better in the coming decades for many countries as a result of accelerated economic growth as we currently witness in Asia, South America and newly accessed EU states. More privileged western European Countries will have the opportunity to assist in training talent to meet future needs of these countries and, at the same time, to profit from this talent that cannot be sufficiently supported by their own countries. A Platform for translational cancer research will provide the structure needed for recruiting researchers. This would have a number of advantages.

Instalment of a high quality training program in translational cancer research for foreign PhD students, post-docs and MM/PhDs would mitigate the shortage of qualified cancer research that we are currently experiencing. The program should offer training in all aspects of the translational research continuum. If combined with a matching fellowship program, this would allow candidates to be trained in translational cancer research in more than one of recognized centres. Obviously such a training program would be beneficial for trainees from within the EU.

A well defined translational cancer research platform will have a greater visibility allowing recruitment of high quality students, post-docs and clinicians interested in translational cancer research. A joint evaluation of candidates will improve the selection process and permit recruiting from first rate institutions in other countries with whom we can make arrangements to facilitate return of the investigators after they have gained expertise in research within the European platform. Such mobility of investigators will enhance interaction between other programs supported by the platform. Mobility should not be limited to training of young investigators. Senior research can contribute immensely to integrate and upgrade research on a more advanced level by spending time in another cancer centre. Training given to individual investigators is easy to manage and very effective. This holds true for many of the current European fellowship programs such as Marie Curie and the EMBO. Therefore, such a system can be easily implemented.

9. Structures needed for translational research

Europe has a number of strong cancer centers with resources for basic cellular and molecular cancer biology. Structures which existing centers are willing to share include, but are not limited to:

- Technology platforms for genomics, proteomics, metabolomics, imaging and functional genomics
- Screening facilities for new anticancer agents
- Animal facilities/animal model
- Bioinformatics
- Clinical trial structures for early clinical trials and trials including biological questions
- Structures for pharmacology
- Biobanks for tumour, normal tissues and biofluids
Quality assured patient registries, some population based and useful for evaluation of innovations

Structures for validation of biomarkers – registries of treated patients and biological materials, molecular epidemiology

Structures for biostatistics and epidemiology

Structures for quality of life assessment

Information exchange platform. The cancer research community has already applied for a science in society grant, under the leadership of the Oncology Institute in Milan to set up a sophisticated third generation web portal.

Clinical structures adjusted to research, implementation and evaluation of new diagnostic and treatment methods

10. Implementing a world-class platform of cancer centres

There are many challenging issues associated with designing and implementing world-class infrastructures and among these membership, management, access mechanisms, funding, and legal issues are crucial as these facilities must be cost-effective and have optimal stability so as to facilitate the development of major advances in knowledge and deliver their benefits to society.

a) Membership

Membership should be limited to a small (15-20) number of excellent Comprehensive Cancer Centres (CCC) and Basic/Preclinical Cancer Centres. Criteria for selection must be clearly defined by a Governing Board body. Individual centres are not expected to do all, but must be synergistic both in term of resources and expertise available.

b) Management

The world-class infrastructure should be managed professionally throughout its life-cycle (preparation, construction, and operation). The facility, which will be distributed or virtual, is expected to be constantly evolving giving the multidisciplinary nature of research and will require a great deal of coordination in order to optimize the input of all the stakeholders and stimulate international collaboration and participation.

The platform will be managed by a Director General assisted by an internal advisory board composed of representatives from the centres themselves. There should also be a Scientific Advisory Board (SAB) and a Council composed of representative from funding agencies, the Commission, patient organisations, the industry and legal bodies. The Director General should be appointed for a period of ...years and should be eligible for re-election only once. The SAB should advise the Director General in matters related to scientific priorities and appointments and should assess the impact of the services and set future directions.

Members of the facility should be evaluated every 3 years, but the platform should work with a 5 year indicative scheme.

c) Access

There should be a group that determines priorities concerning access to the facilities. This issue needs to be carefully addressed as the resources are limited. The European Molecular Biology
Laboratory (EMBL) has a good and long standing track-record in dealing with access to infrastructures and the platform should incorporate this knowledge.

Other questions that will need to be addressed include:

How to deal with remote/virtual accesses versus physical access

Who should cover the cost of access?

Should we distinguish between different types of access (access to equipment, data, and training, as well as non-protected and protected research program results)?

How to deal with pre-commercial access, access from third country researchers / organizations

Publishing results (through publishing bodies) or open access to data?

Ownership of data / results?

d) Funding

One of the mayor barriers we foresee in establishing the World-Class infrastructure is the fact that there is no financial framework at the European Union (EU) level that may support the construction or optimal operation of this large facility at a pan-European level. We see the development of the platform in two steps. The first involves the creation of an ERA-NET, while the second will involve the creation of the world-class infrastructure using most likely a variable geometry approach to funding (Member States, the Commission, and perhaps the industry).

e) Legal issues

The platform must have a legal personality recognized by all member states of the European Union. A new EU directive may be required to deal with the legal questions that will arise.

13. Steps towards developing a world-class infrastructure: Role of the scientific community

Transforming the idea into reality will entail the following steps:

Preparation of a programme that includes structuring benchmarking and objective criteria for quality assessment, making a full inventory of research projects and existing technological platforms, as well as identifying key competences and pilot projects.

Engage the whole cancer community by establishing a Forum for discussion with all relevant stakeholders (science policy makers at the Member States level, the European Commission, the European Parliament, the industry, patient organizations, etc).

Mobilize the support of the pharmaceutical and biotechnology sector as well as patient advocacy groups.

Work towards the creation of an instrument to identify, prioritise and fund world-class infrastructures
12. Relationship with existing organisations

Member Countries have grasped the far-reaching value of research infrastructures (RI’s) and through the European Strategy Forum on Research Infrastructures (ESFRI) they have taken the first step towards implementing some of these instruments. Building on the ESFRI list of priorities, the Commission has taken the initiative to support the preparatory phase for the construction of several facilities, and has recently taken a leading role by proposing in the ERA Green Paper the development of world-class RI’s of pan-European interest that should be “integrated, networked, and accessible to research teams from across Europe and the world, notably thanks to new generation of electronic communication infrastructures”. The current ESFRI roadmap is however only a snapshot of what is a continuously developing set of infrastructures throughout Europe, and as a result it is crucial to identify and prioritise world-class infrastructures. The platform will not replace existing research organisations or infrastructures; instead it will work with them to further develop their possibilities. The platform will establish contacts with EATRIS, European Bio-banking and Molecular Resources, INFRAFRONTIER, Infrastructures for Clinical Trials and Biotherapy Resources, Integrated Structural Biology Infrastructure and the European Bioinformatics Infrastructure, to investigate mutually beneficial programs.

The European Organisation for Research and Treatment of Cancer (EORTC) has already set-up an innovative program for excellence in clinical research, the Network of Cancer Institutes (NOCI), which would be a natural partner for organising clinical trails originating from the platform activities. Indeed, the six centres that currently are part of NOCI have clearly indicated that they would like to collaborate on more formalized bases.

The Organisation of European Cancer Institutes (OECI) has through its many members the possibility to disseminate research findings to all the cancer centres in Europe. It has also started an accreditation and labelisation process among cancer centres which could be used for selection and quality assurance of centres.

13. Recommendations

The creation of a world-class platform for translational research among the best comprehensive and basic cancer research centres in Europe will have a major positive impact on the way cancer will be diagnosed, treated and monitored in the near future. To achieve these goals we propose the following recommendations:

Short-term

Create an ERA-NET, a CA, or equivalent funding mechanism, to implement the preparation phase of the infrastructure. Besides addressing management, access, and legal issues, the consortia should deal specifically with scientific pilot activities that will be undertaken by the platform

Long-term

Create a world-class infrastructure to ensure that the patient remains at the centre of cancer research. This will require the creation of a European instrument(s) to fund long-term sustainable infrastructures

Improve collaboration between the Member States, the Commission, and other stakeholders to promote and coordinate translational research activities.
14. List of Participants:

Members of WP 10 of the Eurocan + Plus

Amalric, François
Asante, Asiedua
Autier, Philippe
Barbacid, Mariano
Bartelink, Harry
Baselga, Jose
Filippo Belardelli
Berns, Anton
Blaes, Pascale
Boissel, Jean Pierre
Boyle, Peter
Cerottini, Jean-Charles
de Valeriola, Dominique
Doré, Jean-François
Dunstan, Diana
Eggermont, Alexander
Escher, Gérard
Gissmann, Lutz
Granger, Caroline
Guillemette, Brigitte
Hackenitz, Erica
Kasler, Miklos
Kerr, David
Khayat, David
Labrosse, Elsa
Lindencrona, Jan Alvar
McVie, Gordon
Nowacki, Marek
Overgaard, Jens
Ponder, Bruce
Ringborg, Ulrik
Tursz, Thomas
Veronesi, Umberto
Wiestler, Otmar

Members of the Stockholm group:

Autier, Philippe
Barbacid, Mariano
Berns, Anton
Boulin, Christian
Boyle, Peter
Börresen, Anne-Lise
Caldas, Carlos
Celis, Julio
Costa, Aurora
de Valeriola, Dominique
Eggermont, Lex
Harrsion, Chris
Harrsion, David
Jones, Nic
Kerr, David
Lindencrona, Jan Alvar
McVie, Gordon
Paradiso, Angelo
Ponder, Bruce
Ringborg, Ulrik
Roman, Sergio
Saghatchian, Mahasti
Tursz, Thomas
Van Harten, Vim
Wistler, Otmar