EUROPEAN COUNCIL FOR HEALTH RESEARCH: ILLUSTRATING ITS MAJOR IMPACT ON FUTURE HEALTH RESEARCH IN EUROPE

Case Studies

1. Interconnectiveness of diseases

It is now increasingly recognised that many chronic diseases occur together, particularly in the elderly. Diseases have traditionally been studied by clinical researchers within a single clinical discipline (oncology, cardiology, endocrinology, respiratory medicine, neurology etc.), as there has been no suitable instrument for cross-talk. There are often similar underlying basic cellular and molecular mechanisms between different diseases, so that there is much wasteful duplication of basic research. Indeed, mechanisms that are explored in one disease area may be ignored within a different disease area, yet might be equally relevant.

Cross-fertilisation of Expertise on Ageing

Nowhere is the interconnectiveness of diseases more apparent than in diseases of ageing, which together are likely to extract an increasingly heavy toll on European health budgets over the next decades. There have been enormous advances in our understanding of the cellular and molecular basis of ageing(senescence) and this is relevant to many of the major chronic diseases afflicting European citizens, including chronic obstructive pulmonary disease (COPD), ischaemic heart disease, diabetes, osteoporosis and Alzheimer's disease, all of which are linked to acceleration of the normal ageing process. The cellular and molecular mechanisms involved in cell ageing are now much better understood, providing exciting new targets for drug discovery that may be applicable to a wide range of common diseases. Thus the integration of basic science research discoveries on ageing and application to the different clinical diseases is likely to lead to novel and more effective therapeutic approaches.

Many common non-communicable diseases, including asthma, COPD, ischaemic heart disease, diabetes and multiple sclerosis are due to chronic inflammation, and although the manifestations of these diseases differ, there are many common underlying cellular and molecular mechanisms involved, so that there are common targets and they may be alleviated by similar therapies. By bringing the different clinical disciplines together and making the link with basic science discoveries, there is enormous synergy to be gained.

In addition to the commonality of basic mechanisms, such as ageing, inflammation and abnormal repair between different diseases, medical disciplines share numerous cross-cutting areas such as bioinformatics, systems biology, the '-omic' platforms (genomics, proteomics, transcriptomics, metabolomics, lipidomics, etc.), clinical trial design and statistical analysis that are common to all disciplines.

What can be achieved in the context of the EuCHR?

Cross-fertilisation between clinical disciplines is vital, in order to accelerate the translation of basic science into clinical practice and to efficiently exploit basic science discoveries. This should result in significant cost savings and the more efficient use of research funding in Europe.

2. Personalised medicine:

Personalised medicine is moving us closer to more precise, predictable and powerful medicine—customised for the individual patient. Our growing understanding of genetics is allowing the medical community to provide better diagnosis, safer drug prescribing, and more effective treatment.

Personalised medicine ensures that patients get the right treatment at the right time with minimum cost and maximum efficacy. To achieve this goal, large-scale research needs to take place, incorporating all the stakeholders involved in the disease continuum, including partnerships between the pharmaceutical industry and academia. Cancer provides a good testing ground for personalised medicine as several targeted therapies are already available or are in the making.

Targeted Therapies

Today's suboptimal development of so-called targeted (personalised) anti-cancer drugs leads to rapidly increasing drug costs in the EU. The example of the drug trastuzumab to treat breast cancer patients illustrates the challenges.

Trastuzumab is the prototype of a successful «targeted drug ». It is an antibody directed at the HER2 receptor, which is expressed at abnormally high levels at the surface of breast cancer cells in approximately one in five women with breast cancer. It can stop these cancer cells from growing or even "kill" them with minimal side effects. When applied early on in the disease, in combination with chemotherapy, it reduces the risk of the disease coming back by half. However, one in two women do not benefit from taking trastuzumab due to the ability of some cancer cells to use alternative survival and growth pathways when exposed to the drug.

Large phase III pivotal randomised trials leading to the approval of new, expensive anticancer drugs are carried out by the pharmaceutical industry, currently with limited influence by the academic community in their design and conduct, and with no financial support from governments. The "HERA" trial for example, which led to the approval of early trastuzumab use in Europe, was no exception to this rule: it arbitrarily selected a one or even two-year duration of trastuzumab administration (with the two-year results still pending) and failed in collecting tumour blocks from a large majority of participating women, making it impossible to identify potential biomarkers of "resistance" to the drug in retrospective studies.

The current situation is illogical: four European trials are now being conducted that are mainly financed by governments to explore shorter treatment duration with trastuzumab (3 to 6 months instead of 1 year). These trials will enrol as many European women (e.g. 13,000) as the number entered in the four large initial pivotal trials (e.g. HERA + 2 American trials, and one additional international trial) which led to the "endorsement" of one year of trastuzumab by the Federal Drug Administration (FDA) and the European Medicines Agency (EMA).

Today's situation in Europe is characterised by high drug costs resulting from an arbitrarily long process of drug administration to patients whose tumours contain the "target", but are not necessarily dependent on that target for survival. A more ideal situation will be to have a strong academia-industry-government partnership in Europe that supervises the launch of the practice-changing trials involving "targeted" drugs. This partnership is essential to "impose" better trial designs (the HERA trial should have included a 3 month treatment arm supported by "governments") and much improved translational research (with collection of all tumour blocks and blood samples for biomarker research using today's powerfully high throughput technologies).

What can be achieved in the context of the EuCHR?

The EuCHR will integrate the input of all the actors in health research (researchers, decision-makers, patient organisations, regulators, industry and funders) and encourage collaborations between academia, the pharmaceutical industry, and policymakers in order to ensure that only patients that react to the drug are offered the treatment, thereby saving huge costs. The EuCHR will provide the right forum to discuss in depth the future conduct of large, pivotal 'practice-changing' trials.

3. Rare Diseases

The added-value of pan-European and international co-operations is probably best seen in the area of rare diseases. Expert stakeholders need to collaborate at a transnational level in order to acquire the critical mass, expertise and identify partners, due the characteristic nature of diseases that are rare.

There are between 6000 and 8000 rare diseases and despite their rarity, such diseases affect 6-8% of the population, representing approximately 30 million EU citizens[1]. Research advances in the area of rare diseases can have positive consequences for medical research in general: indeed, rare disease research has already made major contributions to research and treatment discoveries of more common diseases and is at the forefront of innovative therapies and new approaches to medicines, such as personalised medicine. Thus, a platform for collaboration between rare disease patients and more common disease experts to exchange best-practice as this disease develops, would be very beneficial.
The importance of providing research opportunities for rare diseases and cross-talk between biomedical experts can be identified using the example of vascular liver diseases.

Rare Diseases: An opportunity for understanding and treating common diseases

A European consortium for the study of rare diseases, specifically vascular liver diseases, was created in 2001. The consortium was successful in obtaining 3-year funding from the 5th Framework Programme (EN-Vie Project, 2002-2005) allowing for several cohort studies to be conducted. Achievements included demonstrating the role of underlying prothrombotic conditions and suggesting a benefit for anticoagulation. A marked improvement in outcome was shown.

Follow-up to these achievements should have been in developing randomised controlled trials of new anti-coagulant agents on the one hand, and extrapolating the results to common chronic liver diseases on the other. Unfortunately this extremely successful consortium had to dismantle due, to a large extent, to a lack of follow-up funding. It has therefore taken 10 additional years to have preliminary results suggesting that anti-coagulation could actually be of major interest for preventing the complications of other, more common, chronic liver diseases. This could have been achieved within 3 years with a follow-up study by the consortium. Drug companies marketing the new anti-coagulant agents have proved extremely reluctant in supporting randomised controlled trials with their product. Had an integrated structure been present to understand the interest of the field and the potential for translation to common diseases, results would have possibly been achieved faster.

Recent pilot studies suggest a gain in survival of at least 25% with anticoagulation therapy. If this is confirmed, the demonstration will have been unduly delayed by 15 years.

What can be achieved in the context of the EuCHR?

An integrated structure for evaluating research could have supported the consortium in furthering its research advances already made and thus shorten the process by approx. 5 to 10 further years.

The EuCHR will encourage interaction and cross-talk between all disciplines to ensure partnerships are fostered and excellent discoveries are fertilised to reach the patient.

[1] Eurordis, the European Organisation for Rare Diseases, 2012. http://www.eurordis.org/about-rare-diseases

4. Imaging

Imaging aims to identify, grade, and map the expression of important biomarkers at a structural and functional level and from a cellular to a macroscopic scale. Personalised and precision medicines are increasingly becoming the target in biomedical research, and the focus of interest in health-care policy. Treatments are tailored to an individual patient's profile. One of the main thrusts of clinical research will be to identify biomarkers able to characterise a cellular alteration which will lead to subclinical or manifest disease status and/or to characterise a specific reaction to various therapeutic attempts. Imaging biomarkers is particularly successful in treating cancer patients.

Tumour Response Evaluation

Accurate definition of tumour response during the initial phase of treatment is essential for assessing the effectiveness of therapy, for planning further treatment and for predicting patient prognosis. Besides morphologic criteria, the search for specific predictors needs to be addressed. In this sense, there is an increasing interest in quantitative imaging, i.e. imaging biomarkers, as objective indicators of the responses to a therapeutic intervention.

Biomarkers fall into two categories: bio-specimen biomarkers or molecular biomarkers, and bio-signal or imaging biomarkers. Molecular biomarkers are derived through the genomic and protein analyses of fluids or tissue samples. Imaging biomarkers remove no material from the patient, but rather analyse and model signals obtained from the patient using imaging technology.

These imaging biomarkers are highly advantageous: they are non-invasive, spatially resolved and repeatable and are therefore invaluable for early therapy evaluation in cancer patients. Often, invasive reference examinations, such as a biopsy, can be inconclusive, and are non-representative of the whole tissue. Imaging biomarkers may be helpful in determining disease staging and grading and for assessing tumour response, as localised biological information is crucial.

Imaging biomarkers must be validated and standardised before they can be used in routine clinical practice. The validation includes the determination of the accuracy and precision ('reproducibility') of the biomarker and standardisation concerns acquisition, modelling and analysis. Moreover, imaging biomarkers should be completely non-invasive, cost-effective, user-friendly and easy to implement into clinical practice.

The validation, standardisation and qualification of these imaging biomarkers will be a huge step in the accurate and fast evaluation of tumour response to therapy in oncologic clinical trials on solid cancers. Innovative approaches aiming to evaluate cellular, vascular and metabolic response rather than mono-or bi-dimensional changes may be more informative and surely require further investigation. Currently, the majority of European trials do not use these biological markers and are therefore lacking due to a non-optimised trial design.

What can be achieved in the context of the EuCHR?

Important benefits of medical imaging include its non-invasive feature. It also offers global anatomical coverage, offers localisation of the disease process, and can provide the relevant biological measurements using imaging biomarkers. The EuCHR will encourage these discoveries and advancements and incorporate all health stakeholders to ensure these important innovations are realised for the benefit of patients.

5. Sustainability of excellent initiatives

European health research has limitations compared with our competitors, such as the United States, in that access to large numbers of both patients and healthy volunteers with specific characteristics in single centres is difficult. Clinical research, from small studies to large-scale pharmaceutical trials, or research into health service provision is more complex and less representative than it could be because of the number of countries, languages and organisational cultures.

Thus networking and multinational collaborations are essential. Many networks and study groups have fostered the sharing of research ideas and best practices across Europe and have been successful to an extent, but they are often short-lived and uncoordinated. Sustained support for European clinical research focused on and for the benefit of patients, is required. In the area of diabetes for example, short-term efforts have been made to better coordinate research in this chronic disease.

Strengthening European research collaborations to promote innovations and improved care

There are increasing numbers of adults and children with diabetes across Europe (and worldwide). Despite guidelines and consensus statements related to approaches, targets and therapies, across Europe there remains huge variation in the quantity and quality of diabetes-related clinical research and healthcare available for people with diabetes. This variability in research activity and ultimately patient care and our population's health, is a consequence of many factors including the lack of structured networks of interested parties with commonly agreed goals.

The EU-funded Seventh Framework Programme (FP7) project, DIAMAP, charted road maps for successful innovation strategies to tackle the growing problem of diabetes, and repeatedly mentioned as roadblocks the need for registries of diabetes patients, networks of specialist researchers, access to biobanks and human biological material, and the need for more standardised evidence-based treatment guidelines. This project, while important, was only a first step and sustainable efforts need to be made to move forward and promote a healthier population in Europe.

A European Platform for Clinical Research in Diabetes is needed. Such an initiative can for example support the provision of a centralised infrastructure to ensure quality assurance and educational back-up for diabetes research, and facilitate access to data and biological samples by providing a uniformly agreed and ethically approved infrastructure to permit sample and data-sharing.

Moreover, investment by and participation of industry and SMEs should encouraged, as well as facilitate access to large numbers of research subjects and to scientists from sub-specialties. Processes for dissemination of research findings should be streamlined through a dedicated communication channel.

The creation of such a platform, incorporating such a market approach to clinical research, has the potential to drive down costs and to increase the competitiveness of Europe as a clinical trial location.

What can be achieved in the context of the EuCHR?

The EuCHR will identify research strengths and opportunities to be integrated into cohesive, competitive and sustainable structures which will facilitate and promote collaborations between academia, patient organisations, the pharmaceutical and biomedical industry, and policymakers.

6. The translational research gap in chronic diseases

Chronic, non-communicable diseases are a challenge of epidemic proportions. In the current financial turmoil, many European countries have adopted drastic measures that have seriously affected access to care for chronic non-communicable disease patients. Yet, the economic crisis should be used as an opportunity to promote a healthier Europe and explore new and innovative ways of tackling chronic diseases. Chronic Obstructive Pulmonary Disease (COPD) is an example of a chronic disease that needs better pan-European research efforts.

Strengthening European research collaborations to promote innovations and improved care and treatment of patients

There is a global epidemic of COPD which has now become one of the most prevalent diseases in Europe, with over 10% of men and women affected. Recent surveys have suggested a life-time prevalence of over 25%, as survival from other disease has improved. COPD is associated with progressive airway obstruction, leading to increasing symptoms of breathlessness and reduced physical activity, which together have a major negative impact on quality of life. COPD is also characterised by acute exacerbations, usually triggered by viral or bacterial infections, which have now become one of the most frequent causes of emergency hospital admission.

Once patients have been admitted to hospital with an acute exacerbation their long-term prognosis is worse than that for many common cancers. COPD has a high mortality in Europe (an estimated 300,000 deaths in Europe each year) and is the only common cause of death that has increased markedly over the last three decades. The high prevalence and morbidity of COPD results in high direct and indirect medical costs, with millions of working days lost each year across Europe. Despite all these concerns COPD has been relatively neglected. This may be due to the fact that it is linked to smoking, although even quitting smoking has little impact once the disease is established. Furthermore, it is now increasingly recognised that COPD also occurs in non-smokers, although this form of the disease is poorly understood. COPD is a disease of poverty and has the largest social gradient between rich and poor of any disease known.

It is now recognised that many other diseases occur together with COPD and these co-morbidities have a deleterious impact on the long-term prognosis of the disease and enormously complicate its management. The commonest cause of death amongst COPD patients is cardiovascular disease, including ischaemic heart disease and cardiac failure. Metabolic diseases, such as diabetes, metabolic syndrome, osteoporosis and renal disease, are far more common in COPD patients than in smokers who do not have airway obstruction. Some of these comorbid diseases may be worsened by systemic inflammation, due to overspill of inflammatory mediators from the lung. The second most common cause of death in COPD patients is lung cancer and the prevalence of lung cancer is up to 6-fold higher in COPD patients than in normal smokers. The high prevalence of comorbidities associated with COPD means that more interaction between physicians of different disciplines is needed.

There are no effective therapies for COPD that slow its progression or reduce mortality. We also have no effective therapies to treat exacerbations. This very likely reflects that fact that we have no effective and safe anti-inflammatory therapies, as the inflammation of COPD fails to respond to corticosteroids that are so effective in many other inflammatory diseases, such as asthma. All of this demands a greater investment in translational research to bridge the gap between clinical studies and basic science. This involves a multi-disciplinary approach and working with specialists in across different disease areas to understand the issues of comorbidity.

What can be achieved in the context of the EuCHR?

The EuCHR would have the capacity to bring an interdisciplinary approach to studying the co-morbidities, involving cardiologists, endocrinologists, oncologists and others, working together to exploit discoveries in basic research to develop personalised medicines relevant to COPD patients with different co-morbidities.

7. Cross-fertilisation of expertise with non-biomedical fields

Europe needs to foster a pioneering culture, where curiosity-driven research thrives and traditional research boundaries are blurred.. Experts in health research should seek new partners in typically non-health sectors, such as ICT, nano-technology and engineering. Moreover, opportunities for partnership with scientists working in animal and plant help should be promoted.

Several modern emerging diseases and epidemics originated from animals (pigs, chicken, cows…). However to date, the biomedical community in Europe has not succeeded in creating major research collaborations with the veterinary disciplines. The concept of a 'One Health' programme could encourage cross-talk and translational research programmes with experts from human, animal and plant health in order to accelerate discoveries in this field.

A 'One Health' Programme

A scientific assessment should be carried out at EU level on the state-of-play of current and possibly future infectious human-animal diseases, assembling the best experts from the biomedical and veterinary fields. The H1N1 and H5N1 viruses, for example, are similar diseases and further research is needed to be better understand the spreading of the disease (especially cross-border transfer of the disease) as well as how to improve treatments and efficiently manage the diseases at national level.

Moreover, further investigation needs to take place on reactions to epidemic diseases, stemming from animals, and public health responses to treatments, dosage and vaccinations for the population.
A more strategic harmonisation of managing such an epidemic event, including communicating the outbreak of such a disease to the public should be examined, especially in the EU where the movement of people, goods and services is encouraged. A strategy for the management of transportation of patients as well as contaminated materials also needs to be discussed amongst all disciplines.

What can be achieved in the context of the EuCHR?

The EuCHR could create the environment for cross-talk and networking between human, animal and plant health specialists and create a strategy for 'One Health' research opportunities. Such a platform can help put into action a comprehensive approach to such 'crisis management' in the EU, assessing the potential dangers for human health if there is an outbreak of an animal infectious disease and proposing adequate organisation of national healthcare systems should it be required.