REPORT OF FEAM'S SPRING CONFERENCE 2013

28-29 May 2013
Hosted by the Irish Academy of Medical Sciences at the Royal College of Surgeons in Ireland (Dublin)

In opening the conference, Professor Jesus A. F. Tresguerres (President of FEAM) noted the significance of the occasion for FEAM, celebrating its 20th Anniversary, hosted by its youngest member at a time when Ireland has the responsibility for the Presidency of EU Council. The programme, covering EU regulatory issues, personalised medicine and the future of clinical research, was designed to explore new science and associated strategic issues in order to maintain the momentum created by FEAM in links with the European Commission and European Parliament on some critical issues for informing public policy development. Throughout the conference, participants would be invited to identify opportunities and priorities for future FEAM work. This report summarises the perspectives contributed by the individual presenters, together with some of the general discussion. Further detail can be found in the accompanying slides[1] and cited publications.

KEYNOTE LECTURE: THE FUTURE OF MEDICAL RESEARCH

Professor Damian O'Connell (Global Head of Clinical Science, Bayer and former Chairman of Molecular Medicine Ireland) contributed a personal view on why medical research matters in Europe as a basis for better healthcare and how the opportunities and challenges should now

[1] Slides presented in Dublin are available on the *Activities* page at www.feam.eu.com.

be addressed in four critical, inter-related, areas: (i) Funding; (ii) Creativity and innovation; (iii) Translational efforts; and (iv) Clinical research.

(i) Funding

Approximately 30% of the global funding invested in medical research comes from the public sector but Europe is perceived to be lagging behind in its support for basic research in the life sciences. Compared with the USA, the EU is regarded as having done too little to encourage "bottom-up", investigator-led research proposals, and in Horizon 2020 the EU faces a major challenge to provide the needed infrastructural support and funding for hypothesis-driven research. Pharmaceutical companies are research-intensive in their spending and employment, and this intensity is expected to be maintained according to future projections, but pharmaceutical innovation is becoming increasingly dominated by the USA. Hence, there is an additional challenge for Europe to sustain and support the continuation of pharmaceutical industry R&D together with extension of the biotechnology sector to contribute to pharmaceutical innovation.

(ii) Creativity and innovation

Current indicators, including Nobel Prizes, scientific publications and their citations, are seen as imperfect measures of creativity and innovation but there is some evidence that the impact of EU research is relatively less than the USA, exacerbated by less EU specialisation in the most dynamic research disciplines in the basic life sciences, although there are some great examples of EU research success. A key challenge is to tackle the large differences in research productivity between EU countries to ensure consistently high quality and productivity throughout the EU.

(iii) Translational biomedical research

There is increasing recognition of the need to support research translation to clinical innovation. This requires attention to many factors, discussed throughout the FEAM conference, including large-scale data collection, progression of platform technologies, extending understanding of drug development science outside of companies, and adoption of new models for open innovation to involve universities and smaller companies in establishing proof-of-concept. Again, there are some useful EU activities, perhaps particularly the Innovative Medicines Initiative (IMI) but much more is needed to tackle the threat of "reverse innovation", whereby the EU would become dependent on healthcare products created by new competitor, developing, economies. The challenge for improving translational research is dependent on continued investment in basic research but also on an increase in clinical and basic researchers in active partnership and on bringing industry and academia together. There may be value in developing new, not-for-profit, organisations that can bridge the sectors.

(iv) Clinical research

As has been noted previously by FEAM[2] and others, there are significant impediments to the efficient conduct of clinical trials by academia in the EU. Many of these problems are also encountered by pharmaceutical companies who, in consequence, expect to reduce trial

[2] FEAM Statement, Opportunities and Challenges for Reforming the EU Clinical Trials Directive: an Academic Perspective, August 2010.

recruitment in the EU. As discussed throughout the conference, there is consensus that change is urgently necessary in the EU framework for regulation of clinical trials. The proposed reforms are likely to be helpful in reducing administrative burden but there is still much to do. Major bottlenecks for companies in European clinical research include difficulties in access to patients, high costs and variable quality infrastructure. Proposals (for example by ECRIN) to address obstacles by integrating clinical research capacity are sensible but, in addition, research must be promoted by identifying and providing needed skill sets and by reshaping the regulatory framework.

Professor O'Connell concluded that there is scope to do considerably better by sharing good practice in funding, performing and using medical research, building on optimism engendered by the European Commission's acknowledgement of the need to improve the research environment. Wide-ranging discussion raised several issues that would also receive further attention throughout the meeting:

- How should pharmaceutical innovation be measured and rewarded by fair pricing policy and fair market access? These fundamental questions need joint exploration by industry with regulators and payers.
- What should the EU do to redress the balance of companies moving to the USA (and new competitor locations)? There is need to extend the current good practice that can be found in some clinical research centres to build critical mass, translational capabilities and awareness of company needs.
- How could clinical trials on novel medicines be improved? There are contradictory expectations: regulators wanting progressively larger trials but payers judge that results from formal trials may be little relevant to the real world. The current phase 1-4 trial paradigm may no longer be fit-for-purpose.

SESSION ON REGULATORY ISSUES

Proposal for EU Regulation on Clinical Trials

Dr Marita Kinsella (Chief Pharmacist, Department of Health and Children, Ireland and Chair of the European Commission Working Party on Pharmaceuticals and Medical Devices) provided an update on the status of the European Commission's 2012 proposal for a Regulation. As mentioned by Professor O'Connell there was widespread agreement that the previous Clinical Trials Directive created problems of inconsistency and excessive burden for researchers and sponsors. Recasting the legislation as a Regulation would expedite direct application into national law with potential for achieving greater harmonisation but with less flexibility to accommodate variations in Member State legal systems and culture. The European Commission's proposal was now under active consideration by the European Parliament and Council of Ministers. Among issues receiving close attention were:

- Practicalities for the proposed modification of trial authorisation and approval procedures, in particular relating to timeframes for unified scientific, technical and ethical reviews (with tacit authorisation if timelines are not met) and the responsibility for the reporting Member State to undertake scientific assessment on behalf of the others.

The remit of ethics committees is still controversial; although not prescribed in the Regulation, being regarded as a national responsibility, some in the medical community hold the view that they should be more closely specified and managed at the EU level (see presentation by Professor Smith for further elaboration).

- Protection of subjects and nature of informed consent in vulnerable research cohorts, for example incapacitated subjects or minors. There is particular controversy relating to emergency situations where it is not always possible to obtain informed consent for research. Currently Member States vary in their support for emergency research and there is a concern that harmonisation may act to deter such studies.
- Simplification of safety reporting, in particular allowing latitude for those sponsors with insufficient resources to report SUSARS in the normal way.
- Specification of obligations of sponsors with regard to documentation, monitoring and reporting, with introduction of the concept of co-sponsorship with division of responsibilities.
- Transparency of data – although there is widespread agreement that trial results must be made available and accessible, there is controversy as to how fast this should be required. The European Parliament request that a summary of results should always be published within one year of the end of the trial may be challenging in some circumstances.

Two main points emerged in discussion. First, as the reform of the clinical trials framework is proceeding at the same time as the reform of the authorisation of medical devices, it is vital to ensure complementarity of principles and requirements. This consistency will be particularly important when evaluating companion diagnostics and therapeutics in personalised medicine, discussed subsequently in the conference. Secondly, the issue of risk-proportionality in the assessment and monitoring of clinical trials remains controversial. The proposal in the Regulation for a classification based on two categories of risk seems to some to be insufficient. However, rather than introducing additional categories in law, which may become complex and inflexible, it might be better to ensure EU guidance on implementation for all Member States to adopt the Regulation in as risk-proportionate manner as possible.

New Draft EU Data Protection Regulation and medical research

Mr Billy Hawkes (Data Protection Commissioner, Ireland) reviewed the status of the new draft Data Protection Regulation (DPR), currently in negotiation with EU Council and Parliament with possible implementation by 2015-2016. The DPR is based on the general principle of the fundamental right to data protection and free movement of personal data accompanied by principles for data minimisation, transparency of requirements, strengthened individual right of access to own data, accountability of the data controller and processor, privacy by design, data portability, data security and “right to be forgotten” (relevant to data retention policy). In determining the lawfulness of data processing, there was a strict definition of consent, “freely given, specific, informed and explicit”, with burden of proof allocated to the data controller. With regard to health research, data may only be processed if “Necessary for health purposes” and subject to conditions in Article 81 of the DPR or “Necessary for historical, statistical or scientific research purposes” and subject to conditions in Article 83. These different rules lead to

potential variation in national provision for handling health data; Article 81 allows scope for specific requirements in national law whereas Article 83 does not.

In consequence, use of personal data for research would only be permitted where anonymised data are not sufficient for the purpose intended. If personal data must be used, identifiers should normally be kept separate. However, uncertainties in interpretation of the rules are further compounded by differing views on the place of pseudonymised data and by recent major amendments proposed during the lead Parliamentary committee review of the proposed Regulation that would render research using personal data very much more difficult to pursue. In discussion it was agreed necessary to find a balance between the public good of medical research and the protection of the individual. This requires the medical community to reinvigorate its efforts to explain the value of research to parliamentarians and other stakeholders in order to prevent the introduction of further impediments to the use of patient data in research. The value of research is exemplified and the issues surrounding the DPR addressed in detail in the Statements by FEAM and its partners[3].

Tobacco control – the role of price

The initial aim of the EU Directives relating to tobacco control was to ensure the proper functioning of the internal market but the EU has now developed a major role in regulating tobacco fiscal policy. Professor Luke Clancy (TobaccoFree Research Institute, Ireland) reviewed the major principal effects of tobacco consumption in terms of disease (primarily, coronary heart disease, cancer, COPD and cerebrovascular disease, although smoking is also implicated in many other disorders) and additional health-related impacts associated with addiction, poverty and inequality. A recent publication quantifies the benefit of previous action in Ireland to control smoking[4].

Evidence collected in Ireland over the period 1985-2006 demonstrates that increased price of tobacco is correlated with decreased consumption. Price, via taxation, is perceived as the most important tool to prevent smoking. Although further increase in price might be deemed inflationary, this consequence could be avoided by removing tobacco from the Consumer Prices Index. Further, although increase in price might be expected to stimulate smuggling of tobacco, a coherent strategy throughout the EU that combined pricing with public health measures to promote cessation of smoking would be more effective in controlling demand in all Member States. The TobaccoFree Research Institute has coordinated the EU Framework Programme 7-funded project “Pricing Policies and Control of Tobacco in Europe” (www.ppacte.eu) and recommendations for alignment of tax rates across the EU were timed to coincide with the current review of the Tobacco Products Directive which is strengthening the rules on how tobacco products can be manufactured, presented and sold (see http://ec.europa.eu/health/tobacco/products/revision).

[3] Joint Statement of the Healthcare Coalition on Data Protection, January 2013; FEAM/Wellcome Trust Briefing, Realising the societal benefits of health research through the Data Protection Regulation, February 2013.

[4] Stalling-Smith et al. Reductions in cardiovascular, cerebrovascular, and respiratory mortality following the National Irish Smoking Ban: Interrupted Time-Series analysis. PLoS ONE 2013 8 (4): e62063. doi: 10.1371/journal.pone.0062063

PERSONALISED MEDICINE

The European Commission Perspective

Dr Karim Berkouk (DG Research and Innovation, Health Directorate) defined personalised medicine in terms of a medical model using molecular profiling for tailoring the right therapeutic strategy for the right person at the right time. Personalised medicine is a rapidly emerging area for the EU with implications throughout the innovation cycle, potentially great benefits for patients, and with large economic impact across both the public and private sectors. Advances in personalised medicine offer the promise of better informed medical decisions, better targeted therapies with higher probability of efficacy, less adverse reactions, earlier disease intervention (accompanying a changing focus from treatment/cure to predict/prevent), and healthcare cost containment. There are multiple implications for science:

- Fundamental research – redefinition of disease taxonomy and new molecular understanding; challenges to gather, analyse and use 'omics data; development of biobanks with associated challenges for sampling, standardisation and harmonisation of data.
- Preclinical research – increasing use of biomarkers for diagnosis, risk estimates, prediction and monitoring; technical challenges associated with evaluating functional significance of genetic variants, interpreting large data sets, integration of biomarker with other information.
- Clinical research – challenges for incorporating stratification of patients within current clinical trial methodologies and development of adaptive trial design and other new statistical approaches.

The European Commission has already invested about one billion € in collaborative research enabling the development of personalised medicine, including validation of 'omics and epigenomics and methodologies for patient stratification, clinical informatics and health technology assessment. Examples of major initiatives include METAHIT (metagenomics for human intestinal tract) and ENGAGE (European network for genetics and genomics epidemiology) and IMI[5], the large public-private precompetitive partnership exemplified by U-BIOPRED, a project to identify and use biomarkers in predicting respiratory disease outcomes. The EU is also very actively involved in wider collaborations, for example the International Cancer Genome Consortium and International Human Epigenome Consortium, to define shared strategic research goals, maximise resources, reduce duplication, and share data and standards. As noted in previous discussion, this is also an important time for establishing the supportive regulatory framework for personalised medicine, in particular to ensure the relevance of the In Vitro Diagnostic Medical Device Regulation to support development of companion diagnostics. Practical challenges for simultaneously developing diagnostics and therapeutics were emphasised in discussion. For the future, personalised medicine is regarded as a key priority to tackle in Horizon 2020, moving away from the previous narrower disease-specific focus in funding programmes and towards the problem-oriented approach, inviting

[5] Further detail on the application of the IMI (and other partnerships) to personalised medicine was published recently by the European Alliance for Personalised Medicine in a report from the Irish Presidency conference, March 2013.

solutions proposed by the research investigator (and as recommended by Professor O'Connell).

Personalised medicine – a project of the German National Academy of Sciences Leopoldina

Professor Philipp U Heitz (Department of Pathology, University of Zurich) provided additional evidence to reinforce many of the points made by Dr Berkouk with regard to the drivers of change for healthcare systems (population ageing, increasing chronic disease and costs, new methodologies) and the opportunities presented by the advances in science and technology underlying personalised medicine. Biomarkers are of tremendous potential: the challenge is to compile all the information from genetics, epigenetics and environmental factors into net risk analysis and then link this with phenotype for polygenic diseases. Significant advances are being made in developing and using tools for comprehensive molecular analysis (including epigenomics, proteomics, lipidomics, metabolomics etc.) and in evaluating large amounts of data, leading to improved understanding of human biology and disease mechanisms, potentially delivering an unprecedented quality of healthcare via risk analysis-prediction-prevention. Although the Leopoldina's project is still in progress, various challenges for delivering personalised medicine were becoming clearer:

- Research and technology – as observed previously, there are issues for validating biomarkers, linking risk analysis and phenotype, developing drugs with companion diagnostics and setting standards for redesigned clinical trials.
- Undesirable developments based on unsound science – for example there are multiple issues associated with provision of consumer genomics through the internet[6].
- IT – a likely bottleneck in integrating various types of data and supplying the data on time, in the right place and form for supporting research and clinical practice.
- Ethical issues – for example relating to informed consent for research, genetic privacy, equity and access.
- Political issues – for example relating to intellectual property protection, regulation of testing, protecting against genetic discrimination, reimbursement of genetic services and use of genomics in non-medical settings.
- Education and training – for interpretation of the results of molecular analysis, handling of sensitive personal data, bioinformatics, and genetic counselling as part of the support and care of patients.
- "From base pairs to bedside" – faster integration of scientific advances into healthcare, including diagnostics, counselling and computation.
- Broader societal issues associated with the impact of genomics knowledge – including issues for understanding human evolution and identity, genetic determinism and individual responsibility.

Advances in personalised medicine are likely to exert a continuous technological and structural shift in healthcare systems, lasting perhaps for more than 20 years according to some recent

[6] Discussed in detail in the EASAC-FEAM report, Direct-to-consumer genetic testing for health-related purposes in the European Union, July 2012.

estimates. Success of personalised healthcare will need to be measured in terms of value to patients, healthcare systems, the medical industry and insurance companies. The issue of cost-benefit was also raised in discussion and there is room to do much more to estimate the costs as well as the benefits for society, insurers and others.

Improving outcomes of lung disease through personal medicine

Professor N Gerry McElvaney (President of Irish Academy of Medical Sciences) presented a series of case studies on lung disease to illustrate how combining insight from laboratory and clinical studies is providing new understanding of pathology and the therapeutic options for the translation of personalised medicine.

COPD - is a disease characterised by airflow limitation that is not fully reversible, that is usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases. The standard GOLD classification reveals that COPD is actually a group of conditions based on physiological symptoms and there is growing interest in reclassifying using combined physiological and biochemical assessments. Alpha-1 antitrypsin (A1AT), a serine protease inhibitor, and acute phase protein has a function in helping to protect lungs from neutrophil elastase on the respiratory epithelial surface. Clinical and animal model data now support a role for neutrophil elastase in emphysema, leading to therapeutic approaches based on modulating the protease-antiprotease balance. A1AT deficiency can lead to COPD due to the reduced levels of A1AT in the lungs, which leads to the proteolytic destruction of alveolar tissue. A1AT replacement was approved as a therapy in the USA based on its biochemical effect and initial clinical evidence for a positive effect on FEV1 decline was contentious. More recently, studies have used Computed Tomography to measure progression of emphysema (lung density), enabling reasonably-sized trials, with pulmonary function assessed only as a secondary endpoint, providing the first definitive proof for a clinical endpoint affected by A1AT replacement.

Screening in Ireland has defined the prevalence of A1AT deficiency[7] and testing indicates that, of the more than 10,000 patients screened, about 30% possess at least one variant of the A1AT gene. The diagnostic advances in A1AT phenotyping led to the hypothesis that a subset of PiMZ variant siblings (where M is the normal AAT allele and Z is defective) are at an increased risk for COPD because of additional genetic and environmental factors. Results presented from the first family-based case control study have confirmed that PiMZ carrier individuals who smoke are indeed at increased risk of COPD.

Cystic fibrosis (CF) – results were presented for a Gene Therapy protocol using AdCFTR (Adenovirus-Cystic Fibrosis Transmembrane Conductance Regulator) infused into the nose and lungs of nine subjects. CFTR mRNA was found transcribed, and CFTR protein detected immunochemically in the nose and lung. However, work with the adenovirus gene therapy approach was stopped after one patient showed a systemic/local inflammatory reaction with increased Interleukin-6 levels. Subsequent studies evaluated A1AT aerosol therapy in CF and have also explored the implications of the gender difference in CF (females more seriously

[7] Carroll et al. Prevalence of alpha-1 antitrypsin deficiency in Ireland. Respiratory Research 2100 12, 91.

affected) in terms of the effect of oestrogen on inflammatory responses in CF bronchial epithelium. A related series of biochemical studies has helped to understand the earlier colonisation by *Pseudomonas aeruginosa* in females with CF, the link with mucoidy and worse clinical phenotype, and provide a good illustration of how translational medicine is providing new ways of looking at lung disease[8].

A patient perspective was contributed by Ms. Orla Keane (representing the Alpha One Foundation, a patient organisation who are members of the Irish Platform for Patients' Organizations, IPPOSI), who had been diagnosed with A1AT deficiency and has participated in lung disease clinical trials. Her personal experience of disease history and symptoms exemplified the uncertainty felt prior to diagnosis and the empowerment experienced by participants in clinical trials, notwithstanding the big commitment involved. This very positive account from a patient of the value of clinical trials strongly augmented the other perspectives articulated in the conference from those who organise, fund, perform and regulate clinical trials or use the results, collectively testifying to the crucial importance of the EU continuing to build a supportive environment for clinical research.

Personalised medicine and genomics – the health and health impact

Drawing on analysis provided for the UK House of Lords Report on Genomic Medicine, Professor Timothy Aitman (MRC Clinical Sciences Centre, London) reinforced the points from previous speakers about the scientific advances now made possible by the dramatic and continuing reduction in costs of genomic sequencing. Although the past decade has been a landmark era for human genetics, the translation to healthcare has often been judged slower. However, three case studies were presented to make the case that personalised medicine is actually already affecting clinical practice:

- Gefitinib and non-small cell cancer. Initial trials struggled to demonstrate efficacy overall but separating treatment groups by EGFR mutation status enabled clear distinction between responders and non-responders and allows targeting of treatment.
- Ivacaftor and cystic fibrosis. Understanding of CFTR potentiation in CF patients with G55ID mutation has led to new insight with dramatic potential for improving therapy[9]. Unfortunately, this case study also illustrates the very long time that may be taken in translating from biology to therapeutic effect – a time that must be shortened.
- Aspirin and colorectal cancer. A recent finding shows that among patients with mutated-PIK3CA colorectal cancers, regular aspirin use was associated with better survival compared with other patients[10]. If the finding is replicated, this significant impact of an established drug shows the potential for future stratification of patients.

[8] Further information on the link between Pseudomonas colonisation, inflammation in CF airway epithelium and CFTR was published recently by Oglesby et al. Journal of immunology 2013 190, 3354-62. CFTR was also discussed in the subsequent presentation by Professor Aitman.

[9] Ramsey et al. for the VX08 Study Group, A CFTR potentiator in patients with cystic fibrosis and the G55ID mutation. New Engl J Med 2011 365, 1663-1672.

[10] Liao et al. Aspirin use, tumor PIK3CA mutation and colorectal-cancer survival. New Engl J Med 2012 367, 1596-1606.

In order to translate these advances into routine clinical practice it is necessary to establish commissioning structures to test for subsets of single gene defects in complex, common diseases (a topic discussed in further detail in the presentation by Professor Villari). Three further examples showed how new sequencing platforms can be expected to advance understanding and care:

- Familial hypercholesterolemia – the present cost of genetic testing is a barrier to screening but next-generation sequencing is facilitating the detection of pathogenic mutations. Results were presented from validation, prospective and population cohort studies to assess sensitivity, speed and cost of the new assays. One other advantage is that a genetic mutation screening test can be combined with a pharmacogenetic test (for SLC01B1, a known statin toxicity gene) to guide management of therapy and reduce side effects.
- Breast and ovarian cancer – current algorithms and guidelines for screening are complex and expensive and often applied idiosyncratically outside the major centres. Use of new platform technologies increases throughput and reduces cost without impairing performance.
- Neonatal intensive care – proof-of-concept has been demonstrated for the use of rapid whole-genome sequencing for genetic disease diagnosis in neonatal intensive care units.

These examples illustrate how medical practice may be transformed by genomics much faster than has often been assumed. Discussion focused on what else was needed to facilitate the early impact of genomic medicine: one potential obstacle is lack of public funding for up-front costs of the technology and another is the concern on how to tackle incidental findings arising from whole-genome sequencing.

Personalised medicine: a paradigm shift for patients care

Professor Florent Soubrier (Genetics Department, CHU Paris-GH Pitie Salpetriere) added more examples of technological breakthroughs with the use of ‘omics in exploring complex disease but also cautioned about the challenges for integrating all of the determinants of the phenotype. A paradigm shift may be expected – from probabilistic strategy for a group of patients to a deterministic approach, defining the appropriate treatment for an individual patient. It was also advised important to adapt the degree of precision to be reached, to the disease to be treated. For example, antithrombotic therapy for leg fractures (clotting status), severe infection (immune status, pharmacogenetics) and cancer (tumour genome). Unnecessary sub-classification could lead to fragmentation of targets with over-interpretation, and wastage of resources.

Further insight was provided from work in cancer genomics in pursuit of the goal to identify “driver” genes which promote tumour growth, to understand their role in signal transduction pathways to be targeted by chemotherapy. Companion biomarkers to predict response or resistance to therapy are essential to guide targeting, minimise unnecessary toxicity and control costs. Recent clinical evaluation was reviewed for anti-HER2, anti-EGFR, anti-BRAF, anti-ALK, PARP inhibitors and imatinib. The classification of driver genes into 12 pathways and

three core cellular processes conferring growth advantage provides a coherent basis for large-scale tumour molecular analysis. Recent progress on the identification of treatment-associated tumour mutational changes from exome sequencing of serial plasma samples was also reviewed.

Turning to the importance of pharmacogenetics for personalised medicine, the example of abacavir was presented. A hypersensitivity reaction in a small proportion of subjects receiving the nucleoside analogue reverse transcriptase inhibitor for the treatment of HIV infection is associated with HLA-B*57:01 and the genotype frequency in different populations has been characterised. Protein structural studies are now elucidating the mechanism of action mediated by HLA-B binding abacavir.

In conclusion, it was reiterated that 'omics are invaluable tools, but progress of personalised/precision medicine will often be incremental despite technological breakthroughs and implementation must be adapted to the consequences of the disease. Integrating all relevant data is the challenge for systems biology. Other practical challenges for cancer treatment were raised in discussion. How would the technological advances impinge on clinical trial design and what are the implications of the finding that early sampling of a tumour may not be indicative of the genomic status at time of intervention?

Public health implications of predictive genetic testing for complex diseases

Professor Paolo Villari (Sapienza University of Rome) introduced another note of caution, observing that genetic screening criteria must be compatible with public health basic screening principles (in particular, the WHO 1968 criteria). Predictive screening for complex diseases differs in important respects from the simpler, single gene disorders, because the co-existence of other determinants imparts a distinction between the analytical and clinical validity of a test.

In clarifying what kind of evidence patients (and clinicians and policy-makers) want from a genetic test, there might be merits in designing a randomised clinical trial: "genetic test plus intervention" versus "traditional surveillance". But this would be difficult and the inherent problems in establishing clinical validity/utility are compounded because rapid advances in genomics makes it difficult to update evidence-based clinical practice guidelines and because there is usually only limited information about the prevalence of genetic markers in different populations, and on the interaction between multiple factors.

Professor Villari recommended that the ideal scenario for introduction of a genetic test into clinical practice is sequential: devising the test is followed by collection of clinical evidence and understanding of the clinical context, evaluation of cost-effectiveness (for the general population and for those with a family history) and agreement on professional recommendations and guidance (whether in specialised services or General Practice). By contrast, in the real world a genetic test may be introduced immediately into practice with little evidence for effectiveness or cost-effectiveness, possibly driven by private organisations and with relatively little genetic counselling. In order to improve the current situation, there must be more health economics analysis and more education for professional development of

physicians in the generation and use of genetic information. The National Prevention Plan for Public Health Genomics in Italy, that appears to be the first in the EU, is focusing on health technology assessment of genomic tests currently on the market or in development, together with the promotion of education for health professionals and the general public. Concomitantly, a study led by Italian universities with support from FEAM is broadly assessing the state of public health genomics in Member States by seeking information from government departments, professional bodies and the academies of medicine.

For the future, predictive genetic testing for complex diseases can be expected to find a valuable place in screening programmes and in the primary care setting if supported by an evidence base to substantiate appropriate use in a safe, effective and cost-effective manner. Discussion explored how best to educate physicians – distance learning programmes are helpful and further support from scientific societies is warranted – and the public, where the media should be involved. The public also need to be consulted further on whether and what they want to know about their genome.

FUTURE OF CLINICAL RESEARCH

Clinical trials: the EU perspective

Dr Karim Berkouk (DG Research and Innovation Health Directorate) set the scene by describing current developments in the EU and those that may be expected as part of Horizon 2020. Within Framework Programme 7, €400 million has been spent on clinical trials between 2010 and 2012. The annual spend has increased 5-fold since 2007; 400,000 patients have been recruited during this time. The rationale for this Framework Programme 7 effort is the EU added value – achieving critical mass in patient numbers, accelerating recruitment rate and drawing on consolidated clinical expertise – together with the contribution to innovation, where a clinical trial is the ultimate validation step for innovation in health research. As well as the increasing investment in clinical trials during the lifetime of Framework Programme 7, there has been a trend to covering broader topics in the Calls, to encourage more investigator-driven clinical trials (urged by both academia and industry). The greatest number of trials supported is in phase 1 but with large numbers also in phase 2. There are more trials in the infectious diseases area > brain > cardiovascular > cancer > metabolic/endocrine, the greatest number relating to pharmaceuticals and advanced therapies > devices and diagnostics. Examples of major initiatives include COGS (Collaborative Oncological Gene-environment Study), the world's biggest genotyping consortium and ECRIN (European Clinical Research Infrastructure Network), providing supportive networks and infrastructure to overcome clinical research fragmentation. The adoption of the Clinical Trials Regulation, as discussed in previous sessions, is regarded as highly important in helping to improve the clinical research environment for Horizon 2020, when taken together with the increasing momentum for closer interaction between pre-clinical and clinical research, developments in trial quality control and professionalism, and integration of health technology assessment, all points previously discussed in this conference.

The health challenge for Horizon 2020 covers a broad area for understanding health, well-being and disease; preventing, treating and managing diseases; supporting active ageing; and developing new methodologies and databases. Clinical trials will be a crucial part of Horizon 2020 in responding to these challenges while building on progress already made in personalised medicine, translational research, cost-effectiveness evaluation, private sector linkages and experience in global cooperation, again pervasive themes throughout the conference. Discussants enquired about the advisory processes for setting priorities in Calls for proposals and emphasised related issues for attaining quality, transparency and accountability in priority-setting in EU clinical research. As a representative of all medical disciplines, FEAM's approach is highly relevant to Horizon 2020. Good link with the InterAcademy Medical Panel allows communication of the global health perspective in Europe.

The risk-based approach

Sir Michael Rawlins (President of Royal Society of Medicine and Chair of UK Academy of Medical Sciences Regulatory Review), in providing a perspective on recent UK developments, emphasised that clinical research has both broad significance – for patients and the public as well as for clinical scientists and the life sciences industry – and broad scope encompassing, for example, experimental medicine and epidemiology as well as clinical trials. In the UK the combination of clinical trial authorisation procedures, national ethics approvals and NHS governance approvals has led to what is now widely seen as disproportionate regulation. In reinforcing points made by previous speakers, Professor Rawlins observed that the EU Clinical Trials Directive has lacked clarity, been implemented inconsistently and suffers from lack of risk proportionality, illustrated by the excessive burden for assessment and monitoring required for an additional investigation using an established product for an established indication. Fundamental revision of clinical trial authorisation is needed in the long-term; for the short-term it is important to ensure authorisation procedures are risk-based and applied consistently in order to rebuild clinical researcher confidence in the system. The draft Regulation is regarded as a substantial improvement on the Directive but there is continuing concern that it still lacks sufficient clarity (such that it will still be liable to differences in interpretation and implementation) and its enactment is taking too long.

The generic ethical approval system provided by the UK National Research Ethics Service works reasonably well but the problem is that there are also many specialist ethics approval bodies (acting according to type or location of the research investigation). The remedy requires that these specialist groups be brought together into one coherent system. The NHS research governance procedures have created a major obstacle for clinical research with delays and lack of timelines, duplication of checks, inconsistent advice and interpretation, and variation in performance and process. The Academy's Regulatory Review Group had recommended that the current multiple layers and overlapping responsibilities are reformed by bringing the relevant activities for ethical review, NHS research governance and clinical trial authorisation (linked with the work of the current Competent Authority) within a national Health Research Authority. Some progress is being made to achieve this, for example by merging many of the specialist ethics bodies and piloting streamlined NHS research governance approvals. In discussion there was widespread agreement:

- That the framework for authorising clinical trials must be made simpler, clearer and less costly, otherwise it will deter innovation.
- That there must be better access, for patients and payers as well as for researchers, to the results of clinical trials, including negative studies.
- That patients should be more involved in informing the options for regulatory reform.
- That progress is needed, and European Commission support required, in developing novel methodologies for clinical research.
- That FEAM can exercise a key role in bridging between the national and EU activities, advising on policy and strategy at all levels.

The patients' perspective

Ms Eibhlin Mulroe (Chief Executive Officer, Irish Platform for Patients' Organisations, Science and Industry, IPPOSI) described the IPPOSI strategy (www.ipposi.ie) to bring patients' perspectives to clinical research in Ireland, to deliver on the vision for prompt uptake of new and developing therapies. This includes actively influencing policy that impacts on research and access to innovative therapies. A survey in 2009 of public attitudes in Ireland demonstrated considerable support for clinical research but also a need to do better in furnishing information about what participation in research means for a patient. IPPOSI has recently been assiduous in expanding the information available for the public about involvement in clinical trials (www.clinicaltrials.ie) as well as continuing its work to provide patient perspectives on new EU legislation. IPPOSI has also been active within the recently-founded European Patients' Academy in Therapeutic Innovation (EUPATI, www.patientsacademy.eu), developed by the IMI. EUPATI aims to provide information to patients about medicines R&D, helping patients to become effective advocates and advisers in medicines research. There are increasing opportunities for patients to be part of the relationship between researchers, regulators and industry, for example in informing the issues for research priorities, trial design, collecting post-marketing data, identifying and understanding end points for quality-of-life measures and assessing value. Developing patient advocacy might also be expected to lessen public mistrust of research and, hence, improve patient recruitment and the faster generation of meaningful data.

There are other significant opportunities for qualified patient advocates to work with regulators at the national and EU levels and in every research ethics committee, as well as in contributing to policy development in health technology assessment. EUPATI is important in providing resources to inform patients and the public at large, to generate tools for patient advocates and to establish Certificate Training Programmes for Patient Ambassadors, Patient Journalists and Patient Trainers. By 2017, EUPATI aims to have a coordinated platform with training sources, education and information in multiple languages, good practice guidelines on patient involvement and an extensive expert network across Member States. FEAM would be welcomed as partners in this work.

Clinical research with a focus on psychiatry/neuroscience

Professor Cyril Hoschl (Director of Prague Psychiatric Centre and FEAM Scientific Adviser) used the example of anti-psychotic treatment to show how approaches to research, and the therapeutic options available, had progressed very significantly during the past 60 years. However, clinical research focused on psychiatry and the neurosciences is now in crisis. Research has slowed because of interrelated methodological problems and ethical and bureaucratic restrictions. This slowing of innovation, despite tremendous progress in basic research in the neurosciences, has resulted in the departure of pharmaceutical companies from the area and worse access to treatment for patients.

Among the methodological problems are: high placebo response and the failure of active treatments to demonstrate significant efficacy; high rate of subject discontinuation; and the questionable generalisation of trial results to patients in clinical practice. Analysis of all published randomised anti-depressant trials reveals that the placebo response rate has increased progressively during the last 30 years; a similar conclusion comes from analysis of acute clinical studies in schizophrenia. The explanation for the increasing placebo rate and decreasing drug efficacy response is that patients are increasingly recruited into studies with less severe symptoms, for example by excluding patients with suicidal thoughts, co-morbities and co-medication. The impaired signal detection, related to patient characteristics allowed in the study design, is compounded by other overlapping factors relevant to outcome measures and rating, sample size and study length.

When considering the impact of ethical and bureaucratic constraints, it is important to realise that, according to recent estimates[11], the cost of brain disorders in Europe is now nearly €800 billion/year, €1,550 per capita. More than 160 million people are affected, contributing about one quarter of the total DALY, more than any other group of medical disorders. There is no evidence for any improvement in this burden of disease since the previous assessment in 2005 and it is likely to worsen in consequence of the ageing European population. The total funding of brain research in Europe, about 1% of the annual cost of brain disease, appears relatively low by comparison, for example, with cancer research. Brain diseases do not represent a sufficiently high priority for politicians, the media and the general public, and this impedes fast and fair access to novel treatment.

The declining psychiatric drug pipeline can be attributed to multiple factors: to the low public sector research funding and limited public awareness of brain disease, but also to the difficulties in clinical evaluation and in pricing and reimbursement in an era of cost containment, lack of standardised resources, in particular disease registries, and the time-consuming nature of guideline implementation, all compounded by the rapidly escalating cost of drug development (9-fold increase in the last 40 years, across all therapeutic areas). In these circumstances, the broader bureaucratic restrictions imposed by the Clinical Trials Directive have had high impact on research in psychiatry. If CNS clinical research is to be revised, then the reform of the clinical trials framework discussed by previous speakers must be addressed, together with a range of other challenges for: developing valid animal models;

[11] Gustavsson et al. on behalf of the CDBE 2010 study group, Cost of disorders of the brain in Europe 2010. European Neuropsychopharmacology 2011 21, 718.

clinical biomarkers predictive of therapeutic outcome and clearer specification of these outcomes; collaboration and networking between academia, research funders, industry, patients and policy-makers; new genetic tools to provide insight in psychiatry; and the application of novel basic cellular and molecular techniques to select targets for drug discovery and development. Progress must also be made in understanding psycho-social factors and their interaction with biological factors, in agreeing a scientific basis for the classification of mental disorders and in ensuring high standards in psychiatry throughout the EU. It is suggested that FEAM and its academies can play a vital role in analysing these multiple issues and encouraging the scientific community to bring about change. Discussants noted how increased research funding would be needed across many relevant disciplines in the social and biological sciences and even where considerable investment had already occurred – in the neurosciences – there was still need for improved connectivity with translational medicine in order to understand the functional consequences.

Clinical research with a focus on cardiovascular diseases

Professor Juan Tamargo (Department of Pharmacology, School of Medicine, Universidad Complutense, Madrid) described how atherosclerotic cardiovascular diseases are the main causes of death in the EU, incurring current healthcare costs of nearly €200 billion/year. Costs are projected to increase significantly in the EU, and globally, despite many advances in cardiovascular medicine and the availability of evidence-based guidelines to manage care[12].

The majority of cardiovascular deaths are preventable at the population level through lifestyle, environmental and structural changes to reduce risk factors. For example, nine modifiable risk factors account for 90% of first heart attacks worldwide. However, there is still substantial room for improvement in public health to reduce risk factors, based on current knowledge about exercise, diet, smoking, blood pressure control and management of weight, lipids and diabetes. Although a "polypill" (combining aspirin, folic acid, generic statin and three blood pressure drugs) might prevent up to 80% of heart attacks, it becomes increasingly difficult for pharmaceutical companies to develop innovative agents to compete with the established, effective generic drugs. Non-adherence to prescribed drugs is also a problem of epidemic proportions.

Professor Tamargo reviewed several major disease areas in detail, ongoing priorities in the European Society of Cardiology observational research programme:

- Hypertension – illustrating the triple paradox. Although it is easy to diagnose, it often remains undiagnosed. Effective drugs are available but quite often the patients does not follow treatment or blood pressure remains uncontrolled.
- Acute heart failure – a major burden to healthcare systems, representing the leading reason for hospitalisation in patients older than 65 years, but treatment has not changed

[12] The Fifth Joint Task Force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice. European guidelines on cardiovascular disease prevention in clinical practice (version 2012). European Heart Journal 2012 33, 1635-1701.

much in the last 25 years. There have been many failed pharmacological targets and it is a continuing challenge to identify what is critically important[13].

- Atrial fibrillation/cardiac arrhythmias – there has been recent progress in understanding this major public health problem, including its association with stroke. Some new oral anticoagulants (for example, direct thrombin inhibition, Factor Xa inhibition, and vitamin K inhibition) are showing better efficacy against stroke and systemic embolism than the warfarin standard, but with the potential for more risk of bleeding.

Significant progress is also being made implicating various DNA polymorphisms in the variable outcomes of drug therapy, highly relevant to the issues previously discussed in the session on personalised medicine, and likely to contribute to the development of better cardiovascular drugs and to ensure their use in a safe and effective manner.

In summary, in order to improve the cardiovascular health of all Europeans, while reducing cardiovascular disease deaths, more must be done to clarify the principal contributors to mortality and morbidity, promote healthy behaviour throughout the lifespan, identify gaps and opportunities in R&D, better understand pathophysiology and introduce better drugs to the market. These conclusions stimulated wide-ranging discussion on the identification of criteria for primary and secondary prevention, understanding optimum healthcare delivery mechanisms (through general practice or as specialist provision) and interpreting risk factors by comparing populations – for example the Mediterranean Member States have relatively low coronary heart disease but high stroke rates.

A call for action to strengthen health research capacity in low and middle income countries

Professor Detlev Ganten (IAMP Executive Committee and President, World Health Summit) summarised the analysis and recommendations from the recent IAMP Working Group (www.iamp-online.org). Currently, 90% of global research investments address the needs of 10% of the world's population and it is vitally important to strengthen capacity worldwide to commission, conduct, communicate and use research. Although many other bodies, including UN agencies, have worked on this problem, global organisations have been created in support, and some progress has been made (for example by the European and Developing Countries Clinical Trials partnership), nonetheless much more must be done, systematically and at the various levels, country, research institution and individual investigator. Among the current challenges for low and middle income countries are:

- Lack of coordination between initiatives.
- Particular emphasis on market-oriented aspects.
- Little infrastructure left behind when specific programme funding ends.
- Data collected for international research may not reach or benefit the country of origin.
- Failure to increase the quality and number of researchers and productivity of research.
- Lack of political will and low public understanding of the importance of research.

[13] Tamargo T & Lopez-Sendon J, Novel therapeutic targets for the treatment of heart failure. Nature Reviews Drug Discovery 2011 10, 536-555.

Weak research in disease endemic countries is often the single most important rate-limiting factor to achieving health priorities. The growing health problems require urgent action, for example to tackle emerging and drug-resistant infection, the impact of climate change, demographic and epidemiological transitions, in particular urbanisation. Wide-ranging recommendations are presented in detail in the IAMP publication, proposing political action at the country, regional and global levels to draw attention to the current deficits and to engage with decision-makers and other stakeholders to support priority-setting. A commitment to research capacity strengthening must be included in all sustainable development strategies alongside increased funding and the inception of high-quality research partnerships, and be accompanied by measures to assess and monitor responses. As part of these partnerships, FEAM and its academies can play an important role in improving health worldwide. This point was amplified in discussion to suggest that FEAM should help bring the IAMP recommendations on global research capacity strengthening to the attention of the EU Institutions.

The penumbra of thalidomide, the litigation culture and the licensing of pharmaceuticals

Sir Peter Lachmann (University of Cambridge and FEAM Scientific Adviser) began by describing the history of the thalidomide disaster, responsible between 1957 and 1961 for more than 10,000 children in 46 countries born with deformities. In consequence of this disaster, testing for teratogenicity became universal for drugs to be used in pregnancy, the licensing for drugs became much more rigorous, lengthy and expensive, and public tolerance of risk for prescribed drugs declined to what is judged to be an unrealistic level. As further unintended consequences, drugs have become ruinously expensive, the drug sector is now dominated by large companies and common diseases, and litigation has led to drugs withdrawn from the market for no adequate reason.

The drug development process encompasses assessment of safety, efficacy, drug metabolism, purity and consistency: the necessity for all these is not in dispute. Furthermore, prospective, randomised trials after licensing provide valuable information and it is not suggested that this process be changed. The problem is that, as described by previous speakers, the cost per new drug (including cost of failure) has increased very greatly, and is expected to continue doing so, accompanied by declining R&D productivity (despite the spectacular advances in medical science), exacerbated by an increasingly cautious regulatory system. The Cooksey report published in the UK in 2006[14] recommended ways to bring drugs to market faster, including using conditional licensing, but no action was taken by government. More recently, Empower, a lobby group formulated the Halpin Protocol[15] to facilitate faster and more efficient access to new medicines, and this is beginning to attract public and parliamentary support.

Professor Lachmann proposed that phase 3 trials – accounting for 50% of total drug development costs despite the drawback of using atypical populations as described by

[14] Cooksey D, A review of UK health research funding. HM Treasury 2006.
[15] Halpin Protocol 2013;

previous speakers – should be abolished to cut costs and time to market. Post-marketing surveillance would then be employed to monitor both efficacy and side effects. The disadvantages would be that some drugs would fail after licensing and some unforeseen effects would occur, but these already happen to an extent. Abolition of phase 3 trials would itself need to be trialled, potential patients would need to be fully informed of the risks and uncertainties and the management of liability and indemnity would need to be explored. These issues are discussed in further detail in a recent publication[16]. A government-funded, insurance-based system might be feasible by analogy, for example, with the US Federal Government indemnification of vaccine companies or the various no-fault insurance schemes for medical malpractice. Broader action to tackle the present litigation culture should require proof of direct causality before compensation is due but should be accompanied by action to ensure that national health systems are adequately financed to provide necessary care for all, including those who have suffered drug side effects.

Discussion focused on potential practical problems associated with abolition of phase 3 trials: the implications for large-scale drug manufacturing if the current development timelines are shortened; the need to ensure research-intensive healthcare systems are capable of detecting late side effects; the difficulty of proceeding beyond conditional licensing unless there is an appropriate biomarker as indicator of efficacy. There is, however, widespread support for the view that the present position cannot be afforded, may be delivering unhelpful information from artificial trial populations, and must be revisited.

Ethics committees: looking forward

Professor David Smith (Royal College of Surgeons in Ireland) addressed a range of issues concerning the roles and responsibilities of Research Ethics Committees (RECs), the impact of the Clinical Trials Regulation and the potential for expansion of the remit. In Ireland, there is no central governance of RECs and multiple applications may be required for a research proposal covering different sites. REC functions are broadly conceived to cover Protection (of research subject, researcher and sponsor), Advice (to researcher), Education (about ethical issues and their legislation), Research Quality (to be scientifically sound) and Conciliation (between investigators and participants). However, the Clinical Trials Regulation could be perceived as acting to marginalise RECs, by removing their role to assess scientific soundness, assigning their specification to the Reporting Member State, and allowing insufficient time for the ethical assessment of research proposals. Apart from these challenges, there are other potential issues to consider in expanding REC remit:

- Monitoring of research – in addition to the current task of reviewing research proposals. This expansion is connected with the involvement of RECs in upholding research integrity but there may be resistance from researchers and there is a practical impediment of lack of resources.
- Audit of other clinical work – ethical considerations should apply to all medical practice but RECs deal only with research and exclude audit studies.

[16] Lachmann PJ, The penumbra of thalidomide, the litigation culture and the licensing of pharmaceuticals. Quarterly Journal of Medicine 2012 105, 1179-1189

- Composition and effectiveness of RECs – the increasing complexity of data sets and advances in data mining have considerable data protection implications that pose new challenges for RECs. Should there be specialised RECs? Member States vary in their requirements on REC composition, particularly in terms of research specialists and lay members. These differences have resulted in large variations in REC working practices and there would be merit in establishing common requirements together with training of REC members.
- Categories of research not involving medicinal products – Member States currently vary in whether or not they cover other types of human research. There needs to be a common management framework.
- Responsibility – Member States vary in defining who RECs are responsible to and whether there is an appeal mechanism after making a negative decision.

In summary there is seen to be need for a fundamental debate on what kinds of changes are desired for further harmonisation of RECs – as part of medical research governance – and how international research can be facilitated. The suggestion that these changes should be made at the EU level and not the country level is controversial. Other practical points were raised in discussion. For example, should RECs have a role in determining the level of risk-dependent proportionality for a study? Should RECs have a role to monitor (and ensure) publication of trial results? This would be difficult, in requiring sustained REC follow up to a study. Harmonisation of RECs between Member States may be contentious because of different ethical perspectives, for example on stem cell research, but there could at least be a common objective to agree on what REC training should be provided. Will coherence in REC functions within a country be easier to achieve than between countries? Not necessarily, because of the magnitude of the reform required to deal with existing structures and assumptions, but a start can be made by agreeing use of common research proposal evaluation criteria.

Future directions for FEAM

During the course of the conference, various proposals were made for future activities by FEAM. In addition to the points made earlier in this report, suggested priorities for collaboration included:

- FEAM has significant strengths in its links with the European Commission. It would now be opportune to stimulate further dialogue with the national academies of medicine to ascertain their objectives and deliverables for informing national and EU policy and to share awareness of what is achievable.
- There is shared interest in increasing systematic interaction between FEAM and IAMP (and through IAMP to the M8 Alliance) to help build critical mass, bring global issues to the attention of the EU Institutions and ensure that relevant FEAM outputs are used at the global level.
- It is timely to develop new models to collaborate with industry on topics of mutual interest in clinical research. The current proposal by FEAM for a Forum to bring together all relevant stakeholders received broad support and the vital scoping work should now be initiated.

- There would also be significant value in acting in concert with other bodies (for example, ECRIN) to tackle issues for policy development and coordination for national-EU clinical research infrastructure.

Brussels, September 2013

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Since 1993, **FEAM**'s mission is to promote cooperation between national Academies of Medicine and Medical Sections of Academies of Sciences in Europe, to provide them with a platform to formulate their collective voice on matters concerning medicine, biomedical research and public health with a European dimension, and to extend to the European authorities the advisory role that they exercise in their own countries on those matters. Our vision is: (1) to underpin European biomedical policy with the best scientific advice drawn from across Europe, through the FEAM network of Academies representing over 3000 high level scientists from the whole biomedical spectrum; (2) to improve the health, safety and wealth of European citizens through research by promoting a nurturing, creative and sustainable environment for medical research and training in Europe. FEAM's strength lies in its member Academies that give it the authority to provide an EU-wide scientific opinion on the European medical science base and evidence to underpin European biomedical policy. The FEAM Academies represent the following EU Member States: Austria, Belgium, Czech Republic, France, Germany, Greece, Hungary, Ireland, Italy, Netherlands, Portugal, Romania, Spain, United Kingdom. Observers include the European Academies Science Advisory Council (EASAC –the European network of Academies of Sciences) and the InterAcademy Medical Panel (IAMP –the global network of Academies of Medicine).

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