Report of the 2014 FEAM Spring conference

Hosted by the Romanian Academy of Medical Sciences

12 and 13 May 2014, Bucharest

INTRODUCTION

The 2014 FEAM Spring conference brought together the member academies, other leading scientists from a range of disciplines, and representatives of the European Commission, patient groups, research funders, industry and Member State governments. The agenda comprised some important topics for One Health, for the future of health research and for encouraging mobility during medical education: there are highly significant scientific advances and societal priorities that underscore the continuing importance of addressing critical issues in these areas. The FEAM conference was held alongside the IXth "Academician Nicolae Cajal" symposium[1], allowing the sharing of perspectives and informal interaction with many younger Romanian scientists.

FEAM continues to expand in size, with academies from Croatia and Switzerland joining the membership at this meeting. FEAM is also striving to continue expanding in stature, based on excellence in science and effective linkages across the biomedical community and beyond. As the presentations and debates during this conference amply demonstrated, there are many opportunities and challenges for FEAM in pursuit of its mission to promote scientific cooperation and to advise policy-makers about matters concerning human and animal medicine, biomedical research, education and health. This report summarises some of the main points: further detail is provided in the slides of the presentations.

[1] Full programme: http://www.adsm.ro/media/dms/PROGRAM%20FEAM-CAJAL%202014_LOW%20RES.pdf

SESSION ON ONE HEALTH – HUMAN, ANIMAL AND ENVIRONMENTAL HEALTH

Co-chairs: Professor Jesus A. F. Tresguerres (Past-President, FEAM; Member, Spanish Royal National Academy of Medicine; Professor of Physiology, Complutense University of Madrid, Spain) and Professor George Griffin (Foreign Secretary, UK Academy of Medical Sciences; Infectious Diseases Division, Department of Cellular and Molecular Medicine, St. George's Hospital Medical School, UK).

The topic of One Health is of long-standing interest for FEAM and its member academies[2] and following the discussion in Bucharest, FEAM issued a Declaration on priorities for One Health[3].

One Health: An EFSA perspective (slides)

Dr. Franck Berthe (EFSA, Parma, Italy) observed that, according to WHO data, 70% of infectious diseases in humans have their origins in animals. Some of these diseases have serious socio-economic, as well as public health, impact. For example, a 2012 World Bank report estimated the total cost of SARS as up to US$ 50 billion and BSE as US$ 10 billion. The longer the delay in understanding the links between exposure and clinical signs in animals and exposure and clinical signs in humans, the higher the costs in health care and disease control – exemplified by analysis of the Q Fever outbreak in the Netherlands[4].

It is vital to gain better understanding of the implications of the animal-human interface and drivers for changes such as in animal production systems.. As an illustration, more intensive dromedary camel farming in the Arabian Peninsula is potentially important in the dissemination of the Middle East Respiratory Syndrome coronavirus (MERS-CoV)[5], although the definitive epidemiological evidence is still awaited.

From the EFSA perspective, it is important to do more to focus on mechanisms of transmission, recognising the inherent complexities, to inform risk assessment as a representation of reality. Case studies were reviewed for:

- Schmallenberg virus[6], where EFSA-ECDC collaborated until the zoonotic potential of the disease could be considered negligible risk. Data collection and analysis was used to model scenarios for the spread of the disease based on knowledge of the vector species, and to forecast potential risk. In preparing for the unexpected, there is a continuing imperative to collect data on the distribution of vectors in all Member States and this requires a network of expertise across the EU.

[2] For example, discussed at the Spring Conference in Rome, 2011, and reported in detail in the Italian Journal of public health: http://ijphjournal.it/issue/view/407
[3] Bucharest One Health Declaration: http://www.feam-site.eu/cms/docs/publications/OneHealth/OneHealthDeclarationBucharestMay2014FINAL.pdf
[4] http://www.efsa.europa.eu/en/topics/topic/qfever.htm
[5] For further discussion see http://www.ecdc.europa.eu/en/healthtopics/coronavirus-infections/Pages/index.aspx
[6] 2013 update of the epidemiological data is on http://www.efsa.europa.eu/en/supporting/pub/429e.htm

- Influenza A virus, integrating epidemiological and molecular data and developing methodological influenza risk assessment framework (IRAF) capable of assessing the pandemic potential of new influenza viruses or viral subtypes emerging in animals[7] (see also presentation by Penttinen).
- Bovine TB, modelling[8] may lead to improved understanding of the ways in which different factor combinations and interactions influence occurrence, surveillance outcomes and control efforts; it provides a conceptual framework and forecast the impact of different interventions.

The case studies all illustrate the importance of partnership between veterinary and public health sectors. The presentation called for increased data sharing and collaboration across disciplines as part of an open risk assessment process, promoting a multi-disciplinary, multi-sectoral and multi-regional approach to risk governance As emphasised in discussion (and subsequent presentations), it is also important to appreciate the large and growing impact of loss of biodiversity on future risk.

Rabies as an illustration of the One Health concept (slides)

Professor Paul-Pierre Pastoret (Vice-President, FEAM; Member, Belgian Royal Academy of Medicine (ARMB), Belgium; Scientific Advisor, World Organisation for Animal Health (OIE), France) highlighted the interconnectedness of environmental, animal and human health, exemplified by rabies, one of the first diseases chosen jointly by OIE, WHO and FAO to illustrate the One Health concept. There are an estimated 70,000 human deaths each year, many of them children bitten by dogs.

Rabies is a negative single stranded RNA virus from the complex genus of lyssaviruses, responsible for several epidemiological cycles: urban rabies (linked to dogs), wildlife rabies (different virus biotypes in mammal species) and aerial rabies (linked to bats), with spill-over between the cycles.

Vaccination against rabies is the best way to protect public health and to prevent the often underestimated suffering and death in domestic and wild animals, including endangered species such as the Ethiopian wolf and African wild dog. Terrestrial rabies could be eliminated by vaccinating at least 70% of dogs, as recommended by WHO (if accompanied by stray dog control according to OIE rules), and most vaccination campaigns manage to achieve this coverage.

The development of the recombinant vaccinia-rabies vaccine has been very successful, when released into the wild, to vaccinate foxes. During discussion, it was noted that generally the use of vaccinia-based virus preparations for human vaccination has not been successful, perhaps because of immune system differences. The question was also asked –

[7] [7] Development of a risk assessment methodological framework for potentially pandemic influenza strains (FLURISK) http://www.efsa.europa.eu/en/supporting/pub/571e.htm

[8] [8] Conceptual framework for bovine tuberculosis http://www.efsa.europa.eu/en/efsajournal/pub/3711.htm

would it have been possible to develop the vaccinia-based rabies vaccine for wildlife today, because of regulatory obstacles to GMO release?

Human infection with avian influenza A (H7N9) virus in China: implications for preparedness and response in Europe (slides)

Dr. Pasi Penttinen (ECDC, Sweden) reviewed recent knowledge about influenza A (H7N9), a novel subtype, first detected in China in March 2013, found to be non-pathogenic in poultry but causing severe flu in humans[9]. Analysis of Chinese CDC data indicates a mortality of about 35%, with highest rates in elderly males. Transmission to humans is mainly from infected poultry, especially in high-density bird markets[10] and there have been only 13 clusters of human-human transmission (and no sustainable human-human transmission). Closure of the live bird markets in Guangdong and Zhejiang appeared to be effective but further evidence is needed to substantiate the association of intervention with impact and, as raised in discussion, to determine if the virus is present in poultry products.

Two main disease scenarios are currently contemplated: (i) continuing as previously, as a zoonosis with occasional human infection from direct exposure, and (ii) pandemic potential with increasing human-to-human transmission. ECDC threat assessment indicates that risk to transmission in the EU is currently low, but imported cases are possible although there is no legal poultry trade with China and it is not yet known if migratory birds could play a role in transmission.

It is important for the EU to have the surveillance capacity to detect this subtype. Potential options to reduce the risks in Europe include action on importation (continuing trade measures on poultry imports and advice to EU citizens travelling in China), managing transmission (contact-tracing for airline passengers and post-exposure chemoprophylaxis) and increasing pandemic readiness (reviewing pandemic preparedness plans and ensuring vaccine production capacity in Europe although there are presently no European countries engaged in H7N9 vaccine development).

In conclusion, although the H7N9 threat is currently confined to China, flu epidemics continue to be unpredictable so that international surveillance is essential and pandemic preparedness must not be weakened.

Emergence of the Nipah virus: a lesson on One Health (slides)

Other Asian experience with emerging viruses has also been very instructive, exemplified by the case study of Nipah virus presented by Professor Lai-Meng Looi (Co-chair, InterAcademy Medical Panel (IAMP); Member, Academy of Sciences of Malaysia; Professor of Pathology, University of Malaya). Nipah virus emerged in Malaysia in 1998 on pig farms, as a human

[9] ECDC information on epidemiology and risk assessment is on http://www.ecdc.europa.eu/en/healthtopics/avian_influenza/Pages/index.aspx

[10] G. F. Gao, *Influenza and the live poultry trade,* Science 2014 344, 235

acute febrile encephalitis with high fatality, preceded by outbreaks of respiratory illness in pigs. Initially mistaken for Japanese encephalitis, the Nipah virus, a new genus of Henipavirus, was isolated from patient CSF in 1999 and demographic analysis confirmed transmission by close contact with pigs. There were 265 cases in total in this outbreak, 105 deaths, and the estimated direct plus indirect costs were assessed as US$ 450 million (mainly the impact on pig farming).

Landmark findings included: identification of pig-human transmission; prevention of human-human transmission by rigorous barrier nursing; disease characteristics of short incubation period and high mortality were followed in the longer term by unique relapsing encephalitis, the virus targeting endothelium and neurons, leading to severe vasculitis. The natural host was identified as the Malaysian flying fox in 2002. Because of anthropogenic deforestation in SE Asia and severe haze and drought in 1997 there was failure of flowering and fruiting in plantations and jungle with consequent migration of the fruit bats to orchards, contiguous to pig farms, and onward transmission of the virus.

Some important lessons have been learned from the Nipah outbreak: the damaging effect of delay to act (partly because of the misdiagnosis as Japanese encephalitis) and the need to be ready for newly emerging pathogens in the health and agriculture sectors; the importance of sharing surveillance information from human, animal and wildlife sources (and developing expertise in wildlife disease surveillance) and of international collaboration; the need for government to be proactive, for example in compensating for threatened livelihoods and to improve public understanding of the issues, including environment management, for One Health. As highlighted in the discussion, the Nipah outbreak taught one other important lesson – emerging pathogens may have significant social and economic impact.

Comparative medicine, a key element of the One Health concept

Professor Nicolae Manolescu (Member, Romanian Academy of Medical Sciences; Corresponding Member, French National Academy of Medicine); Professor of Veterinary Medicine, University of Agronomic Science and Veterinary Medicine of Bucharest) reviewed the contributions made by Romania, particularly in research centres in Bucharest, Cluj, Iasi and Timisoara, to comparative medicine. Comparative oncology connects human and veterinary oncology, supports new specialisms in environmental oncology and food oncology, and covers activities in four main areas: (i) comparative aetiology, diagnosis and therapy, especially in companion animals, and with regard to their role as bio-sentinels for cancer; (ii) identification of causative factors, biotic and abiotic; (iii) quality control for “eco” foods to reduce cancer-inducing risk factors and (iv) specialised consulting for human and animal patients in terminal stages of cancer, to improve life quality. Taken together, these activities can help to support the objective to reduce the incidence and impact of cancers in Romania: by clarifying and mapping the main chemical and environmental carcinogens and by improving the quality of life of humans and pets suffering from cancer.

Professor Manolescu also provided examples of comparative medicine relating to zoonoses in Romania, particularly the reservoir of infection in companion animals. Especially significant in Romania are trichinellosis, Leptospirosis, visceral Leishmaniasis and Borreliosis. Detailed epidemiological study of hepatitis E has revealed 5 genotypes globally – often common in the environment yet not usually perceived as a major clinical problem.

In support of points made by previous speakers, it was emphasised that human and veterinary clinicians, together with epidemiologists and ecologists, must work together to identify causes and to minimise the effects of zoonotic diseases.

Environmental health in rare cancers: the example of sarcoma

Professor Bernard Charpentier (Vice-President, FEAM; Member, French National Academy of Medicine; Professor of Medicine and Honorary Dean of the Medical Faculty, Past-Head of the Department of Nephrology, University of Paris Sud 11; France) presented slides on behalf of Professor Jean-Yves Blay (Member, French National Academy of Medicine; Medical Oncology, Centre Léon Bérard, Lyon, France) to continue the discussion on environmental oncology, describing the role of exogenous factors, particularly those associated with rare cancers.

Projections of increasing cancer incidence, the association with societal development, and the changing spectrum of incidence in countries such as France (355,000 new cases in 2012), are stimulating the search for environmental factors. Quantifying the net contribution made by environmental factors depends on whether the definition encompasses behavioural factors: according to WHO, 15% of all cancers are attributable to the environment, including the workplace setting. Carcinogens may operate by many different biological mechanisms, there may be multiple risk factors and a complex sequence of pathology. This has led to increasing interest in the "exposome", the sum of all cancer inducing factors and to a focus on critical windows of exposure, low-dose effects and epigenetics. A necessary emphasis on translational research is required to link basic, clinical and population sciences.

Rare cancers are not so rare: accounting for 22% of total cancer prevalence (in the EU27) and often exhibiting poorer long-term survival than the commoner cancers. There are particular problems associated with late or incorrect diagnosis, lack of access to therapy, few available disease registries and tissue banks, and limited clinical research insight. The Framework Programme 6 Network of Excellence Conticanet[11] was an initiative to create critical mass to overcome lack of data, data fragmentation, the heterogeneities of methodologies and approaches. Conticanet analysed incidence and mechanism of sarcomas and aggressive connective tissue tumours, mapping geographical distribution across the EU relative to employment and level of social deprivation. Such research helps to understand the complex aetiology of environmental factors in rare cancer as well as correcting the previous underestimates of the burden of rare cancers. In discussion, the comparative roles

[11] Conticanet, Connective Tissue Cancers' Network to integrate the European Experience in Adults and Children, see ftp://ftp.cordis.europa.eu/pub/lifescihealth/docs/cenpr103_en.pdf

of genetic, environmental and behavioural factors were considered further and it was noted that environmental factor primary prevention can be particularly cost-effective.

Diagnosis and surveillance of infectious diseases in wildlife (WildTech) (slides – abstract)

Returning to the topic of infectious diseases, Professor Duncan Hannant (Coordinator, EU WildTech project; Professor of Applied Immunology, Faculty of Medicine and Health Sciences, University of Nottingham, UK) observed that although the majority of infections in farm animals and humans may originate from wild life (as exemplified by the case studies of previous speakers), and diverse diseases will continue to emerge, there had been little coordinated effort to monitor disease spread within and between EU countries. The Framework Programme 7 project WildTech created a pan-European technology platform for the surveillance of (re-)emerging infections of wildlife, with rapid, accurate diagnosis using microarray technology to assay DNA, to identify pathogens, plus high-throughput serological screening (protein antigen arrays). Priority pathogens (viruses, bacteria and parasites), priority species (wild boar, cervids, urban rodents and hares) and methodologies have been discussed in detail[12].

This project has delivered proof of concept for the potential to develop Europe-wide surveillance using accessible and standardised tools, and with applications in syndromic surveillance, tracking infection dynamics, risk assessment and informing disease control strategies. Already the diagnosis and epidemiological characterisation of the European Brown Hare Syndrome has led to new information on pathogenesis and to proposals for control. More generally there has been a significant degree of technology transfer to countries outside of the EU. In discussion, it was also emphasised that these validated microarrays have further potential in replacing current reference methods. For example, as a DNA assay could distinguish between infected and vaccinated animals it could underpin new control measures for bovine TB.

One Health genomics at the interface between animal and human health

Professor Michel Georges (Member, Royal Belgian Academy of Medicine (ARMB); Director, Animal Genomics Research Unit, GIGA, University of Liège, Belgium) reviewed the historical development of genomic selection in farm animals and explored the implications for human medicine. There has been considerable effort applied to determining the heritability of production traits, such as milk yield in dairy cattle, at the same time as the search for genetic factors in human disease. For example, Crohn's disease demonstrates high twin concordance and genotyping studies have identified polymorphisms that help to explain the predisposition to Crohn's disease and its pathogenesis.

[12] Top five pathogen priorities are Mycobacterium bovis, Bluetongue virus, European Brown Hare Syndrome Virus and Francisella tularensis. For further information on WildTech see http://www.wildtechproject.com.

However, for many common, complex diseases there has appeared to be "missing heritability", that is the heritability cannot be fully explained by what is currently known about the genetic determinants. To an extent, the gap can be attributed to the existence of rare variants or to methodological weaknesses (for instance, incomplete coverage of SNP arrays) but the notion of "quasi-infinitesimal architecture" has also emerged. That is, a very large number of genes may contribute to the missing heritability of a particular trait but their contribution has commonly been ignored previously in association studies because the effect was below the statistical threshold used to claim significance. However, incorporating the influence of multiple genes below the statistical threshold can lead to very high predictive assessment of the individual phenotype (assuming the environment is neutral) and this approach has served to transform the strategy – genomic selection – of animal breeding programmes. It has been posited that the same concept can be applied to predicting genetic predisposition in humans[13], assuming large databases of genotypic and phenotypic information. Although this approach may not be applicable to individual prediction, because of lack of sufficient information about the individual's environment, it may be useful at the population level, particularly in an era of limited national resources, for example to predict who is more likely to respond to a specific treatment. The Belgian Medical Genomics Initiative[14] has recently initiated a platform to promote awareness, open communication channels, motivate collaboration and realise the application of genomics research and technologies in the clinic, including predicting clinical outcome from genomic information. This platform also incorporates work on genomics and society, to address the ethical, legal and social implications.

One Health – the point of view of the animal health industry

Dr. Olivier Espeisse (International Federation for Animal Health (IFAH); Elanco Animal Health, Paris, France – a division of Eli Lilly and Company) described the work of IFAH-Europe, comprising companies and national trade associations, to promote animal health and the responsible use of medicines, contributing to human health by controlling zoonoses and supporting One Health activities. IFAH-Europe recognises the concerns expressed by many about the industrialisation of food production that involves the confinement of farm animals, but it is likely that this intensification will persist given the very large global demand for human protein. There are challenges for the animal health industry to face, for instance in understanding and promoting animal welfare and in tackling the contributions that farming make to climate change. Historically there have been close links between veterinary and human medicine and the development of human therapeutics has involved observation of animal diseases and use of animal models.

Among recent initiatives involving IFAH are:

[13] G. de los Campos, D. Gianola and D.B. Allison, *Predicting genetic predisposition in humans: the promise of whole-genome markers,* Nature Reviews Genetics 2010 11, 880-886
[14] http://www.bemgi.be

- Responsible Use of Medicines in Agriculture (RUMA, http://www.ruma.org.uk) – involvement in national strategy to combat antimicrobial resistance by producing food with as little antibiotic use as possible in order to minimise resistance selection pressure (a point picked up in discussion in the context of ensuring the global prevention of antibiotic use for growth promotion)[15].
- European Technology Platform for Global Animal Health (ETPGAH, http://www.etpgah.eu) – a Framework Programme 7-funded mechanism for focusing and prioritising research that delivers new or improved tools, such as veterinary vaccines and diagnostic tests.
- DISCONTOOLS (http://www.discontools.eu) – a joint initiative based on gap analysis and prioritisation of diseases for delivering effective tools.
- STAR-IDAZ (http://www.star-idaz.net) – a global network for addressing animal diseases, including EU research funders and agencies.

Discussion on Education and Policy in One Health

Co-chairs: Professor Ian McConnell (Council Member, UK Academy of Medical Sciences; Professor of Veterinary Science, University of Cambridge, UK) and Professor Jesus A. F. Tresguerres (Past-President, FEAM; Member, Spanish Royal National Academy of Medicine; Professor of Physiology, Complutense University of Madrid, Spain)

Wide-ranging discussion among the speakers and audience clarified some important points for developing the FEAM remit in One Health:

1. One Health has a broad agenda and it is vital for FEAM to focus on where it can add value to the efforts made by many other groups.
2. With regard to education, there was consensus that it is highly important to restore the teaching on first principles in basic science (for example, relating to pathology) that has tended to be lost from the human medical curriculum. This re-emphasis on first principles is equally important for the veterinary curriculum. A renewed focus on basic science would help to achieve coherence in education for One Health and is considered to be a practical objective, even allowing for the present crowded syllabus in medical education. Clearly, the medical curriculum will continue to change in other ways, to reflect the changing nature of medicine, but there will always be a need to appreciate the first principles, and this requires basic science.
3. There must be increased awareness of the clinical and public health impacts of One Health, and the bioethical implications. Funders and policy-makers have a responsibility to promote One Health and support the necessary research. This requires better communication between the human and animal health communities. EU policy-makers need help from the scientific community in considering how to prepare and respond to the challenges in One Health, exemplified by some of the

[15] Further information on the priorities of academies of science and medicine worldwide for tackling antimicrobial resistance is provided in the joint IAP-IAMP Statement, *Antimicrobial resistance: a call for action,* November 2013, http://www.interacademies.net/10878/call_for_action.aspx

disease threats discussed in this conference. The actions must include better strategic coordination between human and animal health, for example in disease surveillance and the development of regulatory frameworks.

4. FEAM has published these points as a Declaration (footnote 3) and FEAM has a core continuing role to engage with the multiple stakeholders to catalyse further debate, inspire action and monitor impact.

SESSION ON THE FUTURE OF HEALTH RESEARCH

Co-chairs: Professor Dermot Kelleher (President, FEAM; Member, UK and Irish Academies of Medicine; Vice-President (Health) and Dean of Medicine, Imperial College London, UK) and Professor Irinel Popescu (Vice-President, FEAM; President, Romanian Academy of Medical Sciences; Professor of Surgery, Faculty of General Medicine, 'Carol Davila' University of Medicine and Pharmacy, Bucharest; Director of 'Dan Setlacec Center for General Surgery and Liver Transplant', Fundeni Clinic Institute, Center for Excellence CNCSIS, Bucharest, Romania) and Professor Ian McConnell (Council Member, UK Academy of Medical Sciences; Professor of Veterinary Science, University of Cambridge, UK)

Future policy needs in European biomedical science

The FEAM Spring conference came at an important point in the policy cycle, just before the European Parliamentary elections and changes to European Commissioners. Previous annual meetings have reinforced the value of FEAM contributing to inform policy development and this responsibility grows in significance.

Dr. Nancy Lee (Senior Policy Advisor, Wellcome Trust, London, UK) reviewed what can be done, and how, to ensure increasing investment in publicly-funded biomedical research in the EU, with a goal to fund at a level of 3% of GDP by 2020, with commensurate attention to education, training and mobility, to create a supportive environment for research and innovation, and maintain public confidence in biomedical research.

Considerable progress has been made by the biomedical community – including the Wellcome Trust, FEAM, Science Europe, patient groups and industry – in communicating to the European Parliament, Commission and Council in critical areas. Past achievements are exemplified by the Clinical Trials Regulation, Animals Directive and Physical Agents Directive. However, there are continuing challenges: for the Data Protection Regulation[16], Medical Devices Regulations and Copyright rules (increasing open access), together with the recent EU Citizens' Petitions on stem cell research[17] and animal research. For example, the current

[16] See recent material on the Data Protection Regulation by FEAM and others on http://www.feam-site.eu/cms/index.php/publications, in particular 10 March 2014, *A joint statement by the Healthcare Coalition on Data Protection.* Implications for specific research areas were discussed by several speakers in the present conference, for example Meunier, Frackowiak, Bergstrom.

[17] Statement by Wellcome Trust, FEAM and others on http://www.feam-site.eu/cms/docs/publications/STEMCELL/StemCellStatement2014.pdf

parliamentary amendments to the Data Protection Regulation, affecting the use of personal data in research without specific consent would prohibit some important research or make it impossible in practice, a point picked up by subsequent speakers.

Valuable lessons have been learned about how best to engage with the policy-making community: to present joined-up messages in lay language, appropriately targeted; to maintain good relationships additionally with policy-makers in the Member States; to seek to inform early on in the legislative process; to ensure provision of a strong evidence base illustrated with case studies; to engage with the media, social media and the public; to work as a pan-European partnership across the biomedical research community and to involve all stakeholders, including patient groups, learned societies and industry. The work of FEAM in mobilising support from the academies has been, and will continue to be, a significant factor in achieving impact.

The European Commission's perspective on funding research in the EU: Horizon 2020 (slides)

Dr. Ruxandra Draghia-Akli (Health Director, DG Research and Innovation, European Commission) reviewed past developments and the current status of EU-funded health research. Since the financial crisis in 2008, biotechnology funding from all sources has declined by 50% and this new funding gap in the biosciences typifies the extra challenges for the EU which, hitherto, had performed well in research although not so well in innovation.

During the last 30 years, EU-funded health research had increased 10-fold and one of the most important outcomes of Framework Programme 7 has been an established culture of EU and global research collaboration. As discussed in the 2013 FEAM meeting in Dublin, Horizon 2020 is designed to have simpler, more coherent participation rules, simpler financial regulation and faster proposal evaluation[18]. Dr. Draghia-Akli highlighted how the unified programme couples research to innovation, with priorities concentrating on excellent science, societal challenges and industrial leadership.

In the health area, the main societal challenges to address are: ageing populations; increasing chronic disease burden; health and care sectors that are unsustainable and under pressure to reform; and industry under pressure to deliver innovation. Horizon 2020 responds by establishing new features in EU funding: challenge-driven with broader topics in the Calls, and a stronger focus on the end-users. The Work Programme for 2014-2015 includes "Personalising health and care", together with coordination activities such as the European Innovation Partnership on Active and Healthy Ageing and the Global Research Collaboration for Infectious Disease Preparedness. Other relevant major activities include IMI-2 and EDCTP-2.

While discussants welcomed the commitment of DG Research and Innovation, it was noted that due to the very large number of applications submitted, the overall success rate in the first call for project proposals would be lower than in previous years. Dr. Draghia pointed

[18] The participant portal is on http://ec.europa.eu/research/participants/portal

out that competition for funding is particularly vigorous because of the impact of austerity programmes on national funding streams and because the broadening of the topic calls encourages more applicants from various relevant fields of activity, while encouraging multidisciplinary, transnational programs and projects. She also encouraged investigators across Europe to apply, and design innovative novel approaches to solving the challenges put forward.

Health priorities of the 2014 Italian EU Presidency

In providing an overview of the provisional programme, Dr. Giuseppe Ruocco (Director General, DG Prevention, Italian Ministry of Health) observed that health-related issues are a top priority of the forthcoming Italian EU Presidency but also that actions in many other sectors influence health (reinforcing the point made by Nancy Lee). The work of Horizon 2020 and other EU actions on global public health development, described previously, provides a very relevant background for the Italian priority areas for intervention:

- Prevention – (i) prevention of non-communicable diseases, including promotion of healthy lifestyles, prevention and management models for chronic respiratory disease, genomics in public health, gender-specificity, and dementia (follow up to UK G8 meeting); and (ii) prevention of infectious diseases, including HIV/AIDS, vaccines as an effective tool for public health, and One Health approach to antimicrobial resistance.
- Healthcare and management for health systems – quality and safety of care and care-related infections, efficacy and cost-effectiveness of healthcare delivery, palliative care and pain therapies.
- Health research and innovation for patients – including medicine and medical devices and ongoing legislation.
- Health in the Mediterranean area – to be defined, perhaps including social determinants of health, climate change, infectious disease, and health and migration, although that was also a Greek Presidency priority.
- Food safety – bridging to Expo 2015 and regulations in the agri-food chain.
- Veterinary issues – regulations on animal health, reinforcement of epidemiological surveillance of infectious diseases.

This is acknowledged to be an ambitious programme but it is an important time, with a new European Commission and Parliament. Many of the priorities are of great interest to FEAM members, as discussed throughout the conference; it is likely that the FEAM conference in 2015 will address relevant issues associated with promotion of healthy lifestyles and support for other public health measures, particularly in adolescence.

Ethical review of clinical research: presentation of the outcomes of a FEAM workshop (slides)

Professor Bernard Charpentier (Vice-President, FEAM; Member, French National Academy of Medicine; Professor of Medicine and Honorary Dean of the Medical Faculty, Past-Head of the Department of Nephrology, University of Paris Sud 11, France) discussed the conclusions of a FEAM workshop held in March and designed to help academies clarify some key issues for assuring the effectiveness of Ethics Committees in the EU. This has been a topic of interest since the time of the discussion leading to the FEAM Statement in 2010 on reforming the Clinical Trials Directive. Recent FEAM work explored issues for the functions of Ethics Committees, their organisation (with national and EU implications) and likely future directions in response to the changing nature of medical research and other policy developments, perhaps particularly the use of personal data in research. The perspectives contributed and areas discussed are recorded in detail in the report of the March workshop[19]. Among the Ethics Committee issues requiring further elaboration are the scope for harmonisation, choices in expanding functions, mechanisms to involve patients in research design, and the clarification and implementation of training opportunities.

From the perspective of Member State authorities, a Member State-oriented Ethics Committee system works well. But from the perspective of international research-based organisations, the current system is not optimal for EU researchers, patients or EU competitiveness. Discussants in Bucharest agreed with the views reported from the earlier workshop that there is a continuing role for FEAM to catalyse debate, assess the implications of the changing nature of clinical research on ethical review, and build engagement with policy-makers involved in developing strategies for ethical review and patient protection. One option for further FEAM activity is to organise a discussion on research ethics as part of an Italian EU Presidency conference on science and society later in 2014.

The Human Brain Project: new paradigm for detecting brain dysfunction, new approaches to defining brain disorders (slides)

One of the likely big future changes in the nature of clinical research is in the neurosciences area. Professor Richard Frackowiak (Chair, Science Europe's Medical Sciences Committee; Head of the Department of Clinical Neurosciences, CHUV University Hospital, Lausanne, Switzerland) considered that clinical neurology using traditional methods has reached an impasse. Advances in genomics, showing that one mutation may underlie variable neurological phenotypes, yet multiple mutations may yield the same phenotype, have highlighted problems of diagnosis and interpretation of pathology. Despite the advances in knowledge, neuroscience is fragmented because there is no unifying theory of how the brain is organised and involved in cognition.

Clinical neuroscience is at a tipping point, with the objective to move from syndromic to mechanistic diagnosis of disease, defined by biological signatures. This transition requires data federation, integration and curation across databases and is the motivation for the

[19] FEAM www to come

Human Brain Project (HBP)[20], developing informatics platforms, building on existing capabilities and designing outputs for use by scientists outside the HBP consortium. The HBP is a ten year European initiative to produce a blueprint for organisation of the human brain, with € 1 billion investment, half-funded by DG Connect, involving 22 countries in Europe, Americas and Asia. The HBP is integrating information and searching for patterns from databases in hospitals, industry research and elsewhere; because of the size of the pooled data, analysis is relatively insensitive to missing data and diagnostic errors. Preliminary work has integrated data of various sorts (including MRI, PET, genes, CSF, proteins) in Alzheimer's patients and healthy controls to analyse patterns of disease and associated pathology, and develop proof-of-principle.

In addition to the research objectives of future medicine, the HBP's other main research areas are concerned with future neuroscience (developing unifying theories) and future computing (developing the neurological basis). To achieve the objectives it is vital to continue accruing data, to increase the processing power encompassing informatics and algorithms, and to ensure an appropriate legislative environment for sharing and the trans-national movement of data. Discussants agreed that, if successful, the impact of the HBP on future medicine in the neurosciences would bring significant implications for medical education (including ethics) and for the design of, and recruitment into, clinical research studies.

The challenge of clinical research in oncology: a European perspective (slides)

Oncology research is also advancing rapidly and Professor Francoise Meunier (Council Member, FEAM; Member, Belgian Royal Academy of Medicine (ARMB); Director General, European Organisation for Research and Treatment of Cancer (EORTC), Belgium) provided a perspective from EORTC, created in 1962 to promote and conduct research to improve cancer care. In 2014, EORTC has 180,000 patients in its database from 2,000 research collaborations in 32 countries.

Clinical research in oncology is distinctive in several ways: considerations of risk are different, clinical trials are integrated into the treatment process, placebo use is infrequent, trials often rely on cooperation between national and regional groups, initiated by academic networks, with industry. As noted by previous speakers, cancer remains a major threat in Europe and there are pervasive challenges: in the regulatory environment, in increasing pressures on the pharmaceutical industry, in assessing necessarily complex therapeutic strategies (multidrug therapies, surgery and radiation) and in terms of the rewards for scientific advance, when basic research may be esteemed more highly than clinical research. Changes in the clinical research environment that must be faced, include disease fragmentation (molecular replacing organ-based classification), unaffordable drug development and treatments, the prospect of "pay for performance" and implications for Health Technology Assessment, the growing need for cooperation between public and private research sectors, and the increasing number of cancer survivors whose health-

[20] https://www.humanbrainproject.eu

related and other problems are not being tackled. The shape of drug development is changing in consequence – to focus on mechanisms early on, followed by highly-targeted pivotal trials and then population-based studies to collect real-life data, incorporating quality-of-life endpoints and health economics.

The new opportunities and challenges require new partnership models: to develop and implement screening and other technical (for example, imaging research) platforms; to provide multidisciplinary linkages; tackle rare tumours; integrate and analyse big data from registries and population-based studies; and address survivorship issues. The partnership models must develop the appropriate infrastructure for local investigators, with coordinating centres providing resource for genome sequencing, imaging and pathology. A roadmap for change has been created, SPECTA (Screening Patients for Effective Clinical Trials Access)[21], encompassing a range of activities for screening and treatment (SPECTAprogram) and for engaging patients, industry, regulators, governments and payors (SPECTAforum), developing economy of scale in application to different cancers.

Reinforcing points made by previous speakers, there are various regulatory challenges – including the Clinical Trials Regulation, Data Protection Regulation, Medical Devices Regulations and Cross-Border Directive, together with related, Member State, regulatory issues. Recent reform introduced by the Clinical Trials Regulation can be regarded as a significant success for the efforts of the biomedical community in communicating their advice to policy-makers but there are residual concerns, for example relating to timelines, harmonisation of patient information, and bureaucratic burden for local investigators. There are additional clinical trial issues that have not yet been resolved, for example, developing the EU forum for Ethics Committees and resolving tissue collection and privacy issues (further detail on the EORTC perspective on the need for an integrated and harmonised framework for handling ethical, legal and social issues is provided in the report of the FEAM ethics review workshop, footnote 17). The draft Data Protection Regulation remains a major concern for public health research: current parliamentary amendments will impede follow-up research in oncology for assessing long-term efficacy and the proposal to require explicit informed consent is impractical as researchers need broad consent to retain flexibility to pursue future research directions for patient benefit.

Innovation in biomedicine: an industry perspective

Many of the points presented by Professors Frackowiak and Meunier were reinforced by Dr. Richard Bergstrom (Director General, European Federation of Pharmaceutical Industries and Associations (EFPIA), Belgium), who agreed that there is need to understand more about the complex systems that form and surround biomedical research and development. Complexity is contributed by the mix of public and private sector activities, the global context for priorities and actions, the range of funding instruments and the impact of the wider economic environment. There is a new optimism in the pharmaceutical industry, based on perceived scientific opportunities, but there is also frustration on how best to deliver

[21] http://www.eortc.org/taxonomy/news-categories/specta

innovation for patient benefit and how to inform policy-makers that the industry is changing, particularly in its increasing transparency, sharing data and disclosing sponsorships.

The pharmaceutical business model is also changing, seen recently in the exchange of expertise and therapeutic franchise between companies to create the necessary scale, and as precompetitive partnerships, most notably IMI, to work on shared challenges. One other big change, already referred to by previous speakers is in the generation of evidence from clinical research. Randomised clinical trials still have a core role but are increasingly augmented by collection of real-world data. Companies have engaged with regulatory authorities to explain the utility of new data collection methodologies but it is now necessary to widen the discussion on evidence needs to include payors, those responsible for Health Technology Assessment and patients.

This evolving evidence base is also a critical issue for determining future decisions on the location of pharmaceutical research and development. The sector still invests heavily in Europe but the geographical basis has been moving, notably toward Eastern Europe. How could more industry investment be attracted to the EU? The solution is probably not, as proposed by some, a centralised European version of the US NIH, but rather:

(i) Better coordination and joint management of national research priorities together with,

(ii) Development of integrative, longitudinal research programmes where data from targeted clinical research studies and routine clinical practice, population-level studies, are brought together for the more systematic use of all patient data in support of innovation.

Perceiving every patient potentially as a research participant, if enshrined within a learning environment to generate quality data, will be a powerful incentive for industry investment in the EU. These ambitions require further attention to the policy environment. Industry is content with the final outcome of the Clinical Trials Regulation but, agrees that the Data Protection Regulation is currently problematic. Partnership is valuable to inform policy as well as to perform research and there is considerable scope for doing better together to protect life sciences research in the EU.

The patient's perspective (slides)

The fundamental necessity of European medical research was underscored by the presentation from Dr. Crina Stefanescu (LIVERTRANS, Liver Transplant Association of Romania), who described the history of liver transplantation in Romania and the formation of the patient group[22]. This group had twin objectives: to raise the voice of the patients who wait for a liver transplant and to increase confidence in the medical system. The personal accounts highlighted the very great importance of patients in advocacy and working in

[22] http://www.transplantdeficat.ro

partnership with medical researchers and medical practitioners to ensure the continuing investment in research and a supportive regulatory environment.

Discussion on the future of health research

Co-chairs: Professor Dermot Kelleher (President, FEAM; Member, UK and Irish Academies of Medicine; Vice-President (Health) and Dean of Medicine, Imperial College London, UK), and Professor Luigi Frati (Council Member, FEAM; President, Italian National Academy of Medicine; Rector, Sapienza University of Rome, Italy)

Panel discussion explored in further detail some key points raised by the presenters:

(i) Regulatory Progress of the Data Protection Regulation is reaching another critical point as the EU Council considers its position. During the trialogue stage, the European Commission will advocate the initial form of the legislation and will introduce compromise amendments to secure the place of broad consent to research, if such consent is approved by an Ethics Committee. It is essential for the scientific community to continue informing the new European Parliament and Commission as well as EU Council and others: the work of FEAM and its partners at the EU level has to be accompanied by activity by individual academies at the national level.

(ii) Research funding The realisation that the initial success rate for proposal funding in Horizon 2020 may be only 3%, compared to the historical success rate of 15% in previous Framework Programmes, suggests that the funding is being spread too thinly. Although the success rate may rise in future Calls and there are other EU funding opportunities for health researchers outside of the Health Call, it is timely to examine the merits of introducing other types of EU research funding instruments, for example analogous to the NIH R01 starting investigator grant. As clinical research is likely to become increasingly mechanism of action-driven, it is also timely to make the case for curiosity-driven research as part of finding ways to help young investigators start their research careers.

(iii) New molecular understanding and the changing clinical research paradigm The presentations on recent experience in neurosciences and oncology emphasised the importance of better characterisation of molecular mechanisms as the basis of novel therapeutic approaches. Advances in this understanding will have many consequences: for disease definition, new diagnostic standards and the development of investigative tools, for clinical trial design (including smaller, focused, adaptive trials) and closer linkages to clinical practice, for maintaining quality assurance between laboratories, as well as for new routes to personalised medicine. New complexity is emerging in many disease areas and the research community needs to be flexible in responding to the challenges. This topic will be considered for a future FEAM meeting.

SESSION ON HIGHER EDUCATION IN THE MEDICAL FIELD

FEAM is a partner in the Med-Motion project[23] that is seeking to identify and overcome barriers to student and staff mobility in the medical/health sector in Europe. As this project nears completion, participants described their expectations, experience and achievements. Karel van Liempt (Project coordinator, Faculty of Medicine, University of Antwerp, Belgium) introduced the project by observing that the mobility of staff and students is one of the key elements of the Bologna process, giving shape to the European Higher Education Area. The Med-Motion project is innovative in several respects: as a small network (seven medical schools) it enables intensive cooperation, with the active input of students and involvement of faculty management. Five pilot projects were initiated: organisation of common course units; undergraduate opportunities for research abroad; pool of excellence for clerkships; training weeks for administrative staff; and joint summer schools for students. Perspectives on these activities were provided by the subsequent speakers. Although it is too soon to measure impact, it was emphasised that the consequences of raising mobility are usually underestimated and that much remains to be done to convince most medical schools that education mobility could be a core activity. (Slides)

Judith Derdelinckx (Medical student, Member of EMSA-Antwerp, University of Antwerp; Member of the Steering Committee, Med-MOTION project) contributed a student's perspective on Med-Motion. Students, at least one from each participating medical school, had been active participants in project meetings, desk research (identifying barriers and incentives for mobility) and in the pilot projects and guideline development. Students regard mobility as important, for example to experience new cultures and how medicine is performed in those other cultures – as one of the attractions is diversity, this should be taken into account when thinking about standardising courses. There are also barriers, arising from differences in the curriculum, lack of transparency in administrative procedures, financial issues, fear of delay to study, as well as language. Student benefits had already been gained in each of the five pilot projects: the early experience shows that mobility barriers can be overcome and the Med-Motion project provides a basis for planning for sustained increases in future mobility. (Slides)

Professor Ingolfur Johannessen (Senior Clinical Lecturer in Medical Virology, Royal Infirmary of Edinburgh and College of Medicine and Veterinary Medicine, University of Edinburgh, UK) presented a view from the teaching faculty with particular regard to designing a common course on infection (i3DC). The initial objective in harmonising this short course was to promote academic staff mobility, with longer-term aims for student mobility. The course content included teaching about veterinary services as part of the resources to prevent and control infection, and provided practical insight into the previous discussion on education for One Health. In addition to its deliverable of a specific teaching course, this pilot project also served as a model with which to formulate guidelines for other common course development. Future work, subject to further EU funding, will embed common courses into the curriculum and recruit additional institutions. (Slides)

[23] Supported by DG Education and Culture, https://www.uantwerp.be/en/projects/med-motion/about-med-motion

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Programme
Slides

FEAM is the European umbrella group of national Academies of Medicine and Medical Sections of Academies of Sciences.

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Mission

- Promoting cooperation between national Academies of Medicine and Medical Sections of Academies of Sciences in Europe
- Providing them with a platform to formulate and express their common position on European matters concerning human and animal medicine, biomedical research, education, and health
- Extending to the European authorities the advisory role that they exercise in their own countries on those matters.

Membership

- 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.
- Its growing membership currently includes **18 national Academies that represent over 5000 among the best scientists across the biomedical spectrum** in Austria, Belgium, Croatia, Czech Republic, France, Germany, Greece, Hungary, Ireland, Italy, Lithuania, Netherlands, Portugal, Romania, Spain, Switzerland, United Kingdom.
- Active collaboration with two sister networks and observers: the European Science Advisory Council (EASAC), representing the national Academies of Sciences in Europe, and the InterAcademy Medical Panel (IAMP), representing the national Academies of Medicine worldwide.

Policy priorities

- EU regulations and directives
- Ethical review of clinical research
- Personalised medicine
- One Health: human, animal and environmental health
- The culture of prevention in health
- Medical education and training in Europe
- The future of health research