

## PROCEEDINGS OF THE IRISH BIOMARKER NETWORK INAUGURAL WORKSHOP



### Opening Address

Molecular Medicine Ireland hosted the Irish Biomarker Inaugural Workshop on November 4<sup>th</sup> 2010 in Croke Park Conference Centre in Dublin which was a great success and a tribute to the active engagement and contribution of the speakers, chairs and audience alike. The Workshop was well attended with over 100 academics, clinicians and industry representatives united in their interest in biomarkers. Dr Ruth Barrington CEO of MMI opened the Workshop and welcomed the attendees from all corners of the island of Ireland, the UK and most especially the keynote speaker Dr Francis Kalush, Network Leader for the Diagnostics (*In vivo* and *In Vitro*) and Personalised Medicine Network from the FDA and the guest Chair Mr Don Black, Director of MHICC/Trialynx Inc. and the International Partnership for Critical Markers of Disease, both having travelled from the USA for this Workshop. Dr Barrington mentioned that MMI had been approached by principal investigators in the partner institutions to assist in the establishment of a Biomarker Network and emphasised that this event was the first public manifestation of work that has been underway for a number of months. The representatives from the MMI partner institutions engaged to date include Prof. Dolores Cahill, UCD, Prof. Louise Kenny UCC, Prof. Mark Lawler TCD, Dr. Nicola Miller, NUIG and Prof. Alice Stanton, RCSI.

Dr Barrington highlighted the key objectives of the Workshop which were as follows;

- To address some of the key hurdles in translating biomarkers to the clinic, in particular the European and FDA regulatory requirements;
- To share the expertise and insights of those who have successfully developed or are currently developing and validating biomarkers for clinical use;

- To explore interest in the establishment of an Irish Biomarker Network and to define the objectives of such a Network and how it could best assist in biomarker discovery, validation and translation to the clinic.

### **Overview of the background to the establishment of an Irish Biomarker Network**

Prof. Dolores Cahill, UCD set the scene by describing discussions that PIs have around biomarker discovery, validation and commercialisation and the issues encountered. The idea of establishing a biomarker forum to address some of these issues was conceived and MMI was approached as the vehicle to facilitate a Network. Prof Cahill acknowledged the support of the Board of MMI which approved the establishment of a Biomarker Network as one of its initiatives and sought representation from each of the MMI partner institutions to progress this agenda. Prof. Cahill presented the proposed objectives of a Biomarker Network that were discussed by the MMI partner institutions which include; coordinating expertise across the biomarker discovery, development and clinical validation spectrum that could support PIs; sharing of biomarker proposals across a secure website; lobbying of funding and enterprise agencies to fund strategic developments in biomarker commercialisation; information on the practical aspects of regulatory compliance; alignment with the national biobanking initiative; building links with international biomarker and biobanking networks; alignment with the clinical trial cooperatives, in particular for the opportunity to procure pre-treatment samples; exploring the potential for a demonstration project as a flagship for the Network; building a biorepository of patient and healthy control samples that could be shared for national and international collaborations. Prof. Cahill concluded by stating that the Network, through embracing the '*art of the possible*', could provide an excellent opportunity to create critical mass in biomarker research and development in Ireland by leveraging the existing expertise and state-of-the-art clinical and translational infrastructure which in turn would expand the number of clinical trials of biomarkers and the development of new assays.

### **The FDA and European perspective on the regulatory requirements for the validation of biomarkers in clinical trials**

Dr Black opened the regulatory session by discussing his long standing interest in biomarkers and introduced the work of Critical Markers of Disease (CMOD) Consortium, which brings together academics, industry and regulatory representatives to advance the development of biomarkers. He announced that the next CMOD international biomarker conference will be held in Dublin Castle on June 26-27 2011 in concert with IMB, EMA, FDA, Health Canada and MMI.

#### **Dr. Francis Kalush – The FDA perspective**

Dr. Francis Kalush, in her comprehensive presentation provided a detailed overview of FDA activities and initiatives for personalised medicine; the regulatory framework developed by the FDA to

accommodate companion drug/diagnostics; the streamlining of the co-development process and details of the different centres in the FDA that provide consultative opportunities for early phase development of a biomarker and a drug. Dr. Kalush described in detail the various FDA processes to bring a diagnostic/device to market based on risk and classification, for example the pre-investigational device exemption process which is an informal consultation for industry/academics for early stage development of a diagnostic/device. Dr. Kalush emphasized that in the drug-diagnostic development pathway when a diagnostic test is used for patient stratification, the efficacy and safety of the drug becomes inextricably linked to the effectiveness and safety of the diagnostic and therefore the diagnostic test needs to be approved with the drug and its use will be included in the drug labelling. Dr. Kalush presented some of the factors that impact on the analytic and clinical validation of a test for example, reproducibility, operator competency, lack of harmonised sample handling, poor sample quality, patient heterogeneity and the choice of assay method. Dr. Kalush discussed the commitment of the FDA to overcome potential regulatory barriers to facilitate the introduction of innovative products to the market through increased harmonisation between FDA Reviewing Centers, the publication of appropriate guidance, increased dialogue between FDA and industry/ researchers and transparency of the regulatory process while still preserving the FDA's mandate to protect and promote public health. Dr. Kalush concluded by highlighting some of the future challenges for the FDA in this area, including the need for a better understanding of regulatory framework and product development life cycles for combination drug/diagnostics, the need for a personalised medicine consultative programme to harmonise practice, a feedback loop to capture outcome of innovative targeted diagnostics/therapeutics.

#### **Dr Sarah O'Meara – the IMB and European perspective**

Dr. Sarah O'Meara presented the current IMB and European perspective on biomarkers and outlined the regulatory considerations and guidance that have been adopted by the EU and globally to assist stakeholders in validating and qualifying new biomarkers. Dr O'Meara provided an overview of the EMA supports for researchers of biomarkers in drug development, including the EMA Pharmacogenomics Working Party informal briefing meetings, the scientific advice offered by the Scientific Advice Working Party on protocol assistance for biomarker qualification, market authorisation evaluation and guidance documents on biomarkers. The Pharmacogenomics WG is a multidisciplinary group composed of 14 experts nominated by the Committee for Medicinal Products for Human Use (CHMP) comprised of academia, regulatory scientists, EMA therapeutic specialists and area specialists as required. The role of the Pharmacogenomics WG is to share experience on issues arising from the integration of pharmacogenomics into drug development; to prepare, review and update guidelines; to support dossier evaluation and contribute to scientific advice and to advise the European Commission on pharmacogenomic related issues. Dr O'Meara mentioned that a key task of the Pharmacogenomics WG relative to the biomarker audience is the hosting of briefing

meetings for informal dialogue between regulators, academia and industrial scientists on emerging science to highlight technical, scientific and regulatory issues related to pharmacogenomic markers. Some examples of issues discussed include the genomic expression signature as a biomarker bridging proof-of-concept from animal models to man and the potential regulatory value in conducting retrospective pharmacogenomic biomarkers analyses and their impact on existing and new drugs. Dr O Meara also referred to the joint FDA-EMA voluntary genomic data submission briefing meetings whereby a sponsor submits data and questions for review by FDA-EMA on a pharmacogenomic biomarker. Dr. O'Meara advised that there are a number of guidance documents published and adopted by the EMA in this area which are available at <http://www.ema.europa.eu>. Dr. O'Meara also provided an overview of the qualification procedure for biomarkers and indicated that the EMA and FDA have concluded the first joint qualification process for biomarkers which included the qualification of seven biomarkers of drug-induced renal toxicity in the context of non-clinical drug development. It was noted that the use of biomarkers in clinical trials is considered interventional according to the Clinical Trial Directive 2001/20/EC and comes within the scope of the legislation thereby requiring Competent Authority approval and the need for the clinical trial to be performed under GMP requirements. Dr. O'Meara acknowledged the lack of harmonization in Europe with regard to the application of the clinical trial legislation for biomarkers which is recognised by the EU Commission and Member States. Dr. O'Meara indicated that clarification will be sought on clinical trials involving biomarkers at the next amendment to the Clinical Trial Directive 2001/20/EC. Dr. O'Meara concluded by stating that the IMB is taking a pragmatic approach to the use of biomarkers in clinical trials and advised of their request to be notified of clinical trials of biomarkers even if they do not come within the scope of the regulations.

### **Shared experiences and lessons learned from the evaluation and clinical validation pathway for biomarker discovery and development**

Dr. Tom Lille from Amgen set the scene for the case study session by outlining how biomarkers underpin personalised medicine through improved efficacy and safety for patients, increased cost effectiveness and improved clinical trial design and outcomes. Dr Lille presented some of the difficulties encountered based on experience of the use of biomarkers in clinical trials, which include the discovery of the biomarker mid-way through the clinical trial requiring analysis of retrospective samples; the need for a model of broad consent to allow for the use of samples in future research studies; the availability of appropriate sample types; the need to test drug combination targeting multiple pathways; the need for the pharma industry to partner with a diagnostic company to develop the accompanying diagnostic; IP issues and difficulties in clinical trial design.

### **Prof. Louise Kenny - *Biobanking for Biomarker Discovery in Obstetrics and Paediatrics***

Prof. Louise Kenny from Cork University Maternity Hospital and UCC presented a comprehensive overview of the need for biomarkers in obstetrics and paediatrics and specifically diseases of late pregnancy. Prof Kenny discussed the specific challenges for biomarker discovery in obstetrics and paediatrics and the strategies her group has adopted to overcome these, in particular for metabolomic biomarkers. Prof Kenny highlighted the lack of predictive screening tests for diseases of late pregnancy which affect 19% of all first time mothers and result in legacy complications for these babies such as learning difficulties and a six fold increase in risk for diabetes in adulthood. It is therefore key to identify mothers who are at high risk of developing diseases of late pregnancy in order to intervene appropriately to prevent adverse outcomes. Prof. Kenny described SCOPE, a global consortium which has developed a unique international pregnancy biobank of samples from 7,500 women with detailed clinical phenotypes, known and novel clinical risk factors, well characterised disease phenotypes and a comprehensive bank of quality specimens for biomarker discovery and evaluation. Prof Kenny also referred to the recently initiated a birth cohort entitled BASELINE that has been developed from SCOPE which aims to detail the genetic, epigenetic and early life environmental factors which predict early childhood body composition and metabolism. Prof Kenny stressed the need for standardised and rigorous sample collection and processing as illustrated by the SCOPE study to avoid false discovery and epiphenomena. SCOPE has achieved harmonisation globally through the implementation of standardised procedures across centres which have been pre-approved by the FDA for biomarker discovery.

***Prof. Joe Duffy - uPA as a biomarker for breast cancer: from pilot studies to clinical use***

Prof. Joe Duffy from St Vincent's University Hospital and UCD presented an important clinical dilemma for clinicians which is treatment of lymph node negative breast cancer patients and how to differentiate those with aggressive from those with indolent cancer. Prof. Duffy advised that to circumvent this dilemma almost all node-negative patients are treated with adjuvant chemotherapy even though only a minority of patients will benefit but the majority will suffer toxic side-effects. Prof. Duffy presented a convincing clinical case for the development and validation of biomarkers that will reliably differentiate between patients with aggressive and indolent disease. Recognising that metastasis is the main cause of mortality in cancer and that uPA is a serine protease known to be causally involved in this processes, Prof Duffy and others hypothesised that uPA should be a strong marker of metastatic potential and thus of prognosis in patients with lymph node negative breast cancer. Prof Duffy's early research demonstrated that uPA and its inhibitor PAI-1 provided additional data for breast cancer patient management to that of conventional prognostic factors, including ER status and lymph node status, a key requirement for the use of biomarkers in clinical decision making. The validation of uPA and PAI-1 as an independent prognostic factor in lymph node negative breast cancer was confirmed by greater than 20 independent groups. Further to the independent verification of uPA and PAI-1 as an independent prognostic risk factor for breast cancer, the next

step was to conduct the clinical validation against a known gold standard or a level one evidence study for routine clinical use. Clinical validation of uPA and PAI-1 in breast cancer has been achieved internationally in two independent level one studies, both in a randomised prospective multi-centre clinical trial and in a pooled meta analysis (with both published and unpublished studies) in over 8,000 patients. The American Society for Clinical Oncology (ASCO) recognised these results for uPA and PAI-1 and recommended their use for the determination of prognosis in patients with newly diagnosed node negative breast cancer. Following this the National Cancer Advisory Board (NCAB) has also recommended the use of uPA and PAI-1 for the clinical management of lymph node negative breast cancer patients. The biomarkers are also widely used in clinical are in Germany.

#### **Dr Thomas Barry - Commercialisation of diagnostic markers for infectious diseases**

Dr Thomas Barry presented the expertise of the Molecular Diagnostics Research Group (MDRG) at NUI Galway which is focused on discovery and development of unique diagnostic markers for infectious disease caused by bacteria and fungi, food pathogens and environmental water contamination pathogens. Dr Barry recognised the potential of nucleic acid testing to revolutionise the traditional laboratory methods for diagnosis of infectious diseases which are manual, slow, require highly skilled personnel, often complex, poorly integrated with slow turn-around time and not compatible with point of care testing. Dr Barry discussed the strategy adopted by the MDRG in bringing diagnostic markers to the clinic. In the absence of a large clinical sample population, the Group focussed on the generation of a significant intellectual property portfolio around the biomarkers they have discovered, which are now in the region of 30-40 infectious disease agents. This required the Group to become industry compliant and to implement good laboratory practice in order to validate the diagnostic markers to a level that was acceptable to industry. Dr Barry detailed the extensive biobank of bacterial and fungal strains that the Group has developed from around the world which are used to validate their infectious disease diagnostic markers. This focus on commercialisation has resulted in the technologies developed being associated with three of the top six *in-vitro* diagnostic multinational companies in the world. Dr Barry presented a case study of one of their commercial partnerships with Beckman Coulter which involves a successful four year research and development programme in Ireland. This relationship recognises Beckman Coulters expertise in verification, validation, regulatory approval and manufacturing of IVDs. Dr Barry highlighted that one of the significant personal challenges in this approach to biomarker discovery and generation of IP was the lack of freedom to publish the research. However, once IP was protected the Group has published 25 peer reviewed publications in the area of molecular diagnostics for infectious diseases.

#### **Dr Isabella Bray - microRNA as biomarkers in cancer**

Dr Isabella Bray, of the Cancer Genetics Group at the RCSI discussed microRNA as biomarkers in cancer and highlighted that several independent studies across different cancers have demonstrated significant differential expression of miRNA associated with this disease, for example upregulation of

miR-21 associated with multiple cancers. This in turn has led to the evaluation of miRNA expression as a biomarker in human cancers. Dr. Bray spoke about the advantages of investigating miRNAs as biomarkers including their durability, detection in highly degraded material and the specificity of current commercial assays to measure miRNA expression. The importance of miRNA signatures has also been recognised in cancer treatment response. Dr Bray's biomarker research identified a miRNA expression signature predictive of clinical outcome in neuroblastoma, one of the most frequent solid tumours in children, being responsible for approximately 15% of all childhood cancer deaths. This miRNA signature was further validated in two independent neuroblastoma tumour cohorts and was able to differentiate tumours with a hemizygous loss of a large segment on chromosome 11q into groups with significantly different clinical outcome. Dr. Bray highlighted the association of the miRNA signature with poor survival in neuroblastoma. Dr. Bray concluded with the potential for the miRNA expression signature, combined with analysis of segmental imbalances, to provide greater prediction of survival outcome in patients with neuroblastoma than current markers used which in turn should improve patient treatment stratification.

**Prof. Paul Harkin - *the DSA™ multigene assays for cancer***

Prof. Paul Harkin, from Queen's University Hospital and Almac Diagnostics provided a comprehensive overview of some of the critical factors in discovering multigene assays, discussed the DSA™ and Xcel Array technology platform developed by Almac Diagnostics for use with formalin fixed paraffin embedded material and discussed Almac's Col-Dx assay which predicts for relapse in stage II colon cancer. Prof. Harkin presented an overview of Almac's product development cycle for biomarker discovery and development. Prof. Harkin highlighted a key point which is not always appreciated in the transition from development to analytical and clinical validation which requires all components of the test to be validated together in order to meet regulatory requirements including how the samples are collected, the assay itself, the instrumentation used to run the assay, reagents and integrated software. Prof Harkin focused on the study design for biomarker discovery and validation, in particular recognising two critical components, biological and technical. Some of the factors to consider from a biological perspective that were presented include, end-point selection, representative population, defining inclusion/exclusion criteria, need to balance for existing factors. Some of the technical factors presented include tissue type, instrumentation, reagents and process randomisation. Prof Harkin presented Almac Diagnostic's choice of technology platform for biomarker discovery and clinical validation which is RNA based biomarker discovery using microarray technology. This technology was chosen based on the need to include the maximum relevant content (transcriptome based), disease specific and cross disease application, the availability of a gold standard technology platform - Affymetrix, a technology that would support GMP manufacture and the ability to work on formalin-fixed, paraffin-embedded tissue. Based on this technology, Almac Diagnostics has developed a number of disease specific microarrays for ovarian, breast, colorectal,

lung and prostate cancer in partnership with Affymetrix, which encodes 50-60,000 transcripts for these disease types for which 30-40% of this content will not be found in any other commercial microarray. Prof Harkin went on to define how this technology has been applied to stage II colon cancer to identify patients at high risk of relapse following surgery. The Col-Dx assay has been validated in a representative sample population from a number of cancer centres across Europe and the USA and also in independent cohorts. Prof. Harkin advised that the Col-Dx assay is undergoing final clinical validation and will be launched in 2011 for use in the clinical patient management.

### **Common threads from the shared experiences for biomarker discovery and development**

- The importance of appropriate study design, accurate statistical methodology and planning for biomarker discovery and validation.
- The need for pristine phenotyped clinical data and high quality standardised samples using rigorous SOPs is essential.
- The need for appropriate patient and/or population cohorts which are adequately powered for biomarker validation studies and verification of the clinical validation in independent studies.
- The importance of future-proofing and harmonisation in biomarker discovery and development programmes especially with regard to samples, phenotypic data and the informed consent model.
- The use of the correct technology platform with appropriate bioinformatics is key.
- Effective biomarker discovery and development needs to control for biological, operator, different centre and reagent effects to distinguish signal from background.
- Advice on IP protection should be sought before any disclosure which may involve complex multi-institution licensing and revenue sharing agreements. It is best that the licensing agreements are signed off before the work begins. One contact, preferably with the correct skill set, should be the key negotiator in this process.
- Commercial partnerships are the most likely endpoint for biomarker development in the academia arena.
- For biomarkers being developed for clinical use, the assay technology needs to be simple to perform.
- Independent clinical data and sample monitoring for quality control and quality assurance is key.
- The true measure of the value of a biomarker is that it drives patient management and influences clinical practice thereby adding value to the healthcare system.

## Facilitated discussion on the value, focus and the key objectives of an Irish Biomarker Network

Prof Dermot Kelleher led a provocative and constructive discussion that focussed on the critical advances and the disappointments that have emerged from research on biomarkers over the last ten years; how networks can provide additional value to biomarker discovery and development; whether there is a role for academia and industry to collaborate through a network on designing critical pathways for use of biomarkers in clinical trials and whether the network should be system or disease based.

The session concluded with enthusiastic agreement on the value of an Irish Biomarker Network. It was agreed that the Network should be inclusive of academics with an interest in biomarkers on the island of Ireland and should involve a relationship with industry and with the regulatory authorities. The Network should also involve key stakeholders including patient organisations and ethicists.

The following objectives were proposed for an effective, co-operative Network;

- To develop a Directory of Biomarker Research in Ireland to catalogue details of the PIs engaged in biomarker research, the key thematic areas, current biomarkers developed and under development for pre-clinical and clinical settings, samples available for sharing from healthy controls and disease cohorts for clinical validation studies.
- To build an Irish Biomarker Web-Portal as a central electronic facility to share knowledge and best practices in biomarker discovery and development including the sharing of standardised procedures for biobanking and biomarker studies, guidelines for study design and statistical methods, standard templates for IP, protocols and links to relevant resources.
- To examine how the Irish Biomarker Network will work with the CRCs in building harmonisation of approach for clinical studies involving biomarkers.
- To propose a common approach to ethical approval to support biomarker discovery and clinical validation incorporating the education of academics on what is ethically permissible and legitimate for biomarker studies, considerations for future-proofing studies and a template for a model of broad informed consent.
- To develop a mathematical modelling system for biomarkers with a view to examine how they interact with / affect each other, their assignment against disease traits and to explore how these can be tested against the disease traits in large patient / population cohorts.
- To identify the data that needs to be harmonised in the area of biomarkers for clinical and translational information technology systems under development.

- To prepare a common position for the Action Group for Health Research Subgroup on Biobanking on the requirements for the national biobank initiative to support biomarker discovery and development.
- To develop and publish a code of practice for clinical trial design involving biomarkers with a particular focus on statistical methodology and adequately powered studies.
- To agree a policy for the engagement of the Irish Biomarker Network with industry to address their requirements in the area of biomarkers.
- To agree the best approach to lobby state and funding agencies on the importance of strategic funding for biomarker discovery and development and how to ensure their inclusion in the prioritisation exercise.
- To consider a flagship project to help launch the network as a success story and to demonstrate that it works.

### The Next Steps

- MMI to convene a meeting in January/February 2011 with those interested in engaging and participating in the Irish Biomarker Network to develop and to agree a work programme based on the key objectives as outlined above.
- MMI to convene a meeting with EI/IDA to determine how they might like to engage with the Irish Biomarker Network and how to fulfil industry requirements in the area of biomarkers.
- MMI to convene a meeting with the IMB to determine how they might like to engage with the Irish Biomarker Network and to ensure that the regulatory perspective is incorporated in the Network work programme.
- The Biomarker Coordinating Group to establish working groups with responsibility for the delivery of specific areas of the work programme.
- MMI to work with the Biomarker Coordinating Group to plan discuss the organisation of a parallel session for the Irish Biomarker Network at the Critical Markers of Disease International Conference on Biomarkers in June 2011
- MMI to propose potential speakers for the Critical Markers of Disease International Conference on Biomarkers to be held in June 2011.