

## **Fostering International Collaboration on Rare Diseases Research**

### **Launch of the International Rare Diseases Research Consortium (IRDiRC)**

**5-8 April 2011**

#### **Executive summary**

The workshop was co-organised by the European Commission and the US National Institutes of Health. This workshop followed the first USA-EU workshop organised in Reykjavik, October 2010, where it was decided to explore the concept of programme level cooperation for stimulating and steering international collaboration in rare disease research (see [http://ec.europa.eu/research/health/medical-research/rare-diseases/events-03\\_en.html](http://ec.europa.eu/research/health/medical-research/rare-diseases/events-03_en.html) ).

The major goal of the workshop in Bethesda was to establish and launch the International Rare Diseases Research Consortium (IRDiRC) to foster international collaboration in rare disease research.

IRDiRC has two ambitious objectives:

- 200 new therapies for rare diseases by 2020
- A diagnostic tool for a majority of rare diseases by 2020

To develop a policy document framing the international effort, 7 breakout sessions were organised to trigger the discussion on the different policy items:

1. Understanding Pathophysiology of Rare Diseases
  - 1.a. Genomics analyses
  - 1.b. Animal models and in vitro systems
2. Ontologies/Disease Classification/Natural History
3. Biomarkers
4. Patient Registries and Biospecimen Repositories
5. Preclinical Research and Clinical Trials
6. Communication/ Publication/ Information/ Intellectual Property Rights (IPR)/ Data Policy

Some 80 participants from research funding agencies, research organisations, industry, patient advocacy groups and regulatory agencies participated to the workshop.

Research funding agencies represented at the workshop were:

- EU: European Commission (DG Research and Innovation; DG Health and Consumers)
- US: National Institutes of Health (NIH)
- Canada: Canadian Institutes of Health Research (CIHR)
- Spain: Instituto de Salud Carlos III
- Italy: Istituto Superiore di Sanita

## Governance

The group of funding agencies representatives agreed to have an **Interim Executive Committee** until the end of 2012. The group chose **Dr Ruxandra Draghia-Akli** from the European Commission, DG Research and Innovation as **Chair**.

Membership of the IRDiRC Executive Committee will require a minimum investment of **\$ 10 million over 5 years**. To be considered, calls for proposals need to explicitly indicate the contribution towards IRDiRC objectives. Investments from 1 Jan 2010 contributing to the initiative objectives will be considered for membership in the IRDiRC governance. "Letters of Intent" concerning IRDiRC membership must be signed by the authorising official committing the research funds, and the letter should be addressed to the Interim Chair. A template for intent letter is made available through the EC website.

A mechanism by which smaller players could be represented in the IRDiRC governance, possibly through a "country or organisations grouping" (such as ERA-Net representation), should be reflected on.

The first country, Spain, already announced its formal commitment at the workshop in Bethesda. The EC contribution is also already clear (€ 100 million in the next call for proposals – publication expected July 2012), as is the Canadian contribution via CIHR. The NIH expresses its full support for this initiative and commitment for a number of the NIH Institutes.

Other research funders will be invited to join the initiative, notably on the occasion of the next Heads of International Research Organisations meeting in June 2011.

## Policy Development

Working groups to develop the draft policy document have been established. These groups will develop the necessary policies that will foster international collaboration and ensure that results from invested research can rapidly be translated to diagnostics and treatments benefiting the patients.

Such policies include: harmonization and standardisation of data and research results, access to data, best practices, communication and intellectual property aspects. These policies will support the development of biomarkers for diagnosis and therapy development, model systems (in vitro and in vivo models), pre-clinical development and clinical trials.

A short summary of the overarching policies will be developed by May 2011, while the complete draft policy document should be available by September 2011 for further discussion at the next meeting.

Working groups identified:

- Genomic analyses
- Animal + *in vitro* models
- Ontologies
- Natural history
- Biomarkers
- Patient registries/biorepositories

- Preclinical research/clinical trials
- Communication of the consortium (also to deal temporarily with IPR and centralise information from other WG on data sharing policies)
- Information on rare diseases

### **Organisational support for IRDiRC activities**

The EC announced its commitment to supporting the logistical organisation of IRDiRC activities through a dedicated support action topic in the next call for proposals (WP2012).

The next meeting of IRDiRC will be organised by CIHR in Montreal in early October 2011 (8-9 October).

## Summary of the sessions

### 1. Understanding of Pathophysiology of Rare Diseases

#### **Part 1a Genomic analyses**

***This session was devoted to discussing policies that should catalyse international collaboration and data sharing on Mendelian disorders sequencing and other genome-based approaches.***

- Mutation databases galore, with no stable situation. IRDiRC does not need more databases, but better databases. All variants of genes should be placed in a common database, efficiently curated, with links to clinical data whenever possible.
- List of diseases being sequenced in the consortium: all members of IRDiRC should be required to publish on the consortium website their list of disorders under study including the approach used and the current progress. A scientific committee will be created to oversee diseases allocation, to encourage collaboration and to avoid duplication of efforts.
- All participating studies will have consent in place that will meet the policies of the consortium for public data release and sample sharing. A common "patient consent form" will be developed for IRDiRC.
- The consortium should implement efficient resource sharing policies to share protocols and experiment designs, samples, and data management and analysis tools.
- Data should be freely shared with the public, with appropriate controlled access when necessary. Timelines and type of data to be released (raw vs. derived data) will need to be agreed upon.
- Sustainability of database resources: funders will need to develop the common data portal for access to whole genome sequencing by networking existing data centres in different countries. Common data standards will need to be developed.
- Common genomic data quality standards should be developed with disease-gene identification.
- Data quality for 'benign' variants database: high quality needed so the dataset is useful for analysis and comparison across patients.
- Open access to resources without interference due to intellectual property: per international rules, primary genomic sequence cannot be claimed.

#### **Part 1b Animal models and in vitro systems**

***This session was devoted to discussing policies that should encourage international collaboration in generating and sharing animal models and in vitro model systems for catalysing rare disease research.***

- Models systems (mouse, rat, zebrafish, *C. elegans*, *D. melanogaster*) can support both the development of diagnostics and therapies.

- For diagnostics, the use is mainly for validating the causative gene. In addition, other animal models such as the dog could also be used for the identification of the causative gene.
- Model systems are of critical importance for developing therapies. They are required to identify the molecular mechanism of disease, then used in selection and preclinical screening of lead compounds. Models can also help in optimising the design of clinical trials when dealing with very rare diseases (“co-clinical trial” concept).
- For the development of therapies, it is recommended to have a dual approach involving model organisms and when appropriate human induced pluripotent stem cells (hiPSC) derived from index cases representative for the rare disease under study. Further development of hiPSC tools should also be duly considered.
- To support and accelerate discoveries in pathophysiology of rare diseases it is recommended that all generated model systems are made freely accessible for research use.
- For the hiPSC system, it will be important to create a resource banking the different lines generated by consortium partners and providing a training environment for iPSC maintenance and differentiation.
- Priority should be given to develop model systems for diseases for which there is a good potential for therapy development.
- Effort should be made to harmonise the ontologies between human and model organisms for phenotype description (see below).

## **2. Ontologies/Disease Classification/Natural History**

***This session was devoted to discussing policies that will promote implementation of common ontologies, disease classification and description of disease natural history.***

- All participants agree that a single disease classification should be used. Discussion will take place to decide which classification will be adopted and when.
- Standardisation of terms is highly recommended and incentives should be made that both researchers and clinicians use common terminology.
- There is a need for common standard procedure to name new diseases and syndromes, as well as agree on the way their classification should be made.
- The scope of use for classification/ontologies should be clarified (short term is agreement on names, synonyms, definition, and organisation for rare diseases to support inventories and coordination of research efforts). Other uses (e.g. clinical data collection), could consider linkage to other ontologies.
- Ontologies are to be made freely available in the community.
- Future work should consider model organisms’ ontologies and specific ontologies to support natural history studies (e.g. drug ontology).
- Natural history studies should be done with a view to develop therapies, in close contact with regulatory agencies. Standardised elements are needed for inclusion in natural history studies in general, resulting in more efficient new drug development.

- Natural history study planning efforts should include the involvement of patient advisory groups and expert networks, and use existing registries or patient databases.
- Standards for longitudinal data capture should be identified, including guidance on which elements should be included (common data elements across diseases?)

### 3. Biomarkers

***This session was devoted to discussing policies that should facilitate international collaboration in biomarker discovery and validation for diagnosis, prognosis and evaluation of treatment efficacy.***

- Over 1000 of potential biomarkers have been identified, but only very few made it to the clinic. How to bring them into clinical landscape? It is difficult to develop surrogate biomarkers for rare diseases because their approval by regulatory agencies is a tedious process. Over 95% of the surrogate markers failed the necessary validation steps.
- Due to the limited amount of patients, it is difficult to assess the disease progression or the efficacy of disease treatment. International studies would definitely help.
- There are many orphan designated drugs that need to undergo clinical development. Without biomarkers to assess the response to a treatment, it is impossible to evaluate its efficacy in clinical trials. Therefore, there is a need to speed up the identification of these biomarkers in order to accelerate the development of already designated potential drugs.
- Diagnostic biomarker: the genomics wave will accelerate the identification of genetic biomarkers for rare diseases. Actions required include: centralise data, improve statistical methods, standardise clinical data, facilitate patient self-recording, develop tools to facilitate access to clinicians, develop policies to oblige data deposition and sharing.
- Therapeutic biomarkers: involvement of industry and regulatory agencies to improve the discovery/validation of biomarkers to accelerate the clinical trials. The focus should be on the diseases for which there exists designated drugs.
- Other biomarkers: bank of samples could facilitate their identification. An international collaborative effort should be organised to streamline the validation process of biomarkers.
- It will be essential to increase interaction with regulatory authorities for developing the criteria for the validation of biomarkers. The regulatory authorities are very supportive to help with the prioritisation of biomarkers research.
- The implementation of an international platform to discover/validate therapeutic biomarkers in a similar way as the cancer programme in US (Early Detection Research Network) could be investigated.

#### 4. Patient registries and biospecimen repositories

***This session was devoted to discussing policies that should promote the use of commonly accepted "Standard Operating Procedures" (SOP) and "informed consent forms" to facilitate data/samples sharing.***

- There was broad agreement that the consortium should be actively involved in these aspects. Policies should include developing common standards for the following issues:
  - common sets of data (common data elements), SOPs, quality control,
  - using open source software, with flexible formats depending on goals and type of registry,
  - data sharing requirements,
  - access to data (if supported by public funding, registries should be open-source) ,
  - ownership of registry and data (governance),
  - data protection/privacy,
  - feedback to data providers (especially patients and their families to whom long-term continuation of registries is essential; diversified sources of funding need to be investigated),
- The development of registries by groups of diseases (instead of single-disease registries) should be encouraged.
- Attention should be paid to data collected and registered by patients and families (“self-reporting”).
- Links between biobanks and registries should be established.
- A sustainability plan should be developed (on a model of business plans) from the beginning of any register.
- Multiple databases exist for many diseases. Harmonisation of data is needed.
- The next meeting should include more focus on biobanks.

#### 5. Preclinical Research and Clinical Trials

***This session was devoted to discussing policies that should facilitate preclinical research and clinical trials. Issues like promoting access to existing chemical libraries, sharing clinical trial information, facilitating international clinical trials and defining and harmonising outcome measures need to be addressed.***

- Access to existing chemical libraries
  - Need for model legal agreements for testing/repurposing of chemicals/biologics.
  - Promote access to screening facilities.
  - Requirement for data sharing of results from molecular screening.

- Sharing clinical trials information

- Mandatory protocol registration, and required sharing of de-identified data, for potential protocol improvement.

- Sharing experiences/information on clinical trials processes: regulatory requirements, ethics committees, legal/insurance requirements, countries and populations involved.

- Required open-source reporting of clinical trials results, be them positive or negative.

- Facilitating international clinical trials

Some aspects are currently not harmonised between US and EU. The conduct of international clinical trials would benefit from guidelines in the following areas:

- definition of sponsorship US vs. EU

- clinical trials applications

- ethics committees approval

- use of investigational medicines

- non-interventional trials

- safety reporting

- insurance/legal liability

- good manufacturing practices

- Data sharing

Harmonisation and common standards are needed on the following aspects:

- common data elements

- common databases

- registry of clinical trials

- requirement for clinical trials reporting

- access to de-identified clinical trials data

- definition and harmonisation of outcome measures.

- Approach to developing a new therapy:

- Repurposing existing therapies for rare diseases
  - Sharing pre-clinical and toxicology information
  - Screening of chemical libraries
  - For new molecular entities, gene and cell-based therapies: requirement to be considered as orphan drug product by regulatory agencies.
  - Perform comparative effectiveness research for proposed therapies to provide evidence of efficacy/safety.
- Patient advocacy groups and patients should be involved in protocol design, and trained in clinical trials methods.

## **6. Communication/Publication/Information/IPR/Data Policy**

***In this session were discussed the consortium communication strategy, and general policy principles for IPR and data sharing. The session also addressed what policy actions are needed to network rare disease information sources.***

### **Communication:**

The communication should be internal and external to the consortium

#### Internal communication:

- Draft policy documents shared internally before their publication
- Minutes of the executive committee
- Sensitive competitive documents
- SOPs should be made public, but remain internal when under development

#### External communication:

- Final policy text
- Finalised SOPs
- Website, logo etc.
- General IRDiRC information; goals, mission, policy document, benchmarking studies
- Interactive forum
- External consultation mechanism
- Name of contact
- Major discoveries, news and views
- Progress to objectives in simple visual scheme
- Should make link to all projects funded at the international level (see for instance the related policy of the International Cancer Genomics Consortium)

### **Rare diseases information**

- Citizens need quality, timely information on all conditions
- Information should be consistent across cultures, but should respect diversity: regional, race, ethnicity, religion, language and culturally appropriate.

- Duplication and reinvention should be avoided, gaps should be filled
- Open and free sharing should be engaged
- Clinical trials central portal
- Push and pull interactivity that improves quality
- Ability to correct misinformation – quality sites

### **Data sharing policy**

- Open platforms, yet must manage privacy considerations
- Robust sharing
- Data quality: common quality and format for the data release
- Timing of data sharing: agreement on open sharing of all types of data, but with potentially different embargo date for different types of data (to be worked by different working groups)
- Encourage journals to only accept data that has been first deposited in the centralised database (biomarker and genomic data)

### **Intellectual Property Rights (IPR)**

- Desire to balance access and innovation
- Any IP registration must only be in support of patients' needs
- The IP working group will produce a policy document taking into account:
  - Bayh Dole Act
  - Open access in research environment, research allowance, research exemption, NIH and EC policies
  - Concerns about IP claims and rare diseases: the principle of non-exclusive licenses should be favoured.

### **Publication policy**

- Publication will be encouraged for the benefit of the consortium and its objectives.
- Individual consortium investigators may publish the results of their own work. Principal investigators within the consortium should notify other consortium members of their intent to publish or to coordinate back to back publications to maximize scientific impact.
- On regular basis, the consortium will make scientific report on the progress to address IRDiRC objectives.