INTERNATIONAL
RARE DISEASES RESEARCH
CONSORTIUM

Minutes of the 8th Executive Committee meeting

10 April 2014

IRDiRC

EXECUTIVE SUMMARY

The Executive Committee (Exec Com) of the International Rare Diseases Research Consortium (IRDiRC) met on 10 April 2014 by teleconference. The eighth meeting of the Exec Com brought together 31 participants including Exec Com members and representatives of the 3 Scientific Committees (Sci Com).

The application of Isis Pharmaceuticals to become an IRDiRC member was approved by the Exec Com.

As the current procedure to nominate members to the Sci Coms will lead to the overpopulation of all the Sci Coms with the growth of the consortium, the Exec Com discussed and agreed on a new procedure based on call for application when nominations are needed to renew members. In the meantime, population of WGs is an alternative.

The chair of the Therapies Sci Com presented the roadmap of this committee. The recommendations aims to guide both the policies and funding strategies to reach the goals of 200 new therapies by 2020, based on the work of the 4 WGs and the Therapies Sci Com.

Two priorities were highlighted:

- Insist on collaborative clinical development of designated orphan products that have received scientific guidance from regulatory agencies, with an emphasis on the highest unmet patients needs and always based on the excellence of science in term of proof of concept
- Make sure that the pipeline beyond 2020 is being enriched with products at non clinical stage to be supported now when they have a strong proof of concept and with a strong commitment to apply for an orphan designation and scientific guidance

Both the Diagnostics Sci Com and Interdisciplinary Sci Com presented an update on their recent activities.

The 2nd IRDIRC conference will be held at the Futian Sheraton hotel in Shenzhen, China, on Nov 7-9, with 2 days of conference (with 4 parallel sessions) and one day of training course.

The highlights of this conference are:

- Opportunities for Chinese clinicians to meet with Chinese and International researchers to help bring genomics technologies
- Educational track
- Training course for mostly Chinese participants on Nov 9th (course of genomic technologies)

The proposal to implement an annual membership fee based on voluntary participation to establish a funding pot to support travel of patient organization to attend Exec Com face-to-face meetings, outreach activities, etc. was further discussed and the members of the committee agreed to include participation in kind as well as scale for membership through 3 categories. Each member of the committee will be contacted by the Scientific Secretariat to specify how they wish to participate.

REPORT

New application for membership

The application of Isis Pharmaceuticals, an antisense RNA technology company based in California, to become an IRDiRC member was approved by the Executive Committee.

Composition of Scientific Committees

Approval of the nomination of members

The nomination of 2 new members of the Sci Com was approved by the Exec Com for a 3-year mandate. The new members are:

Diagnostics Sci Com:

- Dr Henk Stunnenberg

Interdisciplinary Sci Com:

- Dr Stephen Groft

New procedure for the nomination of Scientific Committee members

The Exec Com members and the Sci Com chairs agreed that the maximal optimal size for the Scientific Committees is 15 members. The Therapies Sci Com has already exceeded its maximum with its composition of 18 members. The Exec Com members agreed on their last call not to accept any more nominations for this committee.

Overcrowding of Sci Com represents two main issues:

- Lost of efficiency
- Cost issues (travel, hotel, catering, etc.)

As IRDiRC is now approaching 40 members, it will be more and more difficult to maintain that limit of 15 members for the Sci Com using the previous procedure for nomination, in which each IRDiRC member of the Exec Com could nominate a Sci Com member. But for the private sector, the nomination of a representative for one of the Sci Com is a strong incentive.

The following alternatives were proposed to avoid overcrowding of Sci Com:

- Populating the Working Groups (WGs) instead of the Sci Com.
- When a member needs to be renewed: have a call for application to all IRDiRC funding members in order to have the choice and to look at competencies in a pool of potential candidates.

- Sci Com will provide information on the expertises that are necessary in their committee and WGs.

Recommendations from the Therapies Scientific Committee to the Executive Committee

The recommendations from the Therapies Sci Com to the Exec Com will need to be consolidated with the Diagnostics Sci Com and the Interdisciplinary Sci Com recommendations into the IRDiRC roadmap.

These recommendations aims to guide both the policies and funding strategies to reach the goals of 200 new therapies by 2020, based on the work of the 4 WGs and the Therapies Sci Com.

The Therapies Sci com decided to minimize the number of recommendations in order to identify the ones with strongest impact and to be sure that they can be well-appropriated by the Exec Com members.

The recommendations were selected on the following criteria:

- Essential actions defined for their highest leverage effect to unlock the potential of rare disease therapy development
- Well-targeted actions with potential to produce results before or by 2020
- Actions identified for their international relevance
- Clarity and flexibility of the actions recommended
- Overall consistency of the set of actions

These recommendations would address the bottlenecks associated with biomedical research with low prevalence, with high needs conditions, and will foster the development of RD on the global scale.

Two important priorities were highlighted:

- Insist on collaborative clinical development of designated orphan products that have received scientific guidance from regulatory agencies, with an emphasis on the highest unmet patients needs and always based on the excellence of science in term of proof of concept
- Make sure that the pipeline beyond 2020 is being enriched with products at non clinical stage to be supported now when they have a strong proof of concept and with a strong commitment to apply for an orphan designation and scientific guidance

Recommendations for implementing IRDiRC Policies

The following recommendations were elaborated by the Therapies Sci Com:

- Encourage, support and establish early and continuous dialogue on clinical development strategy and wide evidence generation.
- Strongly support scientific guidance at regulatory agencies, and encourage more joint scientific advice by regulators.
- Develop more guidelines for clinical development of medicinal products for specific RD (or related groups of RD). The guidelines should be developed by regulators in collaboration with all relevant stakeholders. They would increase the quality of the development of the products and provide a more robust and consistent guidance over time by the regulators as well as a point of reference for the clinicians and the researchers involved, patient advocates, etc.).
- Encourage, support and develop patient focused/relevant outcomes. This should be developed early in the development of the product (before marketing authorization).
- Develop information, education, dialogue and support among regulatory agencies and sponsors.
- Encourage adaptive clinical trial design and new statistical methodology through the support of research projects, information, education and regulatory guidance. This should be recognized as an official policy. IRDiRC could help regulatory agencies reaching this goal.
- Support the development and use of optimized and standardized technologies and assays for biomarkers to further accelerate overall development and reduce fragmentation of knowledge on the same disease or the same therapeutic actions. Ensure that these techniques are qualified and validated by the regulatory agencies.
- Repurposing and repositioning of drugs is strongly encouraged. A particular focus on medicines having a long standing experience of use and known for their safety profile should be done.
- Study and learn lessons from failed developments between orphan designation and approval and pave the way to increase the success rate and bring more therapies to the market.
- Encourage flexibility of regulatory processes, particularly for RD.

Recommendations of Funding Priorities for IRDiRC funding organisations

IRDiRC funders should consider funding through two possible mechanisms:

- International collaborative rare disease research and orphan medicine development that takes best advantage of unique expertise and availability of special resources, irrespective of geography or nationality of the applicants.
- International alignment of themes and coordination of the process for calls for proposals so to enable shared funding of same research projects by agencies from several relevant countries.

<u>Funding of new therapies for rare diseases:</u>

The Therapies Sci Com recommends that the criteria below are taken into consideration:

- **Mandatory shared criteria to fund clinical research of rare disease therapies:**
  - Excellence of the scientific rationale, proof-of-concept and development plan,
  - Preferentially concentrated to product that obtained an orphan designation from FDA and/or EMA and (cumulative criteria) that the sponsor has received Scientific Guidance from both or either Regulatory Agency (e.g. Scientific Advice/Protocol Assistance at EMA, or, pre-IND meeting or other structured product scientific meetings at FDA) and (cumulative criteria) for which the sponsor adheres to the guidelines of Good Practice (i.e., GXP).

Non-clinical work should be highly supported with an adjusted level of funding, without the requirement of orphan designation or scientific guidance from regulatory agencies at the time of grant application but with an explicit commitment from the grant applicant to apply for orphan designation in both EMA and FDA (facilitated by the common application form) or either and to seek scientific guidance from regulatory agencies in due time.

- **Other criteria:**
  - Unmet medical need/absence of alternative treatments
  - Most life threatening, severe or debilitating diseases
  - Innovative therapeutic approaches with potential use in clusters of several diseases
  - Existing knowledge of natural history of the conditions or intention to develop it
  - Existence of a quality patient registry or database or intention to develop it
  - Existence of active patient groups
  - Existing data for a medicine's safety profile (e.g. approved for other therapeutic indication, off-label use, well-established use)

<u>Funding of research:</u>

- Funding new methodological and statistical approaches (e.g. adaptive design, adaptive statistical methods) for clinical development in small populations. These new methodological and statistical approaches may help to register medicines faster with a much lower cost of R&D.
- Support the identification and timely development of new and more effective biomarkers and outcome measures with sufficient lead-time in the R&D process. Make best use of large international cohorts for biomarker/outcome measure identification and qualification.
- Support the qualification and validation of new or existing biomarkers and outcome measures for conditions where there are any orphan medicinal products in development.
- Establish and support mechanisms for medicinal products with potential for development and identify how they are linked to rare clinical conditions. The product properties, disease history, connections between products and new indications should

be investigated prior to embarking on therapeutic development. These mechanisms will optimise the use of the currently available compendia of medicines and bring significant medical benefit to rare disease patients at a low cost of R&D.

Funding of gap analysis:

The Therapies Sci Com has also gathered a set of recommendations for funding to identify gaps and opportunities for therapeutic development in the field of rare disease:

- Gap analysis of unmet medical needs that could potentially be addressed by 2020
- Analyse outcomes from previously funded projects (FP6, FP7, E-Rare, NIH…) with a medicines development aspect in order to understand the reasons of success or failure
- Analyse off-label use of current therapies that may be of relevance for the patient needs
- Conduct a survey of biomarker and natural history project leaders in order to perform a gap analysis, identify potential clusters of biomarkers by disease and find information on biomarkers used in failed clinical trials
- Perform a review of the currently funded IRDiRC projects (on the data available since 2010): to identify 'clusters' of compounds of the same therapeutic class or by conditions, and to identify gaps that may deserve further discussion

Other topics:

The Therapies Sci Com also recommends indicators to monitor progress towards the goal of 200 new rare disease therapies by 2020 as well as the implementation of the main policy and funding recommendations formulated.

Next steps

Once the Therapies Sci Com recommendations will be adopted by the Exec Com, the Therapies Sci Com will ask its WGs to develop a short action plan on what they will do concretely to realize some of these recommendations, and encourage them to do a communication work (publications of editorials, articles in scientific journals, etc.).

The Exec Com welcomed these recommendations even if they cautioned that some areas represent real challenges and might be unrealistic. The Exec Com members were asked to review these recommendations.

Update from the Diagnostics Scientific Committee

All WGs received feedback about guidelines and tools to build as defined by the Diagnostics Sci Com in Prague and they are working on it.

The development of the integrated roadmap is in process, with the help of Support-IRDiRC.

There are overlaps between the aims of some of the WGs of this committee and other initiatives:

- An overlap between the IRDiRC WG on Ontologies and rare disease prioritization, the Global Alliance for Genomics and Health, and the Human Variome Project exists on the topics of how to handle large amount of genomics information and data sharing: all these 3 WGs will merge into one WG, which will be chaired by Peter Robinson and supported by the IRDiRC Scientific Secretariat. In consequence, 7 members will be added to that WG.
- The WG on Genome/Phenome and the Data WG of the Global Alliance for Genomics and Health are both working on bringing together existing data bases that match genotype and phenotype for patient with unsolved RD. 5 other members could be added to the Genome/Phenome WG.

If this model of integrating several initiatives in the same WG to avoid redundancies is effective, it may be expended to other WGs.

Update from the Interdisciplinary Scientific Committee

The Interdisciplinary Sci Com had a teleconference that focused on the roadmap, to adjust it after review of the Diagnostics Sci Com roadmap.

The next meeting of the Interdiscplinary Sci Com will be held on May 8, 2014, in Berlin, Germany.

There was no WG call recently as the Interdisciplinary Sci Com decided to wait for the consolidation of the IRDiRC roadmap before providing feedback to the WGs and launching round of teleconference.

Update on the IRDiRC Conference in Shenzhen, China, on 7-9 November 2014

The conference will be held on 7-9 November 2014, with two days of conference and one day of training course, at the Futian Sheraton hotel in the center of Shenzhen, China. This hotel will present the possibility to hold 4 concurrent sessions (3 rooms with a capacity of 200 people each and 1 room with a capacity of 100 people) throughout the meeting.

There will be new highlights compared to Dublin:

- Opportunities for Chinese clinicians to meet with Chinese and International researchers to help bring genomics technologies
- Educational track
- Training course for mostly Chinese participants on Nov 9th (course of genomic technologies)

A space will be dedicated to exhibitors, and another one to posters session (around 30 posters in English).

The website of the conference is about to be launched. It has been prepared in collaboration with BGI, Support-IRDiRC and the University of McGill.

Program

Invitations were sent to international speakers (20 agreed) + 16 Chinese speakers.

The tentative program is the following:

- **Friday 7 November**
  - Plenary session 1: welcoming remarks, plenary theme TBC
  - Plenary session 2: RD research in 2014 – an overview
  - Parallel session 1
    - Track 1: Sequencing and other omics technologies
    - Track 2: Registries and biobanks
    - Track 3: Gene/Cell therapy
    - Track 4: TBC
  - Parallel session 2
    - Track 1: Interpretation of sequence data
    - Track 2: National plans and policies
    - Track 3: Exon skipping and new drugs
    - Track 4: TBC
- **Saturday 8 November**
  - Parallel session 3
    - Track 1: Impact of diagnosing RD on patients and on the healthcare system
    - Track 2: Patient involvement and ethics in RD research
    - Track 3: Regulatory challenges for drug development in RD
    - Track 4: TBC
  - Parallel session 4
    - Track 1: Sharing information on RD
    - Track 2: Health technology assessment and access to orphan drugs
    - Track 3: Clinical trials: challenges and possibilities
    - Track 4: TBC
  - Plenary session 3: Success stories, closing remarks

The next face to face meeting of the Executive Committee could be held in Shenzhen, in conjunction with the IRDiRC Conference.

Modification of the proposal for an optional membership fee

Considering that different members have access to different resources, the proposal for an optional membership fee was reviewed to propose the following options:

- Proposition of a scale for membership categories, each with a different annual fee.
- Inclusion of a participation in kind (travels for patients associations, catering, reception of Committees, etc.) in order to make the model flexible. Credit will be given for participations in kind.

The Sci Sec will contact each member to ask them how they would like to contribute (fee or in kind).

The activities supported will be out of the scope of Support-IRDiRC.

Agenda of the Executive Committee face-to-face meeting in Berlin

The following items need to be added on the agenda, in addition to the ones already proposed:

- Development of a mechanism for formal association with other organizations with related and overlapping but not identical mandate to IRDIRC (i.e.: Global Alliance for Genomics and Health, International Conference on Rare Diseases and Orphan Drugs, International Human Epigenome Consortium, Genomic Medicine Alliance, Human Variome Project, etc.).
- Development of associations with organizations that do not fit the criteria to become an IRDiRC member (patient organizations, etc.) and that would like to be associated with IRDiRC.

Annex - List of participants

Members	Representative
Western Australian Department of Health, Australia	Hugh Dawkins
IRDiRC Chair Executive Committee, Canadian Institutes of Health Research, Canada	Paul Lasko
Genome Canada, Canada	Pierre Meulien
Chinese Rare Disease Research Consortium, China	Qing Wang
E-RARE-2 (E-Rare Group of Funders), Europe	Daria Julkowska
European Commission, (DG Health and Consumer Protection), EU	Helmut Walerius and Jaroslaw Waligora
European Commission, (DG Research and Innovation), EU	Anders Colver and Irene Nordsted
EURORDIS (Patient Advocacy Group), Europe	Valentina Bottarelli
Academy of Finland, Finland	Heikki Vilen
AFM- French Association against Myopathies, France	Marie-Christine Ouillade
FMR – Rare Disease Foundation, France	Nicolas Levy
Federal Ministry of Education and Research, Germany	Ralph Schuster
Children's New Hospitals Management Group, Georgia	Oleg Kvlividize
Shire, Ireland	Phil Vickers
Telethon Foundation, Italy	Anna Ambrosini
Prosensa, The Netherlands	Luc Dochez
The Netherlands Organisation for Health Research and Development, The Netherlands	Sonja van Weely
Carlos III Health Institute, Spain	Rafael de Andreas Medina and Pedro Cortegoso Fernandez
Food and Drug Administration, USA	Katherine Needleman
Genetic Alliance, USA	Sharon Terry
Isis Pharmaceuticals, USA	Brett Monia
National Eye Institute, NIH, USA	Santa Tumminia
National Human Genome Research Institute, NIH, USA	Jeff Schloss and Lu Wang
National Institute of Neurological Disorders and Stroke, NIH, USA	Danilo Tagle
NKT Therapeutics, USA	Robert Mashal
Office of Rare Diseases, USA	Stephen Groft

Sanford Research, USA	David Pearce
Scientific Committees	
Chair Diagnostic Sci Com	Kym Boycott
Chair Interdisciplinary Sci Com	Hanns Lochmüller
Chair Therapies Sci Com	Yann Le Cam
IRDIRC Scientific Secretariat	
SUPPORT-IRDiRC project	Sophie Höhn

Apologies

Members	Representative
BGI, China	Ning Li
ANR- French National Research Agency, France	Bertrand Schwartz
Lysogene, France	Karen Aiach
Instituto Superiore de Sanita, Italy	Enrico Garaci
Korea National Institute of Health, Korea	Hyun-Young Park
National Institute for Health Research, United Kingdom	Willem Ouwehand
Genzyme, USA	Carlo Incerti
National Cancer Institute, NIH, USA	Edward Trimble
National Center for Advancing Translational Sciences, NIH, USA	Christopher Austin
National Institute of Arthritis and Muskoloskeletal and Skin Diseases, NIH, USA	Stephen Katz
National Institute of Child Health and Human Development, NIH, USA	Melissa Parisi
NORD, USA	Peter Saltonstall
PTC Therapeutics, USA	Diane Goetz

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