

## Meeting report series

### Report of the 6th Therapies Scientific Committee teleconference

6 October 2014

#### Organization

Organized by: Scientific Secretariat

#### Participants

Yann Le Cam, Paris, France (Chair)  
Dr Seng Cheng, Framingham, USA  
Dr Shuling Guo, Carlsbad, USA  
Dr Adam Heathfield, Sandwich, UK  
Dr Virginie Hivert, Paris, France  
Dr Elizabeth McNeil, Bethesda, USA  
Dr Luigi Naldini, Milan, Italy  
Dr Asla Pitkänen, Kuopio, Finland  
Prof Gert-Jan Van Ommen, Leiden, the Netherlands  
Dr Ellen Welch, South Plainfield, USA  
Dr Anne Zadicek, Bethesda, USA

Dr Ramaiah Muthyala (Co-chair WG on Chemically-Derived Products including Repurposing), Minneapolis, USA

Dr Barbara Cagniard, Scientific Secretariat  
Mr Gustavo Barros Sabino, Scientific Secretariat

#### Apologies

Dr Giles Campion, Leiden, the Netherlands  
Dr Fulvio Mavilio, Evry, France  
Dr John McKew, Bethesda, USA  
Dr Glen Nuckolls, Bethesda, USA  
Dr Karin Rademaker, Utrecht, the Netherlands  
Dr Robert Schaub, Waltham, USA

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## **Agenda**

1. Update from the Executive Committee meetings
2. Update on TSC membership
3. Adoption of the TSC recommendations
4. Review of each WG progress
5. Synthesis and adoption of the TSC milestones
6. Interaction between WGs and Scientific Committees
7. Short-term and long-term funding recommendations
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## REPORT

### 1. Update from the Executive Committee meetings

The IRDiRC Executive Committee (Exec Com) met face-to-face in May in Berlin and by teleconference in June and in October. Two topics of discussion are of particular relevance to the Scientific Committees (SCs).

#### Funding of short-term projects

Exec Com is discussing the means and process to support short-term projects (gap analysis, workshop, tools) proposed by the Diagnostics SC (DSC) and Interdisciplinary SC (ISC). The SCs submitted 1-2 pages proposals to Exec Com for consideration. Funding of such projects is challenging as there is no adapted process to coordinate international funding from several types of funders with different constraints, and the outcome seems uncertain for the moment.

From the discussion of the Exec Com, it appears that:

- ▶ Recommendations developed by SCs are appreciated by the Exec Com.
- ▶ Development of background paper to guide future calls is useful.
- ▶ Organization of workshop is possible as it can be supported by one of the IRDiRC members.
- ▶ Funding of more complex projects is problematic.

#### “IRDiRC Recommended” label

Exec Com is adopting the label “IRDiRC Recommended” for tools/standards/guidelines useful to the community at large, and approved the principle of the process:

- ▶ Identification of tools/standards/guidelines by WGs and SCs and preparation of application
- ▶ Review by SCs
- ▶ Submission to Exec Com for approval

Practicality will be developed in the next few weeks to be adopted in November by the Exec Com meeting at their next meeting in Shenzhen.

### 2. Update on TSC membership

Two members quit the TSC due to departure from their organization:

- ▶ Marc Walton (FDA)
- ▶ Maria Mavris (EURORDIS)

Two new members were recently nominated:

- ▶ Shuling Guo (Isis Pharmaceuticals). Her main responsibility is exploratory drug discovery with focus on rare genetic diseases.
- ▶ Virginie Hivert (EURORDIS, to replace Maria Mavris). Virginie joined Eurordis in early June as Therapeutic Development Director. She previously worked for Orphanet for 6 years and was already following the SC as a member of the IRDiRC Scientific Secretariat.

### 3. Adoption of the TSC recommendations

The first draft of the TSC recommendations was circulated at the beginning of the year, discussed and modified during the last face-to-face meeting of the TSC in March in Paris. The recommendations were then presented to the Exec Com in Berlin in May. The latest version, reorganized and modified to include the comments of the Exec Com was circulated to the TSC members during the summer.

The purpose of this document is to provide guidance to the Exec Com members on strategy to use and where to allocate resources. Funding level and funding mechanisms depend on each member. As such, the document does not include any cost evaluation as not relevant. In Europe, all these recommendations translate into practice such as policies implemented by European Commission itself in Horizon 2020 program and in the E-Rare project which coordinates the policy strategy and budget allocation of 14 countries between themselves.

The best way to impact the financial instrument is for the TSC to ask the WGs to prepare 1-2 pages documents to guide the funders for the preparation of their future funding calls (background, status and recommendations to funders on what they should do).

- ⇒ A version of the TSC recommendations with track changes will be sent to the TSC members at their request.
- ⇒ The document was approved by all members present.

### 4. Review of each WG progress

#### **WG on Biomarkers for Disease Progression and Therapy Response**

This WG had one teleconference since the last TSC meeting.

Their two main topics of discussion are still the same:

- ▶ Analysis of the field of research for biomarkers: the Chair of the WG is preparing a 2-pages proposal to obtain funding.
- ▶ Biomarkers criteria: discussion on that topic was not continued as the last teleconference was cancelled.

A member of the TSC mentioned the Guidelines on genomics biomarkers drafted by the EMA. The document is interesting in principle but only discuss SNPs as biomarkers. A few additional possibilities should be included in the guidelines that are more specific to rare diseases.

- ⇒ Members of the TSC would like the comments of the WG on the concept paper. The Scientific Secretariat will circulate the document to the WG.
- ⇒ Members of the TSC are invited to send to the Scientific Secretariat suggestions for new members of this WG which is down to six members.

### **WG on Biotechnology-Derived Products Including Cell- & Gene-Based Therapies**

The last teleconference of this WG was held in January, when the issue of the recommendations at the European parliament for experimentation and the difficulty to compare a new therapy for rare diseases with a standard treatment when lacking was discussed.

A teleconference will be scheduled soon as it was difficult to gather people during summer time.

### **WG on Chemically-Derived Products Including Repurposing**

In the last teleconference of this WG that was held in July, the members mostly commented the TSC recommendations.

The WG is now working on a proposal to organize a workshop on Repurposing as from their previous discussion, it appears that there is matter of scope and matter of strategy for such topic.

The workshop would gather for 2 days 20-30 participants from NCATS, European Commission, regulatory agencies, institutional/funders, industries/SMEs, clinicians, statisticians, researchers, patient associations, etc. to bring recommendations for action and possibly the beginning of action implementation.

Proposition of topics/sessions:

- ▶ Definition of repurposing
- ▶ Sourcing: how to identify clinical candidates?
- ▶ Regulatory aspects
- ▶ Which area of research would benefit from funding?
- ▶ Fostering partnerships accelerate the development of repurposing drugs
- ▶ Conclusion and points for action

Comments from the TSC:

- ▶ Experts in rare cancer should be invited to the workshop as there is a great potential for application in this field.
- ▶ Reaching industries outside IRDiRC will be possible through the “Joint task force on Orphan Medicinal Products and Rare Diseases” which gathers many size and model of companies. A short document with background and plan will be necessary for this purpose.
- ▶ Workshop on Repurposing and the workshop on Biomarkers – both planned for the 1<sup>st</sup> semester of 2015 – should be either organized in common or spread over time.

- ⇒ TSC encourages the WG to finalize the document: why, objectives, etc.
- ⇒ TSC would like the WG to produce the outline of program and a 1-page concept paper with a proposal for a program committee of 3-5 people by the end of the next teleconference of this WG. The proposal will then be presented to the Exec Com for comments/suggestions and possibly for funding decision by one of the member.

## **WG on Orphan Drug-Development and Regulatory Processes**

There were two teleconferences with the FDA, EMA and the Chair of the TSC, in presence of the Scientific Secretariat, to discuss possible topics of discussion for this WG.

FDA is currently developing Guidelines on Clinical trials in Rare Diseases, sending a signal of flexibility to the community (adaptive design, adaptive statistical methods, biomarkers surrogate endpoints, etc.). These guidelines should soon be open to public consultation and the WG will review and comment them. EMA adopted in 2006 guidelines on Clinical Trials in Small Populations and is now considering to revise its guidelines and to include guidelines under development on adaptive statistical methods, following on the FDA initiative to publish its guidelines and recommendations by IRDiRC. If this is confirmed, there will be guidelines from EMA and FDA, almost coordinated in term of timing and content.

- ⇒ As the FDA process and EMA process are slightly different, TSC insists on the need of exchange on the content of the guidelines between the two regulatory agencies.

## **5. Synthesis and adoption of the TSC milestones**

The milestones of DSC, of the ISC and the combination of both SC milestones organized by area of work show what the two other committees wish to achieve. Some milestones can be linked to projects presented by these committees to the Exec Com.

The development of the TSC milestones based on the feedback from the WGs and TSC was difficult.

There are three different types of milestones:

- ▶ Workshop
- ▶ Gap analysis/identification of opportunities
- ▶ Development of guidelines

Major efforts like “Identification of opportunities for biomarkers development”, “Identification of optimized/standardized technologies and assay for development and use”, or “Assessment of off-label use” may seem as a wish list that will be moved every 6 months without being accomplished.

There is a necessity to be more creative on the deliverables and the expertise of the WGs as it is difficult to have these WGs work only in teleconferences with a turn-over of participants that are not always the same in the calls.

The TSC reviewed and discussed several milestones.

### **Identification of opportunities for biomarkers – WG on Biomarkers for Disease Progression and Therapy Response**

Development of biomarkers is essential to both the development of treatments and the validation of the efficacy of a treatment.

Members of the committee agreed on the proposition of identifying priorities areas, more specifically, groups of diseases with a well credential on science today, preferably close to translation into clinic, where better knowledge or research on biomarkers could accelerate the application of the knowledge for biomarkers development in support of this group of diseases. It would indeed be useful to focus on a subset of diseases where biomarkers may be particularly helpful to try to show progress in this area.

First two area of focus could be:

- ▶ Rare cancers
  - ▶ Neurodegenerative conditions
- ⇒ The TSC would like the WG to consider the possibility and means to develop background paper for the funders on needs for specific groups of diseases as recommendation for funding priorities, starting with rare cancers. Another area could be considered in the next 6-12 months.
- ⇒ That could led the way to a future workshop on Biomarkers

### **Assessment of off-label use – WG on Chemically-derived Products Including Repurposing**

Use of off-label is common in pediatrics in US and would be an important source of information.

There are initiatives to assess off-label use in Both US and Europe:

- ▶ The NIH has been tasked with a project participating to the “Best pharmaceutical for Children Act”, which consist of performing studies of medication in children that are being used off-label in order to get labeling indication. Assessment is very difficult in the US because of the way data are available or not. It necessitates to compare the medicate claims, insurance claims and so on with ICD-10 code to know which diseases were considered.
- ▶ In France, a survey was conducted to centers of expertise on RD in France in the context of the National policy to see which drug was used off-label frequently. Experts themselves reported on the topic. There is no outcome yet as the process is still ongoing.
- ▶ At European level, there is an ongoing survey, through EURORDIS, where patient associations report on off-label use. Patient groups are indeed an important source of information on use and concerns (safety, lack of evidence-based practice, drug to be taken out of the portfolio by the company in its regular indication and thus become unavailable).

From the discussion, it appears that the two main problems in off-label use are:

- ▶ The difficulty to gather information.
- ▶ The unwillingness of companies to explore the generation of more evidence for a new indication as new clinical trials may reveal some specific adverse effects that could impact the marketing of the drug in the main indication.

Status quo seems to be satisfactory to everybody, even the patients.

- ⇒ Members of the TSC agreed to encourage funders to support collection of off-label use.

### **Analysis of annual report of orphan designated products - WG on Orphan Drug-Development and Regulatory Processes**

This gap analysis can only be performed by the regulatory agencies as the reports are confidential, unless there is a partner assigned to do the works with confidential agreement.

- ⇒ The Chair of the TSC will bring this topic to the next teleconference with the FDA and EMA to inquire what can be done, what resources are necessary and can be allocated, and if not possible, to ask the WG to develop a 2-pages proposal for the Exec.

### **Gap analysis of unmet medical - WG on Orphan Drug-Development and Regulatory Processes**

This gap analysis, which does not seem to be doable with the resources of the Scientific Secretariat, should be performed with partners (Orphanet, patient groups and an academy team).

Although this analysis would be an enormous task, a horizon scan or pipeline update across RD would be incredibly useful. Most information is available online. It is possible to compare information about ongoing clinical trials with lists of open designated medicine to determine where the progress and gaps are.

- ⇒ The WG should develop a 2-pages proposal for recommendation of funding to submit to the Exec Com.

### **Joint/Coordinated Guidelines for Clinical development of clusters of medicinal products in specific Rare Diseases - WG on Orphan Drug-Development and Regulatory Processes**

Both FDA and EMA recognize the need for more guidelines on development of treatment for rare diseases, but guidelines can only be developed when information are available. The regulatory agencies already published guidelines occasionally but the process for Joint Guidelines is more complex.



- ⇒ The milestones document will be modified to include the comments and circulated to the TSC members before the end of the month.

## 6. Interaction between WGs and Scientific Committees

It is recognized that there is overlap and need of communication between SC and also some WGs. Discussion between the Chairs of the three SCs led to the identification of need of stronger link between:

- ▶ WG on Model Systems (DSC) – a member of TSC.
  - ▶ WG on Biobanks (ISC) – a member of TSC.
  - ▶ WG on Registries and Natural History (ISC) – a member of TSC.
  - ▶ WG on Models Systems (DSC) – WG on Biomarkers for Diseases Progression (TSC): common teleconference.
- ⇒ Members of the TSC agreed on the principle of this kind of communication
  - ⇒ Elizabeth McNeil volunteered to liaise with the WG on Model Systems

## 7. Short-term and long-term funding recommendations

### Short-term funding proposals to enable roadmap milestones

Discussion of the TSC milestones highlighted four projects requiring short-term funding:

- ▶ Workshop on Repurposing
- ▶ Workshop on Biomarkers
- ▶ Horizon Scanning of Unmet Medical Needs
- ▶ Analysis of annual report of Orphan Designated Products

### Long-term funding recommendations

The WG will be asked to write 1-2 pages background paper to inform and guide funders with their calls for research, based on the TSC recommendations.

## 8. Other topics

- ▶ Organization of the 2<sup>nd</sup> IRDiRC Conference (Shenzhen, China, Nov 2014) is going well. Program will be circulated to the TSC members and is available online.
- ▶ Next teleconference of this committee will be scheduled for February or early March. The Scientific Secretariat will send a Doodle.
- ▶ Next face-to-face meeting of this committee is planned on 5 June 2015 in Glasgow, UK, right before the ESHG meeting. The idea is to have first a meeting of the TSC followed by a joint meeting of the 3 IRDiRC SCs (half-day each).

## **Deliverables**

- ▶ Circulate the “Concept paper on good genomics biomarkers practices” to the WG on Biomarkers
- ▶ TSC Members to send suggestions for new members for the WG on Biomarkers to the Scientific Secretariat
- ▶ Contact the TSC members for volunteers to liaise with the ISC WG on Biobanks and WG on Registries and Natural History.
- ▶ Organize the next teleconference and next face-to-face meeting