IRDiRC
INTERNATIONAL RARE DISEASES RESEARCH CONSORTIUM

Meeting report series

Report of the 1st Therapies Scientific Committee (TSC) Meeting

Milan, San Raffaele Telethon Institute for Gene Therapy
19 July 2012; 9:30-16:30

Organization

Organized by: Dr Lucia Monaco and Ms Elena Bruno, Fondazione Telethon, Milan, Italy
Hosted by: San Raffale Telethon Institute for Gene Therapy (HSR-TIGET), Via Olgettina 60, Milan, Italy

Participants

Prof. Alessandro Aiuti, Milan, Italy
Dr. Giles Campion, Leiden, The Netherlands
Dr. Marcela del Rio Nechaevsky, Madrid, Spain
Prof. Marianne de Visser, Amsterdam, The Netherlands (leaving the meeting at 15:00)
Dr. Maria Mavris, Paris, France
Dr. Elizabeth McNeil, Bethesda, USA
Prof. Luigi Naldini, Milan, Italy
Prof. Josep Torrent I Farnell, Barcelona, Spain
Dr. Fulvio Mavilio, Evry, France (joining the meeting at 11:30)

Participants via teleconference

Dr. John McKew, Bethesda, USA
Dr. Glen Nuckolls, Bethesda, USA (connected from approximately 11:30 to 12:30)
Dr. Melissa Parisi, Bethesda, USA
Dr. Elad Sharon (representing Dr. Jack Welch), Rockville, USA
Prof. Gert-Jan B. van Ommen, Leiden, The Netherlands (connected from 10:00 to 11:00 and from 14:30 to 15:30 approximately)

EXECUTIVE SUMMARY

The first meeting of the IRDiRC Therapies Scientific Committee (TSC) took place in Milan on 19 July 2012. The meeting was organized by the Italian Telethon Foundation and hosted by the San Raffaele-Telethon Institute for Gene Therapy (HSR-TIGET).

TSC members participated either in person or via teleconference.

The meeting was primarily dedicated to a thorough discussion of the key task assigned to the Therapies Scientific Committee, namely the prioritization of therapies to be developed for rare diseases, and to the identification of roadblocks and bottlenecks hampering such development process.

The discussion's outcomes were as follows:

- The group of therapies designated as orphan drugs by the European and/or American regulatory agencies EMA and FDA was identified as the primary source of candidate therapies.
- A set of selection criteria was outlined, to be proposed to the IRDiRC member organizations as a means to prioritize funding and support to the development of therapies.
- Recommendations and enabling actions were envisaged, which could facilitate the pathway to registration of new therapies for rare diseases.

In addition, the TSC agreed on electing two co-chairs, from Europe and the USA respectively. Prof. Josep Torrent I Farnell (Spain) and Dr. Elad Sharon (USA) provisionally accepted appointment as co-chairs. Definitive appointments are due early in September.

Finally, a timeline for the next actions, including revision of the Policies and Guidelines document and definition of Working Groups, was set out.

REPORT

Introduction

The organizer thanked the Therapies Scientific Committee (TSC) members for their participation in the first TSC meeting.
All participants were invited to introduce themselves and to illustrate their background.
Subsequently, the organizer gave a presentation provided by the IRDiRC Scientific Secretariat, describing IRDiRC's objectives, governance structure and working model and illustrating the mandate, expectations and deliverables of the TSC.

Questions and answers

A brief Q&A session allowed clarification of key concepts regarding IRDiRC's objectives and modus operandi. For the sake of consistency, similar issues raised during the following sessions are also reported here. Similarly, points that were addressed right away in this Q&A session but that pertain general themes extensively discussed later on during the meeting are reported in the General discussion section below.

IRDiRC's objectives

- The goal of 200 new therapies by 2020 will be achieved (also) by building on ongoing studies both in the academia and in the industrial pipeline. Attracting more companies and more academic organizations to IRDiRC will allow to increase this count. All Committee members are invited to promote IRDiRC within their professional network of contacts.
- Each drug/therapy obtaining marketing authorization for a rare disease will be considered a new therapy.
- Each new marketing authorization will count as one, also in case of more drugs/therapies reaching marketing authorization for the same disease.
- A map of all IRDiRC projects will be built by the IRDiRC secretariat and made accessible to all participants to allow full exploitation of the available knowledge and resources.

IRDiRC's modus operandi

- It was reminded that the IRDiRC Scientific Committees will meet twice a year.
- The chair(s) of the Scientific Committees will also participate in the Executive Committee's meetings (2/year).
- IRDiRC member organizations are to support travel expenses of the Scientific Committee members they have nominated.
- Travel expenses of other members (not nominated by any member organization) are supported by the EU Commission (or by the NIH for NIH employees).
- Funding of IRDiRC projects will be supported by IRDiRC member organizations; no extra money will be made available through IRDiRC.

Election of the Committee's chair(s)

The TSC agreed to elect two co-chairs, from Europe (EU) and the USA respectively, for a two-year term at least. Election was postponed to the end of the meeting, following a full analysis of the Committee's scope and activities.
At the end of the meeting, Prof. Josep Torrent I Farnell and Dr. Elad Sharon provisionally accepted to chair the TSC.
Prof. Gert-Jan van Ommen and Dr. Welsh, who did not participate in the final part of the meeting, were also mentioned as possible chairs and will be invited to express their availability.
Definitive appointment is expected at the beginning of September 2012.

Comments and discussion on the Policies and Guidelines document

The nature and scope of the Policies and Guidelines document and the distinction between policies and guidelines were briefly recalled.
In general, it was suggested that the document's language be revised especially as far as regulatory terms are concerned to reflect the international (not just European) breadth of the initiative.
Due to time constraints, the TSC agreed to focus on section D.7 (Preclinical research and clinical trials). It was noted that this section will need expansion, to include themes that are not addressed in the current draft.
For instance, it was noted that phase I/II trials are not listed among interventional trials. It was discussed that not all exploratory (Phase I/II) trials are intended to support a marketing application (US)/ registration (EU). It was recommended that only trials that are intended to provide support for a future marketing application(US) /registration application (EU) be supported within IRDiRC, in that they imply higher commitment and regulatory control. Other kinds of trials, for instance trials conducted under hospital exemption, should not be endorsed by IRDiRC.
Before going into further analysis, however, the TSC found it important to address more general themes connected with the TSC goals, as reported in the General discussion section. At the end of the meeting, it was agreed that TSC members will share suggestions and annotations regarding the D7 section of the document via email by 14 September 2012.

General discussion

Key issues regarding the development of therapies for rare diseases within IRDiRC were extensively discussed and are summarized below.

The regulatory pathway

Interaction of IRDiRC with regulatory bodies was recommended. Experts from regulatory bodies should be invited at IRDiRC meetings and IRDiRC representatives should be acknowledged by regulatory bodies and invited to attend regulatory meetings.
It was remarked that orphan drug designation (ODD) is the first step of the regulatory pathway for rare

disease therapies and can be undertaken by academic organizations. Subsequently, transfer to industry is needed to proceed to marketing authorization. Scientific advice (protocol assistance) should be sought and is very helpful for marketing authorization.
Obtaining ODD from both FDA and EMA should be strongly encouraged, in order to promote synergies in the two regions and to avoid redundancies.

Priority list

Prioritization of 100 new or repurposed therapies with high potential is the first expected outcome of the TSC by the end of 2012.
This point was extensively discussed by the TSC.

Three possible sources of such candidate therapies, belonging to either advanced (cell/gene/tissue) therapies or to small molecules/repurposed drugs, were identified:

- Therapies that have obtained ODD from the EMA (approximately one thousand) or the FDA (approximately 2.400), or both; these are regarded as the most mature therapies that already passed regulatory validation of the rarity of the disease and the validity of the scientific/therapeutic approach. Being able to identify the ones that are blocked by one single problem could be useful; those already in the industrial pipeline should not represent a priority, as support is already available through the company.
- Drugs undergoing repurposing studies. These are typically being addressed by companies (e.g. Pfizer, Astra Zeneca, …), also in collaboration with academic bodies (NIH, MRC, …): it would be interesting to have access to specific information in this regard. In this context, lists of approved drugs used off-label for rare diseases and of medicines stalled in development not for safety reasons (e.g. because there are better molecules for the chosen indication) could be made available from the NIH.
- Therapies that went through protocol assistance and could obtain ODD within a short time (2-3 years), or advanced preclinical studies with a demonstrated proof of concept, which could feed the pipeline in future years.

In this regard, a document was distributed produced by a joint EMA/FDA working group in Bethesda (in 2011) that already addressed these issues (file attached).
The TSC did not deem it possible/feasible to select specific therapies/drugs to be nominated from among the above lists.
Nonetheless, it was suggested that **criteria for prioritization** be identified and proposed to the IRDiRC Executive Committee, such as:

- unmet medical need/absence of alternative treatments;
- rare disease with significant burden to patients, families or communities;
- feasibility of development;
- innovative therapeutic approaches addressing families of diseases;
- demonstrated need for additional support;
- existing knowledge on natural history of the disease;
- ODD in both EU and US

Dedicated **Working Groups** (specific to each category of therapies, i.e. advanced therapies vs. small

molecules) should be set up to address and refine such criteria, which would then help IRDiRC member organizations set their funding priorities.

Roadblocks and bottlenecks

When considering the >3.000 designated therapies as the primary source of therapies to be selected for development, it was highlighted that ignoring what roadblocks are hampering progress towards registration represents a major roadblock itself. Regulatory agencies do possess such information, but it is not accessible, since it was not collected in a searchable way. Suggestions were advanced as to ways to address this problem, either by asking the agencies or the investigators themselves, but none seemed practical.

Bottlenecks were also discussed, with particular attention to advanced therapies. In this regard:

- The regulatory pathway should be facilitated for advanced/innovative therapies. Preclinical studies required by regulatory agencies are quite heavy and represent a burden for the academia. Reconsidering regulatory policies and requirements might make this path easier to address and would not induce into alternative ways that would be less controlled. Provisional registration could be one way to facilitate the pathway.
- Although it is recognized that proper regulatory bodies are already in place to address the issues of innovative therapies, it is also known that the process is not efficient nor effective. For instance, although joint meetings between EMA and FDA are already taking place, such meetings are not frequent and the ensuing advice could be conflicting. Prioritizing proposals would be a way to make the path more effective for high-potential studies.
- Partnerships between academic groups and industry is essential to reach registration, not only because of the economic resources. Nonetheless, partnerships will not usually involve early stages of preclinical studies, before proof of concept. Identifying opportunities for early partnerships through grants or other opportunities would be beneficial.

It was suggested that a Working Group should be set up to address regulatory bottlenecks.
Enabling actions could be encouraged to allow academic groups to perform these studies according to regulatory requirements. Such actions might include resource sharing, knowledge support, centralized facilities, core laboratories for preclinical GLP studies, GMP vector core labs, etc.

Funding and collaborative models

It was acknowledged that, while no dedicated money is available through IRDiRC to support therapies development, recommendations ensuing from the TSC will be relayed to IRDiRC's Executive Committee and will serve as guidelines for funding decisions by IRDiRC member organizations.
Steering funds towards clinical investigation for rare diseases was the obvious recommendation from the TSC. It was noted that the NIH is supporting clinical trials and is promoting collaboration with companies for registration purposes. Their experience could be shared with European funding bodies.
Collaborative models between Astra Zeneca and the MRC in the UK, or similar collaborative programs led by the NCI/NIH were mentioned and could provide interesting models that could be taken as examples in the field of repurposing drugs. Appropriate information and links will be shared.

IRDiRC interactions

It was acknowledged that enabling processes for clinical development include natural history, registries, biomarkers, and outcome measures, and that most of these are being addressed by other IRDiRC Scientific Committees. The need for a strong interaction among the Committees was therefore highlighted. In this respect, holding joint Scientific Committee meetings would be optimal.

Main deliverables

- **The minutes of the first TSC** meeting are to be circulated to TSC members within the first week in August. Feedbacks from participants expected by 27 August 2012. Final document submitted to the Executive Committee by 7 September 2012.
- **Definitive appointment** of the TSC chairs will be confirmed by 7 September 2012.
- All TSC members are invited to **revise the "Policies & Guidelines" document** and to share and circulate suggestions/modifications by 14 September 2012 at the latest.
- The **TSC Working Groups** identified during the meeting should be **confirmed** and consolidated into a list by 14 September 2012. Additional Working Groups may be proposed.
- The **second TSC meeting** is planned in Fall 2012. If possible, a 2-day meeting will be organized. A Doodle poll will be set up to identify suitable dates. Volunteers to organize and host the meeting are kindly invited. The next EORTC-NCI-AACR meeting in Dublin, 6-9 November, was suggested.
- 2012, might offer the opportunity for some of the US TSC members to be in Europe. The TSC meeting could be organized in Europe close to those dates.
- **Next Executive Committee meeting**: 25-26 September 2012, Evry. Participants: members of the Executive Committee, chairs of the scientific committees (one each).
- **First IRDiRC Conference**: week starting 15 April 2013 in Dublin - exact dates to be confirmed. Participants: members of the Executive Committee, members of the Scientific Committees, members of the Working Groups, …