IRDiRC
INTERNATIONAL RARE DISEASES RESEARCH CONSORTIUM

Meeting report series

Report of the 4th DSC Working Group on Model Systems teleconference

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Organization

Organized by: IRDiRC Scientific Secretariat
Teleconference

Participants

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Agenda

- Brief introduction
- Mission Statement of the Model System WG
- WG initiatives – developing ideas of "market place", parallel phenotyping resources, education
- Next steps

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REPORT

Brief Introduction

The discussion points of this teleconference relate to:

- finalization of the mission statement of the WG
- discussion of ideas related to funding calls, i.e., market place and parallel phenotyping

Documents should be finalized and submitted to the Chair of the Diagnostic Scientific Committee within 2 weeks, ahead of the face-to-face Executive Committee meeting which will be held in Berlin on 7-8 May. The purposes are:

- To incorporate the WG's ideas into the roadmap to visualize how things would move forward in 2-5 years
- To present ideas for funding calls to Executive Committee for them to integrate in their future calls. As an example, E-Rare 2 2014 call has similar direction to that of IRDiRC and is planning to use the same strategy for future call (under E-rare 3). Suggestion of WGs will help with the formulation of future calls, either for specific or broad proposals.

Mission Statement of the Model System WG

The statement version of 11 April 2014 – a 2-page document which described the basic mission of the working group – was considered as finalized at this point of time. It will remain a working document that could evolve and expand as needed, especially in the area of recommendation.

WG Initiatives

"Functional Genomics Marketplace"

Members agreed on the previous teleconference that the data repository is the best model to implement. The corpus of the project remains essentially the same as before.

It is imperative to consider how this project could be funded considering its transnational nature: funding by multiple national organizations or alternatively, to have one national organization which would take on the lead role.

There are two parts to take into consideration:

- To establish and to run the marketplace,
- To use it as a vehicle for seed funding.

<u>Implementation of the project</u>

Members agreed that the best approach would be to use an existing infrastructure to develop this project, such as NCBI, EBI, Orphanet, Clinvar or other. This approach would increase the credibility of the

Marketplace, bring gain in terms of expertise, and facilitate ontology assignment and mapping to human situations. However, it could also loose potential uniqueness.
Two parameters to consider in the choice of the infrastructure are the level of data security necessary and risk of burying the marketplace among many other details already present in the infrastructure.
Investment for the creation of the back-end relational database and the front-end website will be needed. Cost for IT personnel is estimated at $100, 000 for constriction and approximately 20% of that figure per year for maintain and update.

⇨ A meeting with the heads of 4-5 structures that could support this concept to present the case could be a way to gauge the level of enthusiasm.

Seed Funding for Marketplace Investigators

Although the development of new collaborations is a sufficient outcome of the project, the availability of modest amounts of seed money to ignite projects of 'matched' investigators would be better. There are two possible systems for funding:

- modest: request supplement funding from national organizations already committed to the marketplace, e.g. in the USA, administrative supplements to R and P grants is a model that has been used by the Undiagnosed Disorders Network to follow up on matched investigations;
- more ambitious (and credible): marketplace itself secures funding through transnational mechanisms and matched investigators could request money directly from governing organizations. An example of cost calculation: $10-20K needed to model most genes → $150K to support about 10 projects per year; could run a pilot of 3 years and measure the return of investment via number of queries, number of matches, number of genes successfully modeled, and amount of and/or funding from companies.

While members agreed on seed funding being a very interesting idea, there were some concerns:

- this model could potentially be oversubscribed, or become last-chance resort for labs, thus adding burden for governing members to also sort out legibility and applicability of projects;
- it may be difficult to ensure/maintain a certain level of quality of the projects funded
- it may be difficult to make decision on project selection due to funding restriction, e.g. money from a national funding agency could only be spent within its border
- it may be difficult to follow up and determine value as different countries may validate quality differently
- small pilot may wither before it take off due to lack of attraction/uptake

Support could also be sought from more flexible, non taxpayer-bound funding organizations, such as Wellcome Trust, Gates Foundation, and Hughes Medical Institute.

Governance of Marketplace

A governing body, run by a chair and consist of a committee that would be made up of members of IRDiRC and/or external persons, would be vital to establish rules and review proposal.

- A rotational system would be essential as time commitment is imperative

- Administrative support would be required, perhaps from IRDiRC or from within own institutions of the members of the governing body.

Parallel Phenotyping Resources

With very few exceptions, model organisms have not really been used in direct drug development to make significant contributions. The number of hits coming from high throughput cell-based screens have very high failure rate (99.9%).

It would be important to show how models have been used to advance therapies but there's very little such information in the literature, especially in the area of rare diseases. A development of standards, (e.g. standard of phenotypic measures for different group of diseases, standard for each model organism that would make it appropriate for drug screening, standard for scalability of assays of phenotypic output), could be a starting point in assuaging the negative perception of model organisms.

For IRDiRC purpose, it is important to have validated disease-relevant output measures, preferably across organism. 2 types of approaches are possible:

- Obvious correlates: investigating phenotypes that resemble hallmarks of human disorders in an obvious manner (i.e. face validity).
- Phenolog correlates: investigating phenotypes seemingly unrelated but with same molecular foundations, thus non-obvious orthologous phenotypes.

There should thus be funding call for the development of the novel disease-relelvant output measures.
It was agreed that the development and validation of animal models would be useful for both:

- The interpretation of genetic variant (short-term).
- Drug development, by helping identify candidate targets acting on pathways to improve disease phenotype, leading to the preparation of pipeline for future (medium- and long-term).

Use of animal models for drug development can be divided in 2 steps:

- Validation of animal models.
- Use of validated models for drug testing.

In addition, idea of phenotypic outcome measures could be specifically applied to repurposing drugs, before expending the bond to other available drugs (screening platform).

Members agreed that the idea of using animal model to study the reversibility of a disease (to determine if disease is truly developmental or from acute deficiency of gene expression in late development phase) should not be included in the proposal as the topic is different.

Note: The Therapies Scientific Committee recommendations aim not only to achieve the goal of 200 new therapies for 2020, but also to ensure the pipeline beyond 2020.

Education (engagement the model organism communities, promoting connections)

- A draft of both abstract (for poster submission) and PowerPoint deck had been prepared and circulated, which can be modified and used at meetings where appropriate. Such presentation has been developed with the idea that it can be used when addressing various audiences, including lay person and government bodies. It also serves as a good beginning point to introduce IRDiRC and its working group, and to show examples of research activities by its members.
- Following discussion with editor and executive editor of AJHG, a review article in the format of a single article by multiple authors with sections for different organisms, each section – by a single author – with similar content, i.e. emphasizing how/advantages/disadvantages of a particular model, in biological and technological terms, for functionalizing human genomics should be published.
- In the meantime, a short perspective piece - to raise awareness of rare diseases, IRDiRC, and model organism in rare diseases research - could be published with the WG as an author.

Recommendations to IRDiRC

- Immediate funding to establish database, perhaps jointly with NCBI/EBI/others
- Finance-permitted, invest a percentage of funding as seed to move matched projects forward
- Proposal of generic call for parallel phenotyping which will be up to the applicants to make the case on why this is needed for their choice of phenotypes
- Consideration of possible research gap and funding to push continuous workflow

Main deliverables

- Update marketplace proposal
- Update parallel phenotyping proposal
- Distribution of documents to all members for feedback
- Read updated proposals and provide comments
- Write a short perspective
- Consultation with Therapies Scientific Committee to discuss points that will bridge the work between this working group and therapies perspective