IRDiRC
INTERNATIONAL RARE DISEASES RESEARCH CONSORTIUM

Meeting report series

Report of the 2nd DSC Working Group on Model Systems teleconference

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Organization

Organized by: IRDiRC Scientific Secretariat
Teleconference

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Agenda

1. Feedback from the Diagnostics Scientific Committee
2. Update on CIHR's decision to fund a call for a national research catalyst network on rare diseases
3. Goals and action plan
4. Main deliverables

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REPORT

Feedback from the Diagnostics Scientific Committee

During the 4th Diagnostics Scientific Committee (DSC) meeting that took place in Prague, the DSC decided that they would like the Working Group (WG) on Model systems to be shared between the Diagnostics Scientific Committee and the Therapies Scientific Committee (TSC). This WG has two roles that are relevant to both the DSC and TSC committees:

- Helping to identify novel disease genes by proving pathogenicity.
- Modelling human disease gene mutant phenotypes in order to create therapies.

In order to achieve these two goals, the WG should layout a concrete agenda with dates for the next six months, with the aim of guiding funding as opportunities arise.

Some guiding principles for new funding calls should be given by the Therapies Scientific Committee in order to identify what should be more tractable in terms of trying to find a therapy.

Update on CIHR's decision to fund a call for a national research catalyst network on rare diseases

The "Research Catalyst Network: Expediting collaboration between basic and clinician scientists in functional studies of novel rare disease genes" call is a funding opportunity in support of a single national network organized by the Canadian Institutes for Health Research (CIHR) in partnership with Genome Canada.

The goal of this call is to establish a national consortium that will enable clinical geneticists who are identifying rare disease gene mutations to collaborate with model organism researchers with expertise in the cognate gene's function. This program will build on Canada's leadership in rare disease gene identification, extending its involvement into developing treatments and therapeutics for rare diseases. Many rare disease genes encode products that have not been well studied in humans, and research in model organisms is a highly efficient strategy to facilitate the functional characterization of such genes.

This national network would:

- Identify instances where Canadian model organism expertise is relevant to a newly discovered disease gene; and when such instances are found, a research project would be initiated to explore the functional characterization of the gene.
- Develop and implement innovative knowledge translation strategies/activities to link the clinical genetics and model organism research communities together.

This network could establish a paradigm for connecting clinician scientists identifying novel disease genes with basic scientists performing gene functional analysis in model organisms, at much earlier time-points after the initial discovery of the disease causing mutation. In order to mobilize the whole country and identify the principal applicants for submitting a grant proposal, CIHR decided to put up a web page

to act as a collaboration tool where people declare their interest (principal investigator, steering committee, network member). The grant application will be submitted in April 2014 and funding wil be available in October 2014. The network is meant to mobilize a large group of researchers and clinicians, to integrate their resources, not compete, and to facilitate collaboration and communication. This aligns with the idea of a rare disease "market place", a concept discussed during the first teleconference of this WG.

Goals and action plan

It was agreed that the Model systems WG should define its mission by developing a one-page summary that describes three major goals. This road map will define the mission of the WG and set concrete priorities.

The three major aims of this WG are:

- To educate basic scientists, clinician scientists, and funding agencies about the power of model organisms for understanding gene function as the basis for developing rational approaches to therapies.
- To catalyse connections between basic scientists and clinician scientists, particularly as new disease genes are discovered, but also on a recurring basis.
- To guide, advise on, and secure funding for programs, community resources, and technologies that will allow models to have the greatest impact.

The DSC and the TSC would need this for the 7th IRDiRC Executive Committee Meeting that will take place on May 7-8, 2014 in Berlin, Germany.

Education

Model organisms are a powerful tool to investigate rare genetic diseases and their aetiology. To address questions such as the underlying molecular pathways or the reversibility of the phenotypes in genetic and pharmacologic rescue experiments, two principles are commonly applied:

- A model experimental organism is investigated using phenotypes that resemble hallmarks of the human disorder in an obvious manner. This approach has the advantage that, if sufficiently specific, these phenotypes readily validate the relevance of a disease model.
- A phenotype that is not a characteristic of the human disease, but is characteristic of the mutant phenotype of the disease gene's ortholog in a model system, is investigated. If the same molecular foundation underlies the disease phenotype in humans and the seemingly unrelated phenotype in a model, the latter can be used to gain further disease-relevant insights, additional candidate genes, and/or a rational strategy for identifying candidate therapeutic targets. Such non-obvious orthologous phenotypes have been termed Phenologs.

Both principles are widely applied in biomedical research, across the range of model organisms. However, for many disorders both obvious and non-obvious model organism equivalents of the disease

hallmarks are still poorly defined. The fact that Phenologs, that do not mimic the human disease but conserve the regulation of a pathway and its defects, can be used to better understand disease mechanism and guide identification of candidate therapeutic targets, is a powerful message to transmit. In this way, model organisms such as yeast, worms, and flies can offer powerful experimental approaches. An education process aimed at physician scientists and the model organism communities highlighting these principles would have a positive impact.

It would be highly valuable to push the experimental field of developing and validating novel test paradigms for model organisms that can be cross-compared between species ("parallel phenotyping") and related to humans. More sophisticated and more specific/characteristic output measures that are directly related to the disease pathology are desirable and could greatly promote taking advantage of experimentally tractable genetic models. Inter-species ontologies should be further developed as well to ensure optimal translatability between species.

An important point was raised during the discussion of both the research and educational missions of this WG regarding the prioritization of model system research to study the mechanisms of human diseases. Two criteria were discussed:

- Prioritize targets or disease genes mutations that are suppressible (reversible).
- Prioritize model organism research on molecular pathways that could be targeted for different diseases (common themes, common molecular networks). Examples could be given.

Connections

A major goal is to develop efficient mechanisms for catalysing connections, collaboration, and cross-talk between basic and clinician scientists. The over-arching goal is to facilitate investigation of the molecular mechanisms of disease early in the process of disease gene mutation discovery particularly when resources and expertise are pre-existing in a research laboratory. The idea is to develop a "market place" to facilitate collaboration between clinician researchers discovering new disease genes and basic researchers performing functional studies in model systems.

Resources

In IRDiRC, there is a one billion dollar envelope which belongs to each of its funders. In order to attract funding of programs that address the mandate of this WG, a road map should be presented to the funders as soon as possible, explaining that the goals and principles of the Model Systems WG will be critical in order to achieve the IRDiRC mission by 2020 and beyond. Part of the mission of this WG is to make the funding agencies aware of pertinent research opportunities and needs.

The implementation of a market place would necessitate resources and could be prioritized for a funding call. This WG needs to make concrete proposals on how the market place would work and what resources it would need in the longer term.

The CIHR Network Catalyst represents an example that uses the market place concept. In this network, a steering committee will act as liaison to the model organism communities by communicating with the clinician scientist community under confidentiality. They will see new discoveries as they are made. They

will also consider recent disease gene discoveries that have been made in Canada within consortia such as Forge, Care for Rare, and others. They will pro-actively link labs that have functional assays for genes or pathways in place or that have genetic resources that could be used immediately to functionalize disease gene variants that have been discovered. The amount of money that is available is very small (25 000 $ per connection/ 700 000 $ total per annum). This will be enough to make 20 or 30 connections per year and it is meant to be catalytic, that is, to provide resources to do very rapid experiments that establish functional validation of a disease gene mutation. These initial connections are expected to seed future grant applications. The model organism communities will be all connected in a central database where people self declare genes or pathways for which they have experimental expertise.

Main deliverables

- Summarize the three missions of this WG.
- Send an email explaining how Google drive works.
- Put the summary of the three missions of this WG on Google Drive and give access to all the WG members in order for them to give a feedback before February 24.
- Summarize the content of the feedback received from members of the WG in one page.
- Send a doodle to plan the next teleconference to be held in early March.