Adjudication Process Workflow

The RDMM Registry

The Registry is a web-based directory of Canadian model organism (MO) scientists where scientists use a combination of a free text summary of their research and structured data fields to enter information about their expertise and resources. This format reduces errors and inconsistencies and enables human-driven queries and algorithmic operations to identify relationships between genes, scientists, and phenotypes. MO scientists are prompted to: enter the identities of the genes they study; list phenotypes, pathways or processes of interest; and link these to formal identifiers.

Genes are matched to their standardized identifiers and displayed with their symbol and descriptive name for the investigator to confirm. For example, if a MO scientist indicated they work on yeast, and types "CHA1" they would be prompted to confirm that they are referring to "Catabolic L-serine (L-threonine) deaminase". If they type a partial identifier such as "YCL06" or "Catabolic L-serine" they will be prompted to choose from one or more matching yeast genes from the reference database. MO scientists will also be able to offer a list of genes which will be similarly confirmed for correct matches (rather than entering them one at a time). The same basic strategy will be used to allow scientists to indicate GO terms and phenotype ontology terms (HPO, MPO) reflecting their interests and analytic capabilities. Through this process, which only takes a few minutes, the MO scientist provides a sketch of their expertise, genes, disorders and phenotypes they study. MO scientists can update their profile at any time. A separate secure search interface is available to SAC to identify potential collaborations.

Step 1: Requests to the RDMM Network for a connection.

Clinicians submit a newly discovered disease gene by completing a Connection Application (**Appendix F**) available through the website. Upon submission to a secure website, the Coordinating Center assigns it a unique identifier and queues it for evaluation by CAC. Proposals need to contain sufficient information such that the CAC can evaluate the potential value of the gene/disease for the network.

Three categories of proposals are considered:

1. Novel gene supported by genetic evidence (mutations in the same gene in unrelated patients with a similar phenotype) and functional data is being rapidly sought prior to publication.
2. Candidate gene for a rare disease in a single patient/family/isolated population such that additional functional data is necessary to support disease-causation. Two types of candidate genes are considered:
    a. Candidate gene has not previously been associated with disease; and,
    b. Novel mutation in known disease gene causing a very distinct disease secondary to a presumed alternate mechanism.
3. Known disease gene that is of therapeutic or biological interest to a unique Canadian population or community (e.g. Hutterite, First Nation, French Canadian, patient group etc.).
    a. Therapeutic opportunities will include projects that propose to develop a model asset for drug screening or develop a model to evaluate efficacy of a treatment; and,
    b. Biological interest will include those genes published by a Canadian group for which further study has the potential to impact a new area of biology.

Three members of CAC evaluate each connection application, according to established criteria:

Criteria	Category 1	Category 2	Category 3
Quality of the genetic data as disease causing	+	+	NA
Disease severity and medical need	NA	+	+
Potential therapeutic tractability	NA	+	+
Impact on unique Canadian population	NA	+	+
Novelty of the implicated biological pathway	NA	+	+

After considering the applicable criteria, each CAC reviewer assigns a priority score to each application, using the following five-point criteria:

5 High priority

4 Moderate priority

3 Appropriate if sufficient funding

2 More data required, may resubmit

1 Not appropriate

Applications are reviewed bimonthly by the CAC and those with scores >3.0 are forwarded to the BIC for analyses by their standard pipeline. Proposals from clinicians who have already partnered with an MO researcher are still subjected to analysis by the BIC to reveal other potential avenues of study, which, if found, come under consideration by the SAC.

Step 2: Search for potential collaborators

For all approved applications, the BIC will analyze submitted genes to identify a MO scientist match and generate a standardized report for the SAC and applicant. The report summarizes connection application relevant to the matching process, provides basic information about the query gene and its orthologs, and lists identified MO scientist matches. The first step in the process is identifying the gene's orthologs in the MOs considered by the RDMM, using the DRSC Integrative Ortholog Prediction Tool (Hu et al., 2011) that integrates a number of ortholog prediction algorithms. The BIC then searches for potential matches in a tiered fashion; it first queries the Registry for direct matches (Tiers 1,2, or 3) using the ortholog list. If none are found the BIC repeats the Registry search with an extended list of human query genes by adding genes in the same family, pathway, and GO group. Finally, if this approach fails, we search the scientific literature using keywords based on the query genes, their biological processes and pathways, as well as phenotypes provided in the connection application to identify Canadian MO scientists who have the potential to undertake the functional characterization study.

The standardized BIC report contains a summary of the application relevant to the gene matching process, information about the query gene and its orthologs and detailed results of the BIC search that provides sufficient information for the SAC to make a decision about who to invite to submit a research proposal.

Step 3: Adjudication by the SAC. Upon review of the BIC work-up, the SAC invites candidate MO scientists to submit a two-page Gene Application (**Appendix I**). No more than four MO researchers per

RD gene are invited. Invitees have up to two weeks to respond to an invitation. Three SAC reviewers are assigned to each Gene Application, with standard conflict of interest rules in effect. Reviewers consider the feasibility for either functional characterization of the RD gene variant, demonstration of an experimental paradigm to probe the function of the MO gene in a context relevant to the human disease, or identification of candidate drug targets. Each reviewer submits a written review of 100 words or less, and presents their impression prior to open discussion at the SAC bi-monthly conference call. A yes or no decision is made by a majority of the SAC voting members present. Unsuccessful applicants may be invited to expand and clarify plans, and resubmit if the majority of SAC considers this warranted. Recommendations for establishing a connection between a MO scientist will be reviewed with the clinician, who will either accept or reject. If no match is made, the SAC asks the clinician if they would be interested in having RDMM forward the gene to the United States-based Model Organisms Screening Center (MOSC) for consideration there.

Step 4: Tracking the outcome of projects. A one page report summarizing findings to date is due six months after a catalyst funding is awarded and upon completion of the seed-funded project.