Gene Nomination Application Information

Round 7 Deadline: May 15, 2017 (Midnight Milwaukee, WI time). Submit completed application to: mcwcustomrats@mcw.edu

Decision on Applications: July 2017

Number of Applications that can be submitted: Up to two per laboratory or PI.

Number of Applications that will be awarded: Up to 25 meritorious applications.

Application review: An External Advisory Board (EAB) and staff from the National Heart, Lung, and Blood Institute (NHLBI) will review completed applications. The EAB will determine the successful applications and the priority of when the models will be made.

Animal Delivery date (Assuming success): 9 to 12 months after acceptance for most animal models.

Cost to investigator: Cost to raise each animal to age of shipping, plus shipping costs and any requested pathological tests on animals not covered by our standard Biomedical Resource Center survey program.

Distribution of Animals: The PI of the successful application will receive the first breeder pair. All other breeder pairs will be sent on a first come, first served basis to any other requesting investigator. There is NO priority period. When we receive the first heterozygous breeding pair the investigator will be notified and requested to begin making arrangements for shipment. At this time the web site (http://rgd.mcw.edu/wg/custom_rats/gerrc) will be updated to indicate that a new model will be available. The strain and mutation/modification will be posted.

Materials Transfer Agreement (MTA): The Applicant will be required to sign a materials transfer agreement prior to shipping the breeder pairs. Animals may not be sold or used for commercial activities.

Frequency of Applications: We anticipate two competitive application deadlines per year.

Gene Nomination Application

Background

The National Heart, Lung, and Blood Institute (NHLBI) has awarded the Medical College of Wisconsin an R24 Resource grant to make ~200 genetically modified rat strains over the next five years. These models will be of interest and value to the mission of the NHLBI. The NHLBI promotes the prevention and treatment of heart, lung, and blood diseases through scientific discovery directed toward the causes of disease and translation of basic discoveries into clinical practice.

We will make these rats using several different gene editing technologies. Gene editing is a new and powerful methodology for site directed mutagenesis, has made it feasible to genetically modify genes in rats in any desired genetic background three times faster than using traditional embryonic stem (ES) cell technology. The ability to make KO rats was recognized as a top 5 technology breakthrough by *The Scientist* in 2009 [1], and the number 8 runner-up for breakthrough of the year in 2010 by *Science* [2] and again by *Nature Methods* in 2011 [3]. The goal of this R24 is to bring access to this technology and corresponding novel and important rat models to more investigators by leveraging our existing infrastructure, personnel, economies of scale and distribution channels. These unique rats, developed by our existing program, have demonstrated the power of gene editing (http://rgd.mcw.edu/wg/physgenknockouts) to study physiological function, to interrogate potential new roles for candidate genes, to test genes nominated by Genome Wide Association Studies (GWAS), to validate genes underlying a quantitative trait locus (QTL), and study the function of genes. Over the last 20 years, we have focused on building genomic infrastructure for the community. This Resource Grant comes at a critical time when the cost to develop a single strain in a single lab or via some commercial laboratories is prohibitive and grant resources are tight. The Medical College of Wisconsin (MCW) Rat Genome Editing Resource Center will enable other investigators by leveraging our existing infrastructure and reducing costs by buying reagents in bulk. An External Advisory Board (EAB), in consultation with the NHLBI Program Officer, will determine which rat models are developed via a competitive application process. (N.B. MCW Investigators are not voting members on the EAB.).

References:

1. *The Scientist 2009 Top 10 Innovations.* The Scientist, 2009. **23**(12): p. 41.
2. *Breakthrough of the year. The runners-up.* Science, 2010. **330**(6011): p. 1605-7.
3. Baker, M., *Gene-editing nucleases.* Nat Methods, 2012. **9**(1): p. 23-6.

Application Process

1. Fill out the application as outlined below (Use application template found on website: http://rgd.mcw.edu/wg/gerrc).
2. Adhere to page lengths and requested information.
3. Failure to adhere to the guidelines will result in the application being returned without review.
4. MCW team will check for completeness and send all qualifying applicants to the Chair of the EAB, who will assign reviewers from the EAB. Reviewers will use the National Institutes of Health (NIH) scoring system (1 to 9 with 1 being best). Each criterion (see below) will be scored.
5. The EAB will score each application and then prioritize the order that each accepted model will be made.
6. PIs of applications not accepted or with low priority scores will be given a brief summary.

Application format

1. Gene name, gene symbol, and gene ID (from Rat Genome Database, http://rgd.mcw.edu)
2. Preferred strain background: select inbred strain (check box) or list other inbred strain and provide brief justification.
3. Hypothesis and relevance to NHLBI for gene requested (0.5 page maximum, include information about human studies if available as for example GWAS, family studies, human cell lines, *etc.*)
4. What type of gene modification is being requested (check box).
5. Rationale for why gene should be modified in rat (0.5 page maximum). If a mouse model exists, justify why a rat model is also needed.
6. Provide a brief rationale for background strain selection (0.5 page maximum). Include the broad utility of nominated model to other NHLBI investigators (0.25 page maximum).
7. Provide list of phenotypes to be measured. Do not provide detailed methods. (0.25 page maximum).
8. MCW can do some VERY limited phenotyping (*e.g.* blood pressure, renal phenotypes, cardiac phenotypes) as part of this R24 resource. If phenotyping is requested, provide proposed phenotyping protocol, articulate why the Applicant cannot do the phenotyping, and provide post-phenotyping study plans for the animals (0.5 page maximum).
9. Commitment to return phenotype data to RGD at time of publication. Data amenable to inclusion in RGD's PhenoMiner (http://rgd.mcw.edu/phenotypes) should be submitted at time of publication.
10. Provide contact information for institutional veterinarian and acknowledgement that assurance to receive genetically modified rats will be provided.
11. Submit a biosketch (up to 4 pages) with the narrative clearly stating the qualifications of the applicant (and/or his/her research team) to study the resultant rat models.

Review criteria – Scientific Merit

1. Hypothesis and need for the rat model requested.
   a. Explain how the model to be made will benefit the NHLBI mission (see above).
2. Experimental plan for the animal model to be developed for the applicant.

3. Need for phenotyping (if requested to be done by MCW).
4. Existing funding to support the animal model developed or likelihood of obtaining funding.
5. Qualifications of the Applicant.
6. Potential utility to more than one investigator.

Review criteria – Cost of making the model

Different strains, types of modifications requested (*e.g.* knockin versus inducible knockin) can impact the cost of making a model. The MCW team will assess the requested model and expected cost, which will be provided to the EAB. The EAB will judge scientific merit AND cost, when evaluating an application.

Scoring. Scoring will be similar to the current NIH methodology with the Overall Impact being the score used to prioritize access to the R24 resources. The reviewers (3 per application) will rank from 1 (best) to 9 (worst). Categories that will be ranked: significance, strain, type of mutation requested, research strategy, PI and cost. The EAB will have the ability to remove aspects of an application, if they believe the overall application is meritorious with these aspects removed.

Review criteria
Hypothesis & relevance to NHLBI
Experimental plan
Need for phenotyping at MCW
Existing funds or likelihood
Applicant qualifications
Potential utility to other investigators
Cost

FAQs (Frequently Asked Questions):

1. ***If my application is not accepted will I receive a review?*** You receive a brief summary of the discussion and main reason(s) not accepted.
2. ***If my application is not accepted can I resubmit?*** Yes, there is no limit on resubmissions.
3. ***Do I need to share my phenotyping results from the rats generated by this project?*** Yes, physiological data generated from these rats should be submitted to the Rat Genome Database's PhenoMiner (http://rgd.mcw.edu/phenotypes) at time of publication. Summary data for phenotypes measured by an experiment (*e.g.* heart rate, blood cell count, serum total cholesterol level, *etc.*) should be submitted to RGD and will be released at time of publication.