NCATS is pleased to offer this valuable resource of sample applications to the small business community. Seeing how successful applicants have presented their ideas brings a wholly new perspective to our own application preparation. In that spirit, with the gracious permission of successful grant applicants, NCATS and other Institutes at NIH provide below samples of funded applications, and summary statements, data or resource sharing plans, leadership plans and more.

Always follow your funding opportunity's instructions for application format. Although these applications demonstrate good grantsmanship, time has passed since these grant recipients applied. The samples may not reflect the latest format or rules.

SUMMARY STATEMENT

PROGRAM CONTACT: **(Privileged Communication)** ***Release Date:*** **07/01/2014**
Lillianne Portilla

Application Number: **1 R44 TR001197-01**

Principal Investigator

GIBSON, CHRISTOPHER

Applicant Organization: RECURSION PHARMACEUTICALS, LLC

Review Group: **ZRG1 IMST-J (15)**
Center for Scientific Review Special Emphasis Panel
Small Business: Cell, Computational, and Molecular Biology

Meeting Date: **06/26/2014**
Council: **OCT 2014**
Requested Start: **12/01/2014**

RFA/PA: **PAR14-088**
PCC: **OSA13**
Dual PCC: **P146SS**
Dual IC(s): **GM**

Project Title: **Expansion of an efficient drug repurposing platform for rare genetic diseases.**

SRG Action: **Impact Score: 15**
Next Steps: **Visit http://grants.nih.gov/grants/next_steps.htm**
Human Subjects: **10-No human subjects involved**
Animal Subjects: **30-Vertebrate animals involved - no SRG concerns noted**

Project Year	Direct Costs Requested	Estimated Total Cost
1	541,210	858,165
2	382,116	605,899
TOTAL	923,326	1,464,064

ADMINISTRATIVE BUDGET NOTE: The budget shown is the requested budget and has not been adjusted to reflect any recommendations made by reviewers. If an award is planned, the costs will be calculated by Institute grants management staff based on the recommendations outlined below in the COMMITTEE BUDGET RECOMMENDATIONS section.

1R44TR001197-01 Gibson, Christopher

RESUME AND SUMMARY OF DISCUSSION: The goal of this Direct-to-Phase2 application is to expand a recently developed cell-based drug discovery platform, combining experimental biology techniques with multi-parametric image data analysis, to screen and repurpose known drugs for the treatment of rare genetic diseases. Reviewers concurred on the high significance of the work proposed which, if successful, could yield a valuable high-throughput drug screening platform for rare genetic diseases that currently lack adequate cell models and approved pharmacological treatment. Innovation was identified in the synergistic integration of existing technologies to generate a state-of-the-art tool that could potentially revolutionize how phenotypic drug screens are done. The outstanding investigative team and excellent research environment were rated as major assets. Reviewers agreed that the high-risk/high-reward experimental strategy is well-designed and logically builds upon the proof-of-concept compellingly demonstrated by previous Phase 1-like work. Negligible concerns were noted regarding the likelihood that not all models of disease will generate a robust phenotype suitable for the proposed screening although even a partial success would represent a significant step towards identifying therapeutic candidates for orphan diseases. The commercialization plan was rated to be comprehensive and quite aggressive for a young company; potential IP limitations are acknowledged and negotiations with a pharmaceutical company are underway. Following the discussion, the panel expressed an outstanding level of enthusiasm for this highly significant project which could exert a very high impact on drug discovery for rare genetic disease.

DESCRIPTION (provided by applicant): There are thousands of rare genetic diseases that have no approved treatment. Recursion Pharmaceuticals has developed a drug discovery platform that seeks to re-purpose known drugs for the treatment of such diseases. The platform consists of high content immunofluorescent image analysis and transcellular resistance measurements. These measurements evaluated using machine-learning algorithms to identify relevant and on- target changes induced by both RNAi and various chemicals. These assays can be simultaneously performed on thousands of rare genetic disease models. In this grant, we specifically propose to: Model 2,000 genetic diseases in multiple human cell types using RNAi technology. Identify and prioritize 200 of these disease models with the most compelling phenotypic changes, according to multi-parametric quantification. Utilize these 200 disease models as the basis of chemical suppressor screens of thousands of known drug candidates. Validate the 20 best drug/disease combinations using an orthogonal genetic manipulation technique in human cells. Study the best five to ten validated drug/disease combinations in relevant animal models. The proposed study would have significant societal and commercial implications.

PUBLIC HEALTH RELEVANCE: There are thousands of rare genetic diseases that together affect millions of Americans. We will use chemical suppressor screens of known drugs, based on structural and functional changes in cellular disease models, to identify potential therapeutics for treatment of these diseases.

CRITIQUE 1:

Significance: 1
Investigator(s): 2
Innovation: 2
Approach: 2
Environment: 2

Overall Impact: This Direct-to-Phase II proposal seeks to develop an innovative platform able to probe simultaneously thousands of rare genetic diseases in human cellular models. Briefly, induced loss-of-function of specific genes associated with monogenetic diseases in primary cells are probed using multiparametric immunofluorescence imaging and transcellular resistance assays to define structural

and functional phenotypes. A selected number of the phenotypes are subjected to chemical suppressor screens using libraries of known drugs. Finally, efficacy of the drug candidates is tested in relevant animal models of the rare disease. Proof-of concept has been achieved with Phase I-like research resulting in two drug candidates for treatment of a hereditary stroke syndrome. An excellent team of investigator covers all levels of expertise needed for the performance of the project in state-of-the-art facilities. An ambitious Commercialization Plan is in place. The approach is powerful and well-designed although is lacking a good understanding of the mechanism of action of the prospective therapeutics. Overall, this reviewer is very enthusiastic about the application given the significance of the possible outcomes of the project.

1. Significance:

Strengths

- Novel therapeutic drugs for treatment of rare genetic diseases are urgently needed. Despite the Orphan Drug Act that creates regulatory and economic incentives, most of these diseases are lacking therapies. Poor understanding of the pathophysiology of the disease and the cost and time needed for the traditional development of drugs discourages investments for such small markets. Therefore, the development of an efficient drug-repurposing platform that simultaneously screens multiple rare diseases is highly significant.
- Proof-of-concept for the project is already achieved.
- Recursion has an exclusive world-wide license to the drug discovery platform from the University of Utah and has plans to develop trade secrets and method-of-use patents.

Weaknesses

- Repurposing drugs with safety clinical data from pharmaceutical companies may be difficult due to patent protection. The company is aware of these limitations.

2. Investigator(s):

Strengths

- The PI is a young investigator and entrepreneur that developed the proposed drug screening platform in the lab of Dr. Li at the University of Utah. He is one of the Founders of Recursion and CEO of the company. Dr. Gibson has assembled an excellent team that covers all the scientific expertise needed for such an ambitious project.
- Dr. Li is the Vice Dean of Research at the University of Utah. His lab focus on pathogenesis of diseases related to vascular stability with expertise in cell signaling and animal models. He is a co-Founder of Recursion and has previous experience with other biotech companies.
- The third co-founder of Recursion, Blake Borgeson, brings expertise in computational biology. He is also a successful entrepreneur.
- Dr. Carpenter is the Director Imaging platform at the Broad Institute of Harvard and MIT and creator of the open-source software CellProfiler used worldwide to automate high content screening assays.
- Dr. Thomas will use his expertise to direct the generation of knockout cell lines and mice using CRISPR/Cas9.
- Dr. Jones will act as a consultant in regulatory approval.

Weaknesses

- None noted.

3. Innovation:

Strengths

- The combination of technologies used in the design of the platform (loss-of-function in primary cells, big data analysis, high content analysis of cell morphology and functionality, HTS of drugs, testing of animal models, in silico approaches, etc.) to simultaneously evaluate thousands of rare diseases is very innovative.
- The company has exclusive license to the platform and Intellectual Property and Commercialization Plans are indicative of commercial potential.

Weaknesses

- None of the individual methods/ techniques used in the platform is novel.
- The use of open-source software is not ideal. The company should aggressively pursue development of proprietary software for their data analysis.

4. Approach:

Strengths

- Knockdown of candidate genes using siRNAs in two primary cell types will be used to screen structural and functional phenotypes. Screening of a library of known compounds for each disease model with selected phenotype and prioritization of confirmed hits. CRISP validation of the hits to generate stable cell line models with the corresponding loss-of-function and finally efficacy testing in animal models of the diseases are the Specific Aims of the application.
- The research plan is well-planned and detailed. Criteria for success at each step of the approach are defined and a timeline for execution of each aim is proposed. Potential challenges and proposed alternatives are also noted in each Aim.

Weaknesses

- Although very well planned, limitations at each step (only 2 cell types, off-target effects, relevance of the chosen phenotypes, lack of animal models, etc.) will challenge the approach for each specific rare genetic disease. It is expected, however, that the parallel screening of 2,000 genes associated with these diseases will render some good drug candidates in a cost-effective manner.

5. Environment:

Strengths

- Facilities and equipment available to the team at Recursion Pharmaceuticals and the University of Utah are excellent for the development of the proposed research.

Weaknesses

- None noted.

Phase II (Type 2 R42 and Type 2 R44 applications):

Acceptable

- The Phase I-like preliminary results support the feasibility of the Phase II approach. The screening of approx. 2000 compounds using the proposed drug discovery platform for a rare

monogenic disease, cerebral cavernous malformation or CCM, resulted in two new therapeutic candidates. One of them, Vitamin D will be studied for treatment of CCM in a collaboration with the Mayo Clinic. Negotiations with a pharmaceutical company to out-licensing or co-develop the second drug candidate, tempol, are underway. The pharmaceutical company has clinical data of tempol and plans to repurpose it as an orphan indication.

- The Commercialization Plan is ambitious but well-designed. The company is aware of the limitations of patent defensibility and will seek method-of-use patents and orphan indication status. Although the initial funding is limited a good strategy is in place for major financial rounds.

Protections for Human Subjects:

Not Applicable (No Human Subjects)

Vertebrate Animals:

Acceptable

- 5 points addressed. IACUC authorization will be seek once the animal murine models to be utilized are defined. No animal model work will be initiated until the corresponding authorizations are in place.

Biohazards:

Not Applicable (No Biohazards)

Resource Sharing Plans:

Acceptable

- According to the Small Business Act, the company will not share data for four years from the end of the award but will publish scientific data that could not commercialize.

Budget and Period of Support:

Recommend as Requested

- Sub-contract agreement with the Univ. of Utah is in place.

CRITIQUE 2:

Significance: 1
Investigator(s): 1
Innovation: 1
Approach: 1
Environment: 1

Overall Impact: This application proposes a highly ambitious, highly risky plan to conduct a broad drug repurposing screen against 2,000 orphan disease indications. If successful, this approach has the potential to revolutionize how phenotypic drug screens are done. And even if unsuccessful in its ultimate goal of identifying drugs for rare diseases, this project would generate a wealth of information on the basic biology of a myriad of genes involved in monogenic disorders. This proposal even with all

of the risk involved will have a major impact on how drug discovery and basic biology is performed. The applicant, while extremely junior, has assembled a very experienced team to help reach the goal and has clearly and thoroughly laid out the project plan with all of the outcomes and risks stated plainly and upfront. I highly and enthusiastically support this project.

1. Significance:

Strengths

- This proposal outlines a highly ambitious plan to repurpose developed drugs for orphan disease indications. If successful, this project will have major impacts on drug discovery in general and the approaches toward the rare disease space. It will revolutionize both fields.

Weaknesses

- None noted.

2. Investigator(s):

Strengths

- Although the applicant is quite junior, his previous work using this approach qualifies him to guide the detailed aspects of the project. The applicant has also assembled a deeply experienced team to cover various aspects of the project.

Weaknesses

- None noted.

3. Innovation:

Strengths

- This project outlined here is novel in the potential synergy of combining several well established approaches high throughput RNAi screening, high content imaging, monolayer impedance measurements, and compound screening. And adds in a newer technology, CRISPR/Cas9, for good measure. This well designed approach has the potential to change how phenotypic assays are currently conducted and how disease targets are approached.

Weaknesses

- None noted.

4. Approach:

Strengths

- The plan is well designed and well thought throughout. And many of the obvious caveats and pitfalls are stated upfront. The milestones and timelines are specific and reasonable.

Weaknesses

- None noted.

5. Environment:

Strengths

- The applicant and his team are well equipped and have the necessary infrastructure to perform the work outlined.

Weaknesses

- None noted.

Phase II (Type 2 R42 and Type 2 R44 applications):

Acceptable

- The progress and results obtained during Phase I equivalent period is outstanding and well justifies a Direct-to-Phase-II application.
- The Commercialization Plan is extremely thorough and well-thought out; it directly and objectively discusses the next steps and their associated risks.

Protections for Human Subjects:

No applicable

Vertebrate Animals:

Acceptable

- The application generally outlines acceptable justification and procedures for animal work, which will be specific, limited, and dependent on the in vitro phase of the work.

Biohazards:

Not Applicable (No Biohazards)

Resource Sharing Plans:

Acceptable

Budget and Period of Support:

Recommend as Requested

CRITIQUE 3:

Significance: 1
Investigator(s): 1
Innovation: 2
Approach: 2
Environment: 1

Overall Impact: Orphan diseases, numbering in the thousands, affect in aggregate a large number of the population. Yet, they are largely disregarded by large pharmaceutical interests. The proposal is to generate and the then phenotypically characterize cellular models of single gene Mendelian orphan diseases. Then, using the models with robust cellular phenotypes, the team will screen for chemical phenotypic suppression using libraries of approved existing pharmaceuticals. The team led by the PI

has shown that this pipeline for therapeutic discovery works for one disease, and is now proposing to apply the same procedures to ~2000 potential disease models. Not all models of disease will generate robust phenotypes at the cellular level amenable to the chemical screens described here. But, the potential to identify even in a minority fraction of 100s of new cellular disease models, new therapeutic agents that are approved and can be moved rapidly into clinical trials, is very exciting.

1. Significance:

Strengths

- PI and team have tested a multitier approach to a cellular model of CCM which includes cellular phenotype by imaging, transcellular resistance, and testing in a mouse model.
- A chemical screen of CCM cell model resulted in potential new therapeutics.
- They propose to screen many orphan disease (1000s) models to identify a large number >100 new cellular disease models to test in a similar way to generate a pipeline to identify existing therapeutic treatments for rare disease.

Weaknesses

- None noted.

2. Investigator(s):

Strengths

- The team as a whole seems well balanced with the appropriate expertise and years of experience, including the Broad Inst.

Weaknesses

- No perceived weaknesses.

3. Innovation:

Strengths

- Cellular models of disease can be generated by CRISPR or RNAi and the high throughput nature of the approach, in aggregate, may be able to identify new novel therapeutics that can quickly be repurposed to treat orphan diseases.

Weaknesses

- Not all diseases will be amenable to the cellular approach, due to the limitations of the specific phenotypic parameters measured. However, the PI is proposing to screen a large number of potential disease models, and then, chemical screens on only those that result in robust phenotypes. The hope is that they will find new therapies for even a minority fraction, which will still be new therapies for orphan diseases.

4. Approach:

Strengths

- Categorizing phenotypes will allow for assays/screens for drugs to ameliorate phenotype.
- Estimates that in screen of 2000, at least 100 cellular phenotypic models of disease, amenable for screening may result.

Weaknesses

- Not all diseases will be well modeled using these parameters and cellular models.

5. Environment:

Strengths

- Excellent.

Weaknesses

- None perceived.

Phase II (Type 2 R42 and Type 2 R44 applications):

Acceptable

- The phase I type data provided here is a really compelling demonstration of the pipeline approach to cellular models of disease. While not all diseases will yield important finding by following this approach, the goal here is to screen 1000s of disease genes to generate a still large number (in the 100s) of disease models for chemical screens to effect phenotypic suppression. If even a small number, let's say 5% of the models yield new therapies, that are still going to be 5-10 new therapies for disease which large pharmaceutical companies will not have considered.
- The commercialization plan is very thorough and promising. As the investigators realize, the potential is to generate far more cellular models of disease than they can utilize, and so these will be made available. The drug screening potential are also discussed as well as longer term plans to sequence into drug trials.

Protections for Human Subjects:

Not Applicable (No Human Subjects)

Vertebrate Animals:

Acceptable

Biohazards:

Acceptable

Resource Sharing Plans:

Acceptable

Budget and Period of Support:

Recommend as Requested

THE FOLLOWING RESUME SECTIONS WERE PREPARED BY THE SCIENTIFIC REVIEW OFFICER TO SUMMARIZE THE OUTCOME OF DISCUSSIONS OF THE REVIEW COMMITTEE ON THE FOLLOWING ISSUES:

VERTEBRATE ANIMAL (Resume): ACCEPTABLE

Mice will used in this study. The panel noted that the five required points for Vertebrate Animal use are adequately addressed by the applicant and rated the proposed plan as acceptable.

COMMITTEE BUDGET RECOMMENDATIONS: The budget was recommended as requested**.**

NIH has modified its policy regarding the receipt of resubmissions (amended applications). See Guide Notice NOT-OD-14-074 at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-074.html. The impact/priority score is calculated after discussion of an application by averaging the overall scores (1-9) given by all voting reviewers on the committee and multiplying by 10. The criterion scores are submitted prior to the meeting by the individual reviewers assigned to an application, and are not discussed specifically at the review meeting or calculated into the overall impact score. Some applications also receive a percentile ranking. For details on the review process, see http://grants.nih.gov/grants/peer_review_process.htm#scoring.

MEETING ROSTER

Center for Scientific Review Special Emphasis Panel
CENTER FOR SCIENTIFIC REVIEW
Small Business: Cell, Computational, and Molecular Biology
ZRG1 IMST-J (15) B
June 26, 2014

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Consultants are required to absent themselves from the room during the review of any application if their presence would constitute or appear to constitute a conflict of interest.