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
(Privileged Communication)

PROGRAM CONTACT: Personal Info

Release Date: **07/01/2014**

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

Principal Investigator

Personal Info

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:** Priority Score
Next Steps: **Visit http://grants.nih.gov/grants/next_steps.htm**
Human Subjects: **10-No human subjects involved**
Animal Subjects: **30-Vertebrate animals involved -** reviewers comments

Project Year	Direct Costs Requested	Estimated Total Cost
1	Itemized Cost	Estimated Costs
2		
TOTAL	Itemized Cost	Estimated Costs

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.

Personal Info

1R44TR001197-01 Personal Info

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 comments

reviewers comments

reviewers comments

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:

reviewers comments

Personal Info

reviewers comments

Personal Info

reviewers comments

Personal Info

reviewers comments

CRITIQUE 2:

reviewers comments

Personal Info

reviewers comments

Personal Info

reviewers comments

CRITIQUE 3:

reviewers comments

Personal Info

reviewers comments

Personal Info

reviewers comments

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): reviewers comments

Per sonal Info

reviewers comments

COMMITTEE BUDGET RECOMMENDATIONS: reviewers comments

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

Personal Info

Personal Info

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.

PI: Personal Info	Title: Expansion of an efficient drug repurposing platform for rare genetic diseases.	
Received: 04/07/2014	Opportunity: PAR-14-088	Council: 10/2014
Competition ID: ADOBE-FORMS-B2	FOA Title: DIRECT PHASE II SBIR GRANTS TO SUPPORT BIOMEDICAL TECHNOLOGY DEVELOPMENT	
1R44TR001197-01	Dual: GM	Accession Number: 3687015
IPF: 10035845	Organization: RECURSION PHARMACEUTICALS, LLC	
Former Number:	Department:	
IRG/SRG: ZRG1 IMST-J (15)B	AIDS: N	Expedited: N
Subtotal Direct Costs (excludes consortium F&A) Year 1: Itemized Cost Year 2:	Animals: Y Humans: N Clinical Trial: N Current HS Code: 10 HESC: N	New Investigator: Early Stage Investigator:
Senior/Key Personnel:	*Organization:*	*Role Category:*
Personal Info		PD/PI
		Co-Investigator
		Co-Investigator
Consultant Info		Consultant
		Consultant
		Consultant

OMB Number: 4040-0001
Expiration Date: 06/30/2011

APPLICATION FOR FEDERAL ASSISTANCE
SF 424 (R&R)

3. DATE RECEIVED BY STATE	State Application Identifier

1. * TYPE OF SUBMISSION
☐ Pre-application ☐ Application ☒ Changed/Corrected Application

2. DATE SUBMITTED: 04/04/2014

Applicant Identifier:

4. a. Federal Identifier: GRANT11623742

b. Agency Routing Identifier:

5. APPLICANT INFORMATION

*** Organizational DUNS:** Proprietary Info

* Legal Name: Recursion Pharmaceuticals, LLC

Department: Division:

* Street1: Proprietary Info

Street2:

* City: Proprietary Info County / Parish: Proprietary Info

* State: Proprietary Info Province:

* Country: Proprietary Info * ZIP / Postal Code: Proprietary Info

Person to be contacted on matters involving this application

Prefix: Personal Info * First Name: Personal Info Middle Name: Personal Info

* Last Name: Personal Info Suffix:

* Phone Number: Personal Info Fax Number: Personal Info

Email: Personal Info

6. * EMPLOYER IDENTIFICATION *(EIN) or (TIN)*: Personal Info

7. * TYPE OF APPLICANT: R: Small Business

Other (Specify):

Small Business Organization Type ☐ Women Owned ☐ Socially and Economically Disadvantaged

8. * TYPE OF APPLICATION:
☒ New ☐ Resubmission
☐ Renewal ☐ Continuation ☐ Revision

If Revision, mark appropriate box(es).
☐ A. Increase Award ☐ B. Decrease Award ☐ C. Increase Duration ☐ D. Decrease Duration
☐ E. Other (specify):

* Is this application being submitted to other agencies? Yes ☐ No ☒ What other Agencies?

9. * NAME OF FEDERAL AGENCY: National Institutes of Health

10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER:

TITLE:

11. * DESCRIPTIVE TITLE OF APPLICANT'S PROJECT:
Expansion of an efficient drug repurposing platform for rare genetic diseases.

12. PROPOSED PROJECT:
* Start Date: 12/01/2014 * Ending Date: 11/30/2016

*** 13. CONGRESSIONAL DISTRICT OF APPLICANT**: UT-002

14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION

Prefix: Personal Info * First Name: Personal Info Middle Name: Personal Info

* Last Name: Personal Info Suffix:

Position/Title: Chief Executive Officer

* Organization Name: Recursion Pharmaceuticals, LLC

Department: Division:

* Street1: Personal Info

Street2:

* City: Personal Info County / Parish: Personal Info

* State: Personal Info Province:

* Country: USA: UNITED STATES * ZIP / Postal Code: Personal Info

* Phone Number: Personal Info Fax Number: Personal Info

* Email: Personal Info

15. ESTIMATED PROJECT FUNDING

a. Total Federal Funds Requested	Itemized Cost
b. Total Non-Federal Funds	
c. Total Federal & Non-Federal Funds	
d. Estimated Program Income	

16. * IS APPLICATION SUBJECT TO REVIEW BY STATE EXECUTIVE ORDER 12372 PROCESS?

a. YES ☐ THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON:

DATE:

b. NO ☒ PROGRAM IS NOT COVERED BY E.O. 12372; OR

☐ PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW

17. By signing this application, I certify (1) to the statements contained in the list of certifications* and (2) that the statements herein are true, complete and accurate to the best of my knowledge. I also provide the required assurances * and agree to comply with any resulting terms if I accept an award. I am aware that any false, fictitious. or fraudulent statements or claims may subject me to criminal, civil, or administrative penalities. (U.S. Code, Title 18, Section 1001)

☒ *** I agree**

**** The list of certifications and assurances, or an Internet site where you may obtain this list, is contained in the announcement or agency specific instructions.***

18. SFLLL or other Explanatory Documentation

Add Attachment | Delete Attachment | View Attachment

19. Authorized Representative

Prefix: Personal Info * First Name: Personal Info Middle Name: Personal Info

* Last Name: Personal Info Suffix:

* Position/Title: Chief Executive Officer

* Organization: Recursion Pharmaceuticals, LLC

Department: Division:

* Street1: Personal Info

Street2:

* City: Personal Info County / Parish: Personal Info

* State: Personal Info Province:

* Country: Personal Info * ZIP / Postal Code: Personal Info

* Phone Number: Personal Info Fax Number: Personal Info

* Email: Personal Info

*** Signature of Authorized Representative**

Personal Info

*** Date Signed**

04/07/2014

20. Pre-application

Add Attachment | Delete Attachment | View Attachment

424 R&R and PHS-398 Specific Table Of Contents

OMB Number: 4040-0010
Expiration Date: 08/31/2011

Project/Performance Site Location(s)

Project/Performance Site Primary Location ☐ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Recursion Pharmaceuticals, LLC

DUNS Number: Proprietary Info

* Street1: Proprietary Info

Street2:

* City: Proprietary Info County: Proprietary Info

* State: Proprietary Info

Province:

* Country: Proprietary Info

* ZIP / Postal Code: Proprietary Info * Project/ Performance Site Congressional District: Proprietary Info

Project/Performance Site Location 1 ☐ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: University of Utah

DUNS Number: Proprietary Info

* Street1: Proprietary Info

Street2:

* City: Proprietary Info County: Proprietary Info

* State: Proprietary Info

Province:

* Country: Proprietary Info

* ZIP / Postal Code: Proprietary Info * Project/ Performance Site Congressional District: Proprietary Info

Additional Location(s) Add Attachment Delete Attachment View Attachment

RESEARCH & RELATED Other Project Information

OMB Number: 4040-0001
Expiration Date: 6/30/2016

1. Are Human Subjects Involved? ☐ Yes ☒ No

1.a. If YES to Human Subjects

Is the Project Exempt from Federal regulations? ☐ Yes ☐ No

If yes, check appropriate exemption number. ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6

If no, is the IRB review Pending? ☐ Yes ☐ No

IRB Approval Date:

Human Subject Assurance Number:

2. Are Vertebrate Animals Used? ☒ Yes ☐ No

2.a. If YES to Vertebrate Animals

Is the IACUC review Pending? ☒ Yes ☐ No

IACUC Approval Date:

Animal Welfare Assurance Number: None

3. Is proprietary/privileged information included in the application? ☒ Yes ☐ No

4.a. Does this Project Have an Actual or Potential Impact - positive or negative - on the environment? ☐ Yes ☒ No

4.b. If yes, please explain:

4.c. If this project has an actual or potential impact on the environment, has an exemption been authorized or an environmental assessment (EA) or environmental impact statement (EIS) been performed? ☐ Yes ☐ No

4.d. If yes, please explain:

5. Is the research performance site designated, or eligible to be designated, as a historic place? ☐ Yes ☒ No

5.a. If yes, please explain:

6. Does this project involve activities outside of the United States or partnerships with international collaborators? ☐ Yes ☒ No

6.a. If yes, identify countries:

6.b. Optional Explanation:

7. Project Summary/Abstract 1241-ProjectSummary_Recursion_Final.p Add Attachment Delete Attachment View Attachment

8. Project Narrative 1242-ProjectNarrative_Recursion_Final Add Attachment Delete Attachment View Attachment

9. Bibliography & References Cited 1243-ReferencesCited_Recursion_Final. Add Attachment Delete Attachment View Attachment

10. Facilities & Other Resources 1244-FacilitiesAndResources_Recursion Add Attachment Delete Attachment View Attachment

11. Equipment 1245-Equipment_Recursion_Final.pdf Add Attachment Delete Attachment View Attachment

12. Other Attachments Add Attachments Delete Attachments View Attachments ☒

PROJECT SUMMARY

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.

PROJECT NARRATIVE

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.

FACILITIES & OTHER RESOURCES

1. Recursion Pharmaceuticals, LLC

Recursion Pharmaceuticals is located at Proprietary Info, in the Research Park Area of Salt Lake City, immediately adjacent to the University of Utah. The Colorow building was originally built as the headquarters of NPS Pharmaceuticals, and was acquired by the University of Utah when NPS relocated to New Jersey. This building is thus highly-modern and was designed specifically for industrial pharmaceutical business. Recursion Pharmaceuticals has leased approximately Square Footage of laboratory space and Square Footage of office space on the second floor. This same building houses the University of Utah Drug Discovery Core Facility, which hosts a wide variety of equipment and reagents useful in drug discovery (see description below).

Our laboratory is complete with three (3) benches, one (1) fume hood, one (1) tissue-culture hoods, one (1) tissue culture carbon dioxide incubator, one (1) tissue culture refrigerator, one (1) tissue culture freezer, one (1) liquid nitrogen dewar, one (1) phase contrast general purpose tissue culture microscope (Zeiss), one (1) thermo water bath, one (1) Sigma refrigerated centrifuge, one (1) Invitrogen Countess automated cell counter, one (1) analytical balance, and one (1) PlateMate automated 96-well pipette. The laboratory also includes a variety of miscellaneous small equipment (micro-centrifuges, hand-held pipettes, etc.). The laboratory is fully-stocked with relevant tissue culture and immunofluorescent reagents.

Our offices are equipped with password-protected personal computers.

2. Center for Investigational Therapeutics and Drug Screening Core, University of Utah

The Drug Screening Core Resource (DSR) is located immediately below Recursion Pharmaceuticals, on the first floor of the Colorow building. This Square Footage laboratory is managed by Personal Info, who offers expertise in assay optimization, medicinal chemistry, and structure-based lead optimization (please see attached letter of support).

Compound Libraries:

The Drug Screening Core has at least 7 compound libraries available for screening. 1) The Chembridge DIVERset (Chembridge, Inc) is a 49,000 drug-like small molecule library selected on the basis of 3-D pharmacophore analysis. 2) The Spectrum Collection (MicroSource Inc.) is a 2000 compound library of varied biologic activity and structural diversity including 1000 known drugs from the U.S., Europe, and Japan. 3) The Kinase Inhibitor Library (EMD Biosciences) is a 160 compound library of well-characterized, cell-permeable, potent, and reversible protein kinase inhibitors (the majority of which are ATP-competitive). 4) The Ireland Collection is a library of 240 natural products isolated from marine invertebrates animals and micro-organisms that reflect a wide array of natural product scaffolds and biosynthetic pathways. 5) The U. Chemistry Department Collection is a diverse collection of 450 molecular skeletons that generally reflect natural product substructures or analogues of proven pharmacophores. 6) The NPS collection includes 120,000 diverse compounds of combinatorial chemistry and natural products (75,000 of which are unique to this library possessed only by the U. of Utah). 7) The Spider Venom library consists of 100 compounds isolated from spider venom. 8) The NIH Clinical Collection and Clinical Collection II, composed of 787 known drugs. Additionally, the core has secured funding for additional libraries that will be added in the near future. The libraries are stored in coded racks in backup-power supported -20°C freezers (except for the NPS collection, which, due to its size, is stored at an offsite facility).

3. Comparative Medicine Center, University of Utah

Mice will be house in the comparative medicine center located across the street from Personal Info lab at the Eccles Institute of Human Genetics (EIHG). This is an approved animal facility that houses the research animals for many of the investigators on the University of Utah's Health Sciences Campus. Mice are housed in standard cages and are supplied with a constant source of food or water, except when protocols dictate otherwise. Technicians check the animals on a daily basis to ensure their health. Veterinary staff is on call 24 hours a day to provide assistance with sick animals. Dedicated cold storage facilities are available on site, as are surgical suites and other treatment rooms. Advanced biometric access protocols are in place to prevent unauthorized access. Infection control and quarantine are also in place to prevent cross-contamination

4. Laboratory of Personal Info **University of Utah**

Personal Info laboratory is a part of the University of Utah Molecular Medicine Program (U2M2) and is located in the Eccles Institute of Human Genetics/ University of Utah, which houses the U2M2, the Department of Human Genetics, the University of Utah Genome Center, the University of Utah Gene Targeting/Transgenic Core, and the Howard Hughes Medical Institute. This building is adjacent to the University of Utah Health Science Center. The Square Footage laboratory consists of 12 benches, 2 fume hoods, a dedicated cell culture room, and a cold room. It is equipped with refrigerators (4), -20°C (8), -80°C (8) and -140°C (2) freezers, orbital shaker (3), microcentrifuges (8), heating blocks (8), water baths (6), tissue-culture hoods (4), tissue-culture incubators (6), and bacterial preparation incubators. The lab has a Jung histoembedder, a PTP 1530 paraffin embedder, a microprobe incubator, a Leica CM 1950 cryostat, a Leica RM 2065 microtome, and microscopes with digital cameras and computers (Zeiss Stemi 2000, Zeiss Axioplan 2, 2 Leica MZ12s).), an Artisan slide stainer instrument, Beckman TL-100 ultracentrifuge, Applied Biophysics ECISZ Theta permeability measurement machines (1 standard 16-well system and 1 high-throughput 96-well system), as well as a 1450 MicroBeta TriLux scintillation counter. Other equipment includes four MJ research PCR machines, carbon dioxide incubators (2), extended range electroporation system, rotisserie hybridization incubators, and an UV crosslinker. The lab is well equipped with standard molecular biology equipment such as protein electrophoresis units (10), western blotting transfer equipment (5), power supplies (10), gel documentation system including a LICOR system, pippettemen, autoradiograph cassettes, and Geiger counter. The lab is equipped with two VisualSonics Vevo 2100 ultrasound machines (Toronto, Canada) capable of 2-D, color Doppler, pulsed wave Doppler, tissue Doppler, contrast and 3-D imaging.

All the laboratories and offices are equipped with password-protected personal computers. Ample office space is available for the investigators and support staff. Color and black and white printers are available in the laboratory office space. Oversize printers for posters are available for use on the first-floor of the building.

EQUIPMENT

In addition to the facilities, resources, and basic equipment listed in the Facilities & Resources section, Recursion has secured the use of several specific pieces of equipment that are housed nearby in the Center for Investigational Therapeutics and Drug Screening Core at the University of Utah.

Imaging Equipment:

The core is equipped with a high-throughput high-content immunofluorescence imaging system. The Molecular Devices ImageXpress Micro XLS includes an oversized CMOS detector, multiple Nikon objectives, a variety of standard filter sets (7 wavelengths plus a triple-pass filter for high-speed imaging), a configurable solid state light engine with customizable and instantly selectable wavelengths from 380nm to NIR, and a dual-monitor workstation for image acquisition and short-term storage. This system is also equipped with a thermo Catalyst Express plate-loading robot. This imaging system has been secured for use by Recursion Pharmaceuticals at a low hourly fee (see letters of support from Personal Info and Personal Info

Liquid Handling Equipment:

The core is equipped with a variety of liquid handling instruments including. 1) Tecan EVO150 96-well automated liquid handling system with sterile enclosure, 2) Tecan EVO 150 384-well automated liquid handling system with sterile enclosure and plate-stackers, 3) Matrix PlateMate Plus 384-well head system for plate replication with a 1.0 ul lower volume limit. 4) Matrix PlateMate 96-well head system for plate replication with a 1.0 ul lower volume limit. 5) Matrix SerialMate 8-chanel system for serial dilution with a 1.0 ul lower volume limit. 6) Two Eppendorf EPMotion 5075 8-channel system for molecular biology assays with a 2.0 ul lower volume limit. Additionally, funding has been secured for a state-of-the-art Labcyte ECHO acoustic energy nano-liter liquid handling system which will be in place shortly. This system, along with plate-handling robotics equipped with database-linked barcode readers, will be setup in a sterile tissue-culture hood for accurate and sterile addition of small molecules to cell-culture plates without the use of tips, pins, or nozzles. The laboratory space housing these systems includes laboratory benches (2) and hoods (2).

U.S. Small Business Administration

SBIR.gov SBC Registration Control ID Form

Company Information

SBC Control ID	Proprietary Info				
Company Name	Recursion Pharmaceuticals, LLC				
Address	Proprietary Info				
City		**State**	Proprietary Info	**Zip**	Proprietary Info
TIN/EIN		**DUNS**	Proprietary Info		
Company URL					
Number of Employees	# OF EMPLOYEES				

Is this SBC majority-owned by multiple venture capital operating companies, hedge funds, or private equity firms?	No
What percentage (%) of the SBC is majority-owned by multiple venture capital operating companies, hedge funds, or private equity firms?	0%

OMB Number: 4040-0001
Expiration Date: 06/30/2011

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator

Prefix: Personal Info * First Name: Personal Info Middle Name: Personal Info
* Last Name: Personal Info Suffix:
Position/Title: Chief Executive Officer Department:
Organization Name: Recursion Pharmaceuticals, LLC Division:
* Street1: Personal Info
Street2:
* City: Personal Info County/ Parish: Personal Info
* State: Personal Info Province:
* Country: Personal Info * Zip / Postal Code: Personal Info
* Phone Number: Personal Info Fax Number: Personal Info
* E-Mail: Personal Info

Credential, e.g., agency login: eRA Commons User Name

*** Project Role:** PD/PI **Other Project Role Category:**

Degree Type: Ph.D.
Degree Year: 2013

***Attach Biographical Sketch** 1235-01 - Biosketch_Personal Info [Add Attachment] [Delete Attachment] [View Attachment]
Attach Current & Pending Support [Add Attachment] [Delete Attachment] [View Attachment]

PROFILE - Senior/Key Person 1

Prefix: Personal Info * First Name: Personal Info Middle Name: Personal Info
* Last Name: Personal Info Suffix:
Position/Title: Professor Department: Internal Medicine
Organization Name: University of Utah Division: Personal Info
* Street1: Personal Info
Street2:
* City: Personal Info County/ Parish: Personal Info
* State: Personal Info Province:
* Country: Personal Info * Zip / Postal Code: Personal Info
* Phone Number: Personal Info Fax Number: Personal Info
* E-Mail: Personal Info

Credential, e.g., agency login: eRA Commons User Name

*** Project Role:** Co-Investigator **Other Project Role Category:**

Degree Type: MD/PhD
Degree Year: 1990

***Attach Biographical Sketch** 1236-02 - Biosketch_Personal Info_Final [Add Attachment] [Delete Attachment] [View Attachment]
Attach Current & Pending Support [Add Attachment] [Delete Attachment] [View Attachment]

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Senior/Key Person 2

Prefix: Personal Info * First Name: Personal Info Middle Name:

* Last Name: Personal Info Suffix:

Position/Title: CTO Department:

Organization Name: Recursion Pharmaceuticals, LLC Division:

* Street1: Personal Info

Street2:

* City: Personal Info County/ Parish:

* State: Province:

* Country: * Zip / Postal Code: Personal Info

* Phone Number: Personal Info Fax Number:

* E-Mail: Personal Info

Credential, e.g., agency login:

*** Project Role:** Co-Investigator **Other Project Role Category:**

Degree Type: BS

Degree Year: 2003

***Attach Biographical Sketch** 1237-03 - Biosketch_Personal Info [Add Attachment] [Delete Attachment] [View Attachment]

Attach Current & Pending Support [Add Attachment] [Delete Attachment] [View Attachment]

PROFILE - Senior/Key Person 3

Consultant Info

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Senior/Key Person 4

Consultant Info

PROFILE - Senior/Key Person 5

Consultant Info

Tracking Number:GRANT11624079 Funding Opportunity Number:PAR-14-088 Received Date:2014-04-07T17:14:41-04:00

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Personal Info	Chief Executive Officer
eRA COMMONS USER NAME (credential, e.g., agency login)	
eRA Commons User Name	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Rice University, Houston, TX	BS	2005	Bioengineering
Rice University, Houston, TX	BA	2005	Managerial Studies
U. Texas Health Science Center/ U. Texas, San Antonio, TX.		2005-2009	MD/PhD Program – transferred to Utah in 2009
Stanford University, Palo Alto, CA.	Certificate	2013	Entrepreneurship
University of Utah, Salt Lake City, UT	PhD	2013	Bioengineering

A. Personal Statement

I have been incredibly fortunate to have been given the opportunity to train with a variety of amazing mentors. Throughout my training, I have felt a strong desire to make a true translational impact on healthcare. During the last two years in Personal Info, where I was finishing the PhD portion of a combined MD/PhD program, I led the development of a new drug screening platform. This platform, which took an engineering approach to addressing a molecular biology challenge, has become one of the most important projects I have ever undertaken. I successfully identified two drugs that could be re-purposed to treat a hereditary stroke syndrome (cerebral cavernous malformation). Unpublished

Unpublished

Unpublished

Unpublished

Simultaneous with my scientific training has been a deep-seated drive toward entrepreneurship and leadership. Personal Info

Personal Info To scratch my urge for translation, I pursued a second bachelor degree at Rice University in the managerial studies honors program in order to improve my management skills, and I was incredibly fortunate to be selected to attend the Stanford Business School's IGNITE residential entrepreneurship program this past summer. At Stanford, I worked with an extremely talented team to develop a business model based on my screening platform, and we were well-received by a number of venture capitalists, professors, and biotech industry mentors. I returned from this program in July of 2013, and we incorporated Recursion Pharmaceuticals November 5th, 2013.

Personal Info

Personal Info My most important professional goal is to make as profound and positive an impact on the world as possible. For me, the potential to bring new treatments to patients suffering from rare genetic diseases in a relatively short time period clearly tracks with my stated professional goals. Personal Info – I have simply chosen to follow the path which I think has the most impact. Personal Info

Personal Info

As I made the decision to start Recursion, I was often reminded of a warning I received from Personal Info (MGH/Partners in Health), Personal Info when I first met him when he visited my medical school. I had

Personal Info where Personal Info approach to healthcare had become famous. Personal Info said, as best as I can remember:

Personal Info

Though it has taken me some years, I've come to find a tremendous amount of wisdom in Personal Info blunt remarks. I've been probing and plotting various opportunities throughout my training since that time, and finally have found my first true chance to 'just do something profound' in the treatment of rare genetic diseases.

I have been specifically drawn toward rare genetic diseases for three reasons:

1. The wide-variety of tools available for genetic study, many of which are compatible with high-throughput technologies, mesh well with the skills I have acquired throughout my scientific training in bioengineering. Further, the opportunity to try to grow a business based on a somewhat disruptive model is something I find highly appealing. Though people often challenge our goal of multiple bringing drugs to market for $5-$10 million each (including failures), I believe that the evidence provided by a variety of re-purposed and orphan successes, suggests this is possible (even if it challenges traditional pharmaceutical dogma).
2. The common mechanism of loss-of-function associated with thousands of these diseases provides a clear path by which efficiency can be gained, which could prove to be the difference between bringing a drug to market or not. Additionally, my training at the University of Utah has had a profound effect on me – I now truly appreciate the awesome power of genetics, having worked with Personal Info and Consultant Info for more than four years. There truly are few places in the world with the depth of experience and knowledge in human genetics as I can find just a short walk away here in Salt Lake City. In some ways, I've been driven to rare genetic diseases by the compelling opportunity they present.
3. Rare genetic diseases Personal Info

   Personal Info

I am under no illusions that the vision we have laid out for Recursion will easily be achieved. I know that many years of hard-work and innovative thinking lie ahead. I am confident that I have the skills, drive, open-mindedness, and innovative core to make this work. I am also confident that I have the maturity to identify the people who need to be a part of this process to improve our odds of success. I've already demonstrated an ability to generate interest among truly amazing people Personal Info and Personal Info who have co-founded Recursion with me, are two of the most intelligent and thoughtful humans I have had the privilege to know. I believe that together we can make a profound impact. As a team, we have prioritized the recruitment of additional advisors and employees, and have had success in recruiting those we need. Consultant Info a real pioneer in high-content analysis and consultant to multiple large pharmaceutical companies, did not know any of us until just 7 or 8 months ago, and we've been able to convince her of our vision and our ability to achieve it. We will continue to strive to bring in amazing employees and advisors. This SBIR grant will provide us with capital resources (and with it new and exciting data and opportunities), as well as credibility (and along with it new partnership and investment opportunities). We take seriously the responsibility that comes with these funds, and will be good stewards of your trust in our proposal and vision.

B. Positions and Honors

Academic Positions

2006 – 2007	Graduate Research Assistant, Laboratory of Dr. Jeffrey Thompson, University of Texas at San Antonio.
2007 – 2009	Graduate Research Assistant, Laboratory of Dr. Rena Bizios, University of Texas at San Antonio.
2007 – 2009	Medical Student, University of Texas Health Science Center at San Antonio.
2009 – 2013	Graduate Research Assistant, Laboratory of Dr. Dean Y. Li, University of Utah.
2009 – present	MD/PhD Student, University of Utah. Now on flexible leave to manage/operate Recursion

Industry Experience

2004 – 2005	Project Manager/Business Development Intern, Medi-Screw, Inc. Portland, Oregon.
2013 – present	Chief Executive Officer and Chairman, Recursion Pharmaceuticals, LLC.

Academic and Professional Honors

2001 – 2002	NCAA Division-I Scholar-Athlete Award, Western Athletic Conference (WAC), Men's Track and Field (Rice University).
2004	Most awarded team (6 awards), Texas Space Grant Consortium Undergraduate R&D Competition Fall Design Challenge. Johnson Space Center, Texas.
2005	Most awarded team (9 awards), Texas Space Grant Consortium Undergraduate R&D Competition Spring Design Challenge. Johnson Space Center, Texas.
2005	First Place, Revolutionary Aerospace Academic Linkage Undergraduate Research and Design Competition. Kennedy Space Center, Florida.
2006 – 2007	President and Founder, Biomedical Engineering Society, Joint Ph.D. Program in Biomedical Engineering at the University of Texas Health Science Center at San Antonio and the University of Texas at San Antonio.
2007 – 2009	UTHSCSA Green Initiative - Founder and Student Leader – Executive VP dedicated >$1M to support our efforts.
2008	UT Health Sciences Center at San Antonio Alumni Merit Award for Service to the University – First year medical student ($1,000).
2008 – 2009	Greehey MD/PhD Scholarship, University of Texas Health Science Center at San Antonio (tuition, benefits, and $21,500 stipend).
2009	Selected Participant, American Medical Student Association Environmental Health Leadership Institute, Mount Sinai School of Medicine.
2009	Member, UTHSCSA Energy Conservation Committee, Appointed by Executive V.P. and COO.

C. Peer-Reviewed Publications

1. Wilson, B.D.*, **Gibson, C.C.***, Sorensen, L.K., Guilhermier, M.Y., Clinger, M., Kelley, L.L., Shiu, Y.T., Li, D.Y. Novel Approach for Endothelializing Vascular Devices: Understanding and Exploiting Elastin-Endothelial Interactions. *Annals of Biomedical Engineering* 39(1): 337-346. 2011 ***Co-First Author**

2. Chan AC, Drakos SG, Ruiz OE, Smith AC, **Gibson CC**, Ling J, Passi SF, Stratman AN, Sacharidou A, Revelo MP, Grossmann AH, Diakos NA, Davis GE, Metzstein MM, Whitehead KJ, Li DY. (2011) Mutations in 2 distinct genetic pathways result in cerebral cavernous malformations in mice. ***Journal of Clinical Investigation***. May 2; 121(5):1871-81. (PMID:21490399)

3. Jones, C.F., Campbell, R.A., Franks, Z., **Gibson, C.C.,** Thiagarajan, G., Vieira-de-Abreu, A., Sukavaneshvar, S., Mohammad, S.F., Li, D.Y., Ghandehari, H., Weyrich, A.S., Brooks, B.D., Grainger, D.W. Cationic PAMAM dendrimers disrupt key platelet functions. ***Molecular Pharmaceutics***. 4:9(6): 1599-1611. 2012.

4. Zhu, W.*, London, N.R.*, **Gibson, C.C.***, Tong, Z., Sorenson, L.K., Shi, D.S., Guo, J., Davis, C.T., Smith, M.C.P., Grossmann, A.H., Thomas, K.R., Li, D.Y. Interleukin receptor activates a MyD88-ARNO-ARF6 cascade to disrupt vascular stability. ***Nature***. 492: 252-255. 2012 ***Co-First Author**

5. Wilkins, J.R., Pike, D.B., **Gibson, C.C.**, Kubota, A., Shiu, Y.T. Differential effects of cyclic stretch on bFGF and VEGF-induced sprouting angiogenesis. *Biotechnology Progress*. Feb 22; doi: 10.1002/btpr.1883

6. Unpublished

7. Unpublished

8. Unpublished

D. Research Support

None

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Personal Info	Professor
eRA COMMONS USER NAME (credential, e.g., agency login)	
eRA Commons User Name	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
University of Chicago, Chicago, IL	BA	06/83	Chemistry
Washington University in St. Louis, St. Louis, MO	MD	05/90	Medicine
Washington University in St. Louis, St. Louis, MO	PhD	05/90	Biochemistry

A. Personal Statement

My lab has focused on elucidating the pathogenesis of diseases related to vascular stability including supravalvular aortic stenosis (SVAS), hereditary hemorrhagic telangiectasia (HHT), and cerebral cavernous malformation (CCM). We have used biochemistry, cell signaling, and animal models including knockout mice to accomplish this goal. Most recently, we have developed endothelial-specific knockout mice for all three genes linked to human CCM disease. We have also utilized cell signaling and biochemistry to contribute significantly to the understanding of CCM-related signaling. A drug discovery system taking advantage of each of our strengths was recently developed in my laboratory by Personal Info and this platform was responsible for the discovery of two promising therapeutics for the treatment of CCM disease. We have spun this platform into a company, Recursion Pharmaceuticals, which seeks to combine this platform and animal model expertise in my laboratory to develop personalized medicines for a large number of monogenetic loss of function diseases.

This current application is focused on studying more than 2,000 monogenetic loss of function diseases, with a goal of bringing two new treatments to the commercialization stage. However, we are acutely aware that our proposed studies generate a much larger number of leads than can be pursued in this single proposal. I am informed by my experience in the biotech industry, as well as by my network of academic collaborators and industry collaborators and advisors at some of the most prestigious pharmaceutical companies (Merck, Novartis, Hydra, Navigen).

B. Positions and Honors

1990 – 1992 PGY 1 and 2 in Internal Medicine, Barnes Hospital at Washington University Medical Center
1992 – 1994 Clinical fellowship in Cardiology, Barnes Hospital at Washington University Medical Center
1994 – 1995 Research Associate, Eccles Institute of Genetics, University of Utah
1995 – 1998 Instructor, Division of Cardiology, University of Utah Medical Center
1998 – 2002 Assistant Professor, Division of Cardiology, and Program in Human Molecular Biology & Genetics, University of Utah Medical Center
2003 – 2006 Associate Professor of Medicine
2003-present Associate Director of the MD/PhD program
2007-present HA and Edna Benning Presidential Endowed Chair Professor in Medicine
2008-present Director, Molecular Medicine Program
2008-present Director & Principal Investigator, Education Core, CCTS
2008-present Adjunct Professor, Oncological Sciences and Human Genetics, University of Utah
2010-present Director & Principal Investigator, University of Utah HHMI Med Into Grad Program
2010-present Director, Adult Cardiology Fellowship
2011-present Vice Dean of Research, University of Utah School of Medicine
2011-present Chief Scientific Officer, University Medical Center, University of Utah
2013-present Associate Vice President for Research, University of Utah Health Sciences

Industry Experience

2001 – 2003	Co-Founder and Head of Research and Development-Hydra Biosciences Inc, Cambridge, Ma
2004 – 2011	Scientific Advisory Board of Hydra Biosciences Inc
2005	Consultant for New Enterprise Associates, Advanced Technology Ventures, Myriad Genetics, Orbus-Neich
2007-present	Co-Founder and CSO, Navigen Inc, Salt Lake City, Utah
2013-present	Co-Founder and CSO, Recursion Pharmaceuticals,LLC, Salt Lake City, Utah

Honors

1983 – 1990	NIH Medical Scientist Training Program Award
1988	Olin Award for Excellence in Biomedical Research at Washington University
1994 – 1997	Howard Hughes Physician Scientist Postdoctoral Fellowship Award
1994 – 1999	Clinician Scientist Award, American Heart Assoc., National Chapter, Resigned Oct 1, 1994
1999	Culpeper Medical Science Scholar
2005	Member-American Society of Clinical Investigations
2006	Established Investigator Award-American Heart Association
2006	Clinical Scientist Award in Translational Medicine: Burroughs Wellcome Foundation
2009	Clinical Faculty Teaching Award (awarded by the Internal Medicine Residents at the University of Utah)
2011	Member-American Association of Physicians

C. Selected Peer-Reviewed Publications (from more than 200)

1. Li DY, Brooke B, Davis EC, Sorensen LK, Boak BB, Eichwald E, Mecham RP and Keating MT. (1998) Elastin is an essential determinant of arterial morphogenesis: **Nature** 393:276-280.
2. **Li, DY**, Sorensen, LK, Brooke B, Urness LD, Davis EC, Taylor D, Boak B and Wendel D (1999) Defective angiogenesis in mice lacking endoglin. **Science** 284: 1534-1537
3. Urness LD, Sorensen LK, and **Li DY**. (2000) Arteriovenous malformations in mice lacking activin-like kinase receptor 1. **Nature Genetics** 26: 328-331.
4. Wilson B, Park KW, Li M, Suli A, Koch GA, Sorensen L, Urness L, Chien CB, Losordo D, and **Li DY.** (2006) Netrins promote developmental and therapeutic angiogenesis. **Science** 313(5787):640-4. (PMC2577078; NIHMS44903)
5. Jones C, London N, Park K, Chen H, Stockton R, Nishiya N Ginsberg M, Zhang K, and **Li DY**. (2008) Robo4 stabilizes the vasculature by inhibiting angiogenesis and endothelial hyperpermeability. **Nature Medicine** 14(4):448-53 (PMC2875252; NIHMS7707)
6. Whitehead, KJ, Chan, AC, Navankasattusas, S, Koh, W, London, MR, Ling, J, Mayo, AH, Drakos, SG, Marchuk, DA, Davis, GE, **Li, DY** (2009) The cerebral cavernous malformation signaling pathway promotes vascular integrity via Rho GTPases. **Nature Medicine** Feb;15(2):177-84. Epub 2009 Jan 18. (PMC2767168; NIHMS103159)
7. Jones CA, Nishiya N, London NR, Zhu W, Sorensen LK, Chan A, Lim CJ, Chen H, Zhang Q, Schultz PG, Hayallah AM, Thomas KR, Famulok M, Zhang K, Ginsberg MH, **Li DY**. (2009) Slit2-Robo4 signalling promotes vascular stability by blocking Arf6 activity. **Nature Cell Biology** 11(11):1325-31. Epub 2009 Oct 18. (PMC2854659; NIHMS 192235)
8. London NR, Zhu W, Bozza FA, Smith MCP, Greif DM, Sorenson LK, Chen L, Kaminoh Y, Chan AC, Passi SF, Day CW, Barnard DL, Zimmerman GA, Krasnow MA, **Li DY**. (2010) Targeting Robo4-dependent slit signaling to survive the cytokine storm in sepsis and influenza. **Science Translational Medicine** Mar 17; 2(23), ra19. (NIHMS191965; PMCID: PMC2875996)
9. Marlow R, Binnewies M, Sorensen LK, Monica SD, Strickland P, Forsberg EC, **Li DY**, Hinck L. (2010) Vascular Robo-4 restricts proangiogenic VEGF signaling in breast. **PNAS** Jun 8; 107(23):10520-5. Epub 2010 May 24. (PMID:20498081; PMC2890778)
10. Niebel B, Weiche B, Mueller AL, **Li DY**, Karnowski N, Famulok M. (2011) A luminescent oxygen channeling biosensor that measures small GTPase activation. **ChemComm** (Camb) July 14; 47(26):7521-3. Epub 2011 May 31. (PMID: 21625685)
11. Jones CF, Campbell RA, Franks Z, Gibson CC, Thiagarajan G, Vieira-de-Abreu A, Sukavaneshvar S, Mohammad SF, **Li DY**, Ghandehari H, Weyrich AS, Brooks BD, Grainger DW. Cationic PAMAM dendrimers disrupt key platelet functions. **Mol Pharm**. 2012 Jun 4;9(6): 1599-611. PubMed PMID: 22497592.

12. Sawada J, Urakami T, Li F, Urakami A, Zhu W, Fukuda M, **Li DY**, Ruoslahti E, Komatsu M. (2012) Small GTPase R-Ras Regulates Integrity and Functionality of Tumor Blood Vessels**. Cancer Cell** 2012 Aug 14; 22(2):235-49 (PMID: 22897853; PMC3422514)
13. Zhu W, London NR, Gibson CC, Davis CT, Tong Z, Sorensen LK, Shi DS, Guo J, Smith MCP, Grossman AH, Thomas KR, **Li DY** (2012) Interleukin receptor activates a MYD88-ARNO-ARF6 cascade to disrupt vascular stability. **Nature** Dec 13; 492:252-255. (PMCID: PMC3521847)
14. Grossmann AH, Yoo JH, Clancy J, Sorensen LK, Sedgwick A, Tong Z, Ostanin K, Rogers A, Grossmann KF, Tripp SR, Thomas KR, D'Souza-Schorey C, Odelberg SJ, **Li DY** (2013) The small GTPase ARF6 stimulates β-catenin transcriptional activity during WNT5A-mediated melanoma invasion and metastasis. **Science Signaling** Mar 5; 6(265):ra14. (PMID: 23462101)
15. Zhang B, Xiao W, Qiu H, Zhang F, Moniz HA, Jaworski A, Condac E, Gutierrez-Sanchez G, Heiss C, Clugston RD, Azadi P, Greer JJ, Bergmann C, Moremen KW, **Li DY**, Linhardt RJ, Esko JD, Wang L. Heparan sulfate deficiency disrupts developmental angiogenesis and causes congenital diaphragmatic hernia. **J Clin Invest**. 2013 Dec 20. PMCID: PMC3871243

D. Active Research Support - Personal Info

1R01NS080893-01A1 Personal Info 09/15/2013 – 07/31/2016
NIH, NINDS
High Content Screening for Hereditary Stroke Syndrome

Cerebral Cavernous Malformation (CCM) is a hereditary stroke syndrome that has no treatment other than neurosurgery. We will use a chemical suppressor screen to identify potential therapeutics for treatment of the disease.
Overlap: None – helped to generate preliminary data used in this application.

2R01HL077671-09 Personal Info 2/1/2014 – 1/31/2019
NIH, NHLBI
Endothelial Toll-like Receptor Signaling and Inflammation

Sepsis is a catastrophic and often-fatal inflammatory response to infection that affects the entire body and usually results from bacterial infections. Despite intense study, few therapeutic strategies other than nonspecific supportive care have been developed and death rates remain as high as 60-70% in patients with the most severe form of sepsis. We have identified a signaling pathway that we think may control the most lethal aspects of bacterial sepsis and propose to examine this pathway in detail, determine the pathway's *in vivo* relevance in bacterial sepsis, and assess the potential value of developing drugs to treat sepsis that target this pathway.
Overlap: None

1R01CA163970-01 09/14/2012 – 06/30/2015
NIH/NCI Personal Info
The development of screening assays for novel inhibitors of ARNO and its effectors

We have unlocked a potential answer as to how β-cadherin, which is critical for stabilizing E-cadherin and N-cadherin on the cell surface, traffics to its intracellular compartment and eventually translocate to the nucleus and transactivates . Control of this trafficking is critical for Wnt signaling and cancer biology. We propose to block Wnt/β-catenin signaling by interfering with this trafficking mechanism.
Overlap: None

1U54 HL112311-01 (Personal Info 05/01/2012-04/30/2017
Personal Info
NIH, National Heart, Lung, and Blood Institute
Reprogrammed Platelets: Effectors of Thrombosis in Metabolic Syndromes

Determine how metabolic factors in the blood and tissues, such as high glucose and lipids, make platelets more prone to induce thrombosis, providing new insights into the treatment and management of diabetes and obesity.
Overlap: None

2R01HL-084516-05A1 Personal Info 06/01/2013 – 05/31/2018
NIH, NHLBI
Opposing Mechanisms of Stabilizing and Destabilizing Receptors

The central premise of this grant application is that vascular stabilizing receptors such as the Robo family of receptors and destabilizing receptors such as interleukin receptors have competing influence on a common downstream small GTPase. Our studies seek to prove this mechanistic model which will explain the constant opposing signaling cascades that act as a rheostat to determine barrier integrity of the endothelium and the epithelium.
Overlap: None

1R01AR064788-01 Personal Info 07/01/2013 – 06/30/2018
NIH, NIAMS
The Role of Vasculature in the Pathogenesis of Arthritis

Current therapies for the treatment of inflammatory diseases such as rheumatoid arthritis often leave the patient more susceptible to infection. We have recently identified a novel molecular pathway that may be responsible for arthritic progression in animal models of disease but does not appear to affect the immune response. We will determine whether this pathway indeed controls the initiation and progression of arthritis and if so, drugs developed in the future that target this pathway may reduce the progression of inflammatory diseases without making the patient more susceptible to infection.
Overlap: None

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Personal Info	Chief Technical Officer
eRA COMMONS USER NAME (credential, e.g., agency login)	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Rice University, Houston, TX	BS	2003	Electrical Engineering
Univ. of Texas at Austin, TX	PhD	2015 (expected)	Cellular/Molecular Biology

A. Personal Statement

With a love of science and learning and a deep desire for direct impact on the world, my history has taken me back and forth multiple times between academia and industry, and on a journey through software, statistics, business and biology. This unique history gives me, I believe, an optimal and complementary set of experiences and skills to successfully execute on the aims of this project and the vision of Recursion Pharmaceuticals together with my co-founders Personal Info and Personal Info

My foundational knowledge in software and statistics comes from my education at Rice University, where I specialized in digital signal processing, information theory, communications theory, and other ways of exploiting computers to perform math on information. My engineering mindset of seeking challenging and impactful problems to solve, along with my mathematical and statistical framework for understanding information, stuck with me and was enhanced through my early career as the technical co-founder of two technology startups. In the course of building BuildASign.com from an idea in our heads into a sizeable and profitable online custom manufacturing business, now with over 250 employees, I was able to explore ways in which I could employ an engineering mindset to the technical operation of a high-volume e-commerce platform, and also to the challenge of profitably growing the business as rapidly as possible through online marketing and constant iteration of our sales platform on the web.

As we grew the business and as I was able to recruit new talented individuals to form and lead the technology and marketing teams, I could see the business was on an exciting and stable trajectory in the hands of my partners, and began the mental journey of seeking out the next big challenge, which I found in biology. Although I was an outsider to the field at the time, I decided that advancing computational capacity, analysis techniques and experimental technology put systems and computational biology at an unprecedented point of leverage in making an impact on the way diseases will be understood and treated in the coming decades, and I resolved to play whatever role I could in helping bring this to fruition. Through self-teaching and volunteering on projects in the lab of Personal Info at the University of Texas at Austin, whom I had identified as a role model and an amazing mentor, I was able to re-enter the walls of academia, become a PhD student in a field where I had no prior background, and benefit from being in the vortex of computational and experimental biology that I believe makes Personal Info lab so special.

In the course of my PhD, my role has been that of a biologist and data scientist. I have worked closely with members of my own lab, and our collaborators at the University of Toronto, to design biological experiments, design and build software to integrate and analyze large data sets incorporating various types of disparate data, and develop machine learning pipelines to make predictions that we can then test and feed back again into the beginning of this cycle of discovery. Although publications for my chief project are only just being written, I believe the effectiveness of my work and its usefulness to biologists is evident to those who know the work, and others who have seen it presented via talks and posters at a number of conferences. My desire to

be involved at all stages of this cycle and truly understand and design the experiments is what led me to pursue studies in molecular biology, rather than the perhaps more expected path of bioinformatics or computational biology, and I believe this strategy has paid off in spades, including at present in my ability to work with [redacted] in designing our experimental and computational approach in parallel, which is critical for a project as technically demanding and data-intensive as we propose.

Personal Info

B. Positions and Honors

Academic Positions

2003 – 2004	Software Research Intern, University of Bern and MEM Research Center for Biomechanics, Bern, Switzerland.
2009 – 2011	Visiting Researcher, Center for Systems and Synthetic Biology, University of Texas at Austin.
2011 – present	Graduate Research Assistant, Laboratory of Dr. Edward Marcotte, University of Texas at Austin. Part-time with expected graduation May 2015.

Industry Experience

2003 – 2005	Co-founder and Lead Developer, Seventh Coast Technologies, Austin, TX
2005 – 2007	Co-founder and Director of Technology, BuildASign.com, Austin, TX
2007 – 2009	Co-founder and Director of E-commerce, BuildASign.com, Austin, TX
2005 – present	Co-founder and Owner, BuildASign.com, Austin, TX
2012 – present	Board of Directors, Central Texas Angel Network, Austin, TX
2013 – present	Chief Technical Officer, Recursion Pharmaceuticals, LLC, Salt Lake City, UT

Other Academic Experience

2012	Invited Talk, “Mapping animal protein complexes: scaling up,” 3D Virtual Cell Conference, San Diego, CA
2013	Ad Hoc Reviewer, PLOS Computational Biology
2013	Selected Talk, “All-by-all learning of protein complexes from mass spectrometry data,” SciPy Scientific Python Conference, Austin, TX
2013	Selected Talk, “Deep proteome fractionation reveals the conserved and dynamic modularity of protein complexes,” Systems Biology: Networks, Cold Spring Harbor Labs, NY
2013	Invited Talk, “Deep proteome fractionation to discover and dissect protein complexes,” Big Data Symposium, University of Texas at Austin

Selected Academic Honors

1999	National Merit Scholar
1999	Walsh and Roy merit-based engineering scholarship at Rice University (4 years)
2003	Graduated Magna Cum Laude from Rice University

C. Peer-Reviewed Publications

1. Pappas, I. P., Ryan, P., Cossmann, P., Kowal, J., **Borgeson, B**., & Caversaccio, M. (2005). Improved targeting device and computer navigation for accurate placement of brachytherapy needles. *Medical physics*, *32*(6), 1796-1801.

2. Wan, Cuihong, Jian Liu, Vincent Fong, Andrew Lugowski, Snejana Stoilova, Dylan Bethune-Waddell, **Blake Borgeson**, Pierre C. Havugimana, Edward M. Marcotte, and Andrew Emili. "ComplexQuant: High-throughput computational pipeline for the global quantitative analysis of endogenous soluble protein complexes using high resolution protein HPLC and precision label-free LC/MS/MS." *Journal of proteomics* 81 (2013): 102-111.

D. Research Support

None

Consultant Info

Consultant Info

Consultant Info

Consultant Info

Consultant Info

Consultant Info

Principal Investigator/Program Director (Last, first, middle) Personal Info

Consultant Info

Consultant Info

Consultant Info

OMB Number: 4040-0001
Expiration Date: 06/30/2011

RESEARCH & RELATED BUDGET - SECTION A & B, BUDGET PERIOD 1

*** ORGANIZATIONAL DUNS:** Proprietary Info

*** Budget Type:** ☒ Project ☐ Subaward/Consortium

Enter name of Organization: Recursion Pharmaceuticals, LLC

Delete Entry *** Start Date:** 12/01/2014 *** End Date:** 11/30/2015 **Budget Period** 1

A. Senior/Key Person

	Prefix	* First Name	Middle Name	* Last Name	Suffix	* Project Role	Base Salary ($)	Cal. Months	Acad. Months	Sum. Months	* Requested Salary ($)	* Fringe Benefits ($)	* Funds Requested ($)
1.	Personal Info					PD/PI	Institutional Base Salary	EFFORT			Itemized Cost		
2.													
3.													
4.													
5.													
6.													
7.													
8.													
9.	**Total Funds requested for all Senior Key Persons in the attached file**												

Total Senior/Key Person Itemized Cost

Additional Senior Key Persons: Add Attachment Delete Attachment View Attachment

B. Other Personnel

* Number of Personnel	* Project Role	Cal. Months	Acad. Months	Sum. Months	* Requested Salary ($)	* Fringe Benefits ($)	* Funds Requested ($)
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
# OF EMPLOYEES	Tissue Culture/Experimental Technician	EFFORT			Itemized Cost		
	Software Developer						
# OF EMPLOYEES	**Total Number Other Personnel**				**Total Other Personnel**		Itemized Cost

Total Salary, Wages and Fringe Benefits (A+B)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 1

* ORGANIZATIONAL DUNS: Proprietary Info

* Budget Type: ☒ Project ☐ Subaward/Consortium

Enter name of Organization: Recursion Pharmaceuticals, LLC

Delete Entry * Start Date: 12/01/2014 * End Date: 11/30/2015 Budget Period 1

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

	Equipment item	* Funds Requested ($)
1.	Image Processing Computation System	Itemized Cost
2.	Data Storage Solution	
3.	Thermo Multidrop 384 Plate Washer	
4.		
5.		
6.		
7.		
8.		
9.		
10.		
11.	**Total funds requested for all equipment listed in the attached file**	
	Total Equipment	Itemized Cost

Additional Equipment: Add Attachment | Delete Attachment | View Attachment

D. Travel

		Funds Requested ($)
1.	Domestic Travel Costs (Incl. Canada, Mexico and U.S. Possessions)	Itemized Cost
2.	Foreign Travel Costs	
	Total Travel Cost	

E. Participant/Trainee Support Costs

		Funds Requested ($)
1.	Tuition/Fees/Health Insurance	Itemized Cost
2.	Stipends	
3.	Travel	
4.	Subsistence	
5.	Other	

0 **Number of Participants/Trainees** **Total Participant/Trainee Support Costs** Itemized Cost

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION F-K, BUDGET PERIOD 1

Next Period

* ORGANIZATIONAL DUNS: Proprietary Info

* Budget Type: ☒ Project ☐ Subaward/Consortium

Enter name of Organization: Recursion Pharmaceuticals, LLC

Delete Entry | Start Date: 12/01/2014 * End Date: 11/30/2015 Budget Period 1

F. Other Direct Costs

		Funds Requested ($)
1.	Materials and Supplies	Itemized Cost
2.	Publication Costs	
3.	Consultant Services	
4.	ADP/Computer Services	
5.	Subawards/Consortium/Contractual Costs	Itemized Cost
6.	Equipment or Facility Rental/User Fees	
7.	Alterations and Renovations	
8.		
9.		
10.		
	Total Other Direct Costs	Itemized Cost

G. Direct Costs

	Funds Requested ($)
Total Direct Costs (A thru F)	Itemized Cost

H. Indirect Costs

	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	* Funds Requested ($)
1.	Total direct costs	Itemized Cost		
2.				
3.				
4.				
	Total Indirect Costs			Itemized Cost

Cognizant Federal Agency

(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs

	Funds Requested ($)
Total Direct and Indirect Institutional Costs (G + H)	Itemized Cost

J. Fee

	Funds Requested ($)
	Fee

K. * Budget Justification 1255-BUDGET JUSTIFICATION.pdf Add Attachment | Delete Attachment | View Attachment

(Only attach one file.)

Previous Period

RESEARCH & RELATED BUDGET - SECTION A & B, BUDGET PERIOD 2

*** ORGANIZATIONAL DUNS:** Proprietary Info

*** Budget Type:** ☒ Project ☐ Subaward/Consortium

Enter name of Organization: Recursion Pharmaceuticals, LLC

Delete Entry *** Start Date:** 12/01/2015 *** End Date:** 11/30/2016 **Budget Period** 2

A. Senior/Key Person

	Prefix	* First Name	Middle Name	* Last Name	Suffix	* Project Role	Base Salary ($)	Cal. Months	Acad. Months	Sum. Months	* Requested Salary ($)	* Fringe Benefits ($)	* Funds Requested ($)
1.		Personal Info				PD/PI	Institutional Base Salary	EFFORT			Itemized Cost		
2.													
3.													
4.													
5.													
6.													
7.													
8.													
9.	**Total Funds requested for all Senior Key Persons in the attached file**												

Total Senior/Key Person Itemized Cost

Additional Senior Key Persons: Add Attachment Delete Attachment View Attachment

B. Other Personnel

* Number of Personnel	* Project Role	Cal. Months	Acad. Months	Sum. Months	* Requested Salary ($)	* Fringe Benefits ($)	* Funds Requested ($)
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
# OF EMPLOYEES	Tissue Culture/ Experimental Technician	EFFORT			Indirect Cost		
	Software Developer						
# OF EMPLOYEES	**Total Number Other Personnel**				**Total Other Personnel**		Itemized Cost

Total Salary, Wages and Fringe Benefits (A+B)

Principal Investigator/Program Director (Last, first, middle): Personal Info

RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 2

* ORGANIZATIONAL DUNS: Proprietary Info

* Budget Type: ☒ Project ☐ Subaward/Consortium

Enter name of Organization: Recursion Pharmaceuticals, LLC

Delete Entry * Start Date: 12/01/2015 * End Date: 11/30/2016 Budget Period 2

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

	Equipment item	* Funds Requested ($)
1.		
2.		
3.		
4.		
5.		
6.		
7.		
8.		
9.		
10.		
11.	**Total funds requested for all equipment listed in the attached file**	
	Total Equipment	

Additional Equipment: Add Attachment Delete Attachment View Attachment

D. Travel **Funds Requested ($)**

1. Domestic Travel Costs (Incl. Canada, Mexico and U.S. Possessions)
2. Foreign Travel Costs

Total Travel Cost Itemized Cost

E. Participant/Trainee Support Costs **Funds Requested ($)**

1. Tuition/Fees/Health Insurance
2. Stipends
3. Travel
4. Subsistence
5. Other

Itemized Cost

0 **Number of Participants/Trainees** **Total Participant/Trainee Support Costs** Itemized Cost

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION F-K, BUDGET PERIOD 2

Next Period

* ORGANIZATIONAL DUNS: Proprietary Info

* Budget Type: ☒ Project ☐ Subaward/Consortium

Enter name of Organization: Recursion Pharmaceuticals, LLC

Delete Entry | Start Date: 12/01/2015 * End Date: 11/30/2016 Budget Period 2

F. Other Direct Costs

		Funds Requested ($)
1.	Materials and Supplies	Itemized Cost
2.	Publication Costs	
3.	Consultant Services	
4.	ADP/Computer Services	
5.	Subawards/Consortium/Contractual Costs	Itemized Cost
6.	Equipment or Facility Rental/User Fees	
7.	Alterations and Renovations	
8.		
9.		
10.		
	Total Other Direct Costs	Itemized Cost

G. Direct Costs

	Funds Requested ($)
Total Direct Costs (A thru F)	Itemized Cost

H. Indirect Costs

	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	* Funds Requested ($)
1.	Total direct costs			Itemized Cost
2.				
3.				
4.				
	Total Indirect Costs			Itemized Cost

Cognizant Federal Agency

(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs

	Funds Requested ($)
Total Direct and Indirect Institutional Costs (G + H)	Itemized Cost

J. Fee

	Funds Requested ($)
	Fee

K. * Budget Justification 1255-BUDGET JUSTIFICATION.pdf | Add Attachment | Delete Attachment | View Attachment

(Only attach one file.)

BUDGET JUSTIFICATION
Recursion Pharmaceuticals

The total 2-year budget request is Itemized Cost
Please note: This budget exceeds customary SBIR phase II award levels. However, we do not exceed the hard-cap of Itemized Cost *We have spoken with Personal Info, SBIR program director at NCATS to confirm that our budget is acceptable.* She has indicated that this is the case, especially since our proposed project fits into the NCATS SBIR Topics of Interest that have received approval from the Small Business Administration for budgets greater than Itemized Cost for phase II. We have also taken steps, such as eliminating the customary fee requested by for-profit companies, to insure that we achieve the most efficient use of the requested funds without exceeding the hard cap.

A. Senior/Key Personnel Itemized Cost
Principal Investigator: Personal Info Institutional Base Salary EFFORT months effort each year at a salary of Institutional Base Salary per year) is CEO of Recursion Pharmaceuticals and has generated a large amount of data as a graduate student in the laboratory of Personal Info contributing to 2 co-first author papers, Unpublished Unpublished as well as 5 other manuscripts from among at least three collaborating labs. Personal Info will oversee the experimental biology aspects of the project, and will oversee a technician who will perform much of the experimentation. Personal Info will work with Personal Info to implement the bioinformatics approach. Personal Info will also oversee the administrative aspects of the project.

Other Senior/Key Personnel Itemized Cost
Research Scientist: Personal Info is CTO of Recursion Pharmaceuticals and is a bioinformatician with a great deal of experience in algorithm development as it relates to e-commerce and manufacturing. He is nearing completion of a Ph.D. in bioinformatics in the laboratory of Personal Info at UT-Austin, and has a major paper in preparation. Personal Info will be responsible for implementation of the CellProfiler software analysis platform, as well as continued development of Recursion's proprietary software systems. Personal Info will work directly with Consultant Info when appropriate to implement specific bioinformatics approaches, and will manage the software developer. receives Itemized Cost from Recursion, as he has been given a significant portion of equity in exchange for his services. Personal Info

B. Other Personnel Itemized Cost
Senior Tissue Culture and Experimental Technician Itemized Cost EFFORT months each year at a salary of Itemized Cost per year). We have just begun to search for our ideal technician. The technician must be capable of handling the majority of the basic culture work, as well as the high throughput liquid handling and high throughput imaging. We will hire the technician before the grant starts using non-SBIR funds so they can be up to speed at the grant start date. Early indications is that there are many qualified candidates seeking the position. The technician will report directly to Personal Info Personal Info

Software Developer Itemized Cost EFFORT months each year at a salary of Itemized Cost per year). We have just begun to search for our ideal software developer. They will be responsible for management of the data, implementation of software analysis, and will report directly to Personal Info We will hire this software developer almost immediately upon submission of this grant, so they will be familiar with the project by the grant start date. We have received a great deal of interest in such a position from a variety of soon-to-be Ph.D. graduates of the Scientific and Computing Institute (SCI) at the University of Utah and do not anticipate any issues filling this position with a highly qualified software developer.

C. Equipment Itemized Cost
Image Processing System Itemized Cost Due to the large quantity of immunofluorescence images we must process (~50 terabytes), specialized computers are required to prevent a bottleneck at the image analysis stage. We will purchase a specialized image processing system to be used exclusively for this project. The system, costing Itemized Cost (including shipping and warranty), will be a quad-CPU system (64 cores) with 512 GB memory and specialized networking capability to connect with our data storage system. We have consulted with the software development team at CellProfiler to determine the exact specifications required, and are confident this computers will achieve the necessary processing

speeds required to keep up with the imaging. This computer system is NOT general-purpose equipment – it is a highly critical and specialized tool to be used exclusively on the proposed project.

Data Storage Solution Itemized Cost Due to the large quantity of immunofluorescence images we must process (~50 terabytes), we will need a specialized data storage solution to insure the fidelity of our data. This system will only be used to store the large amount of data generated in the proposed grant. The system will be a 50TB, RAID-1 system, which will be connected to our Image Processing System, both of which will be built in a rack-mount configuration.

Thermo Scientific Multidrop 384 Itemized Cost Due to the hundreds of 384 well plates that need to be processed, we will require usage of a highly efficient plate washer. The Drug Screening core has plate washing systems, but they are not sufficient for our needs (4 or more reagents required). The TECAN evo systems in the drug screening core are too slow (instead being built largely for precision) for our plate washing needs. Therefore, we propose to purchase this simple and efficient system to enable high-throughput processing of all plates proposed in this budget. This equipment will only be used for the proposed research.

D. Travel Itemized Cost

Itemized Cost We will, however, travel extensively to build a foundation for partnerships, but this will be at the exclusive cost of Recursion.

E. Participant/Trainee Support Costs Itemized Cost

Itemized Cost

F. Other Direct Costs Itemized Cost

Materials and Supplies

High-throughput 384-well imaging plates
Tissue Culture Supplies and Reagents
Fluorescent/Immunofluorescent Reagents
RNAi Library (2,000 genes x 3 siRNA/gene)
Validating RNAi (200 genes)
Compound Libraries (20 uL @ 10mM MSSpec, NIHCC, and NIHCC2)
Transcellular Resistance MicroPlates (ACEA Biosciences)
CRISPR Cell Modeling Reagents
Liquid Handling Supplies (Specialty Pipette Tips for Tecan EVO)

Itemized Cost

Publication Costs Itemized Cost

We intend to publish any findings which cannot be directly commercialized but which may improve the treatment of rare diseases (such as the use of Vitamin D to treat CCM disease, as discussed in our preliminary data). We expect to publish 2-5 such manuscripts, and expect page fees and other costs of documenting and preparing such work to amount to (entirely during the second budget period). These publications will be in collaboration with the Laboratory of Dr. Dean Li, and they will handle any fees above the requested amount.

Itemized Cost

Consultant Services Itemized Cost

Consultant Info EFFORT Itemized Cost Consultant Info

Consultant Info

Consultant Info Consultant Info will consult on all prioritization phases of the proposed research to insure that the drugs and diseases for which commercialization is most likely are investigated. The proposed hourly cost was negotiated at less than of standard rates, in exchange for a small portion of equity in Recursion.

Itemized Cost

Consortium Costs Itemized Cost

University of Utah – Please see consortium/sub-award budget justification.

Equipment or Facility Rental/User Fees Itemized Cost

HTS Immunofluorescence User Fee Itemized Cost We have obtained approval to use a University of Utah Core Facility microscope that is ideal for our imaging needs. Using the fully robotized system (up to 36 plates can be run automatically), we intend to run 12 plates each weekday during the overnight hours. This will allow us more than 100 full nights (12 hours) of imaging at the overnight fee. We have already used this system with great success in overnight trials.

HTS Liquid Handling User Fees Itemized Cost Due to the large number of 384-well plates we will use, automated liquid handling is essential. Two Tecan Evo150 systems are located just a few feet from our laboratory (complete with sterility enclosures) in the University of Utah Drug Screening Core Facility. We will use these systems for drug dosing, addition of expensive immunofluorescence reagents, and siRNA transfection. The cost of specialty tips will be our own (not included in the hourly rate), and is reflected in the requested materials and supplies.

ACEA MP Lease Itemized Cost for 12 months). We have access to a single 96-well transcellular resistance system in Personal Info However, our early experiments will require higher throughput than a single 96-well system can offer. ACEA has provided us with lease terms allowing for a 12-month lease of an MP system (6 x 96-well plates). This system uses the same plates and software as we are already familiar with using. We will be able to perform all of the highest-demand use of transcellular resistance during the 12 months we lease this system, and it will be exclusively utilized for the proposed grant project.

G. Total Direct Costs Itemized Cost
This includes all direct costs for both budget periods, as described above (including all subaward/consortium costs)

H. Indirect Costs Itemized Cost
We have not yet negotiated an indirect cost rate, but request Itemized Cost indirect costs according to normal guidance for first-time SBIR submissions without a pre-negotiated rate. We have applied this indirect cost rate to all direct costs as directed in the SBIR grant budget instructions.

I. Total Direct and Indirect Institutional Costs Itemized Cost
The total combined direct and indirect costs associated with this proposal are Itemized Cost This exceeds the budgetary guidance for Phase II SBIR grants to NINDS. However, we do not exceed the hard cap for costs Itemized Cost and have discussed the proposed budget with Personal Info at NCATS. She is aware of our budget request and agrees it is reasonable given the extent of our proposal.

J. Fee Fee Fee
Though a fee of up to is customarily applied to SBIR grants awarded to for-profit institutions, in an effort to perform the proposed research in the most efficient way possible, Recursion Fee due to a budget already exceeding normal SBIR-phase II suggestions (though our budget remains below the phase II hard-cap).

RESEARCH & RELATED BUDGET - Cumulative Budget

	Totals ($)
Section A, Senior/Key Person	Itemized Cost
Section B, Other Personnel	
Total Number Other Personnel	# OF EMPLOYEES
Total Salary, Wages and Fringe Benefits (A+B)	Itemized Cost
Section C, Equipment	
Section D, Travel	
1. Domestic	Itemized Cost
2. Foreign	Itemized Cost
Section E, Participant/Trainee Support Costs	
1. Tuition/Fees/Health Insurance	Itemized Cost
2. Stipends	
3. Travel	
4. Subsistence	
5. Other	
6. Number of Participants/Trainees	Itemized Cost
Section F, Other Direct Costs	Itemized Cost
1. Materials and Supplies	Itemized Cost
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	Itemized Cost
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8. Other 1	
9. Other 2	
10. Other 3	
Section G, Direct Costs (A thru F)	Itemized Cost
Section H, Indirect Costs	
Section I, Total Direct and Indirect Costs (G + H)	
Section J, Fee	Fee

Principal Investigator/Program Director (Last, first, middle): Personal Info

RESEARCH & RELATED BUDGET - SECTION A & B, BUDGET PERIOD 1

*** ORGANIZATIONAL DUNS:** Proprietary Info

*** Budget Type:** ○ Project ● Subaward/Consortium

Enter name of Organization: University of Utah

*** Start Date:** 12-01-2014 *** End Date:** 11-30-2015 **Budget Period: 1**

A. Senior/Key Person

	Prefix	* First Name	Middle Name	* Last Name	Suffix	* Project Role	Base Salary ($)	Cal. Months	Acad. Months	Sum. Months	* Requested Salary ($)	* Fringe Benefits ($)	* Funds Requested ($)
1.		Personal Info				PD/PI		EFFORT			Itemized Cost		

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name: Mime Type: **Total Senior/Key Person** Itemized Cost

B. Other Personnel

* Number of Personnel		* Project Role	Cal. Months	Acad. Months	Sum. Months	* Requested Salary ($)	* Fringe Benefits	* Funds Requested ($)
	Post Doctoral Associates							
	Graduate Students							
	Undergraduate Students							
	Secretarial/Clerical							
# OF EMPLOYEES	**Total Number Other Personnel**						**Total Other Personnel**	

Total Salary, Wages and Fringe Benefits (A+B) Itemized Cost

RESEARCH & RELATED Budget {A-B} (Funds Requested)

Tracking Number: GRANT11624079

OMB Number: 4040-0001
Expiration Date: 06/30/2011

RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 1

*** ORGANIZATIONAL DUNS:** Proprietary Info

*** Budget Type:** ❍ Project ● Subaward/Consortium

Enter name of Organization: University of Utah

*** Start Date:** 12-01-2014 *** End Date:** 11-30-2015 **Budget Period: 1**

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

Equipment Item	* Funds Requested ($)

Total funds requested for all equipment listed in the attached file

Total Equipment

Additional Equipment: File Name: Mime Type:

D. Travel **Funds Requested ($)**

1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)
2. Foreign Travel Costs

Total Travel Cost

E. Participant/Trainee Support Costs **Funds Requested ($)**

1. Tuition/Fees/Health Insurance
2. Stipends
3. Travel
4. Subsistence
5. Other:

Number of Participants/Trainees **Total Participant/Trainee Support Costs**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, BUDGET PERIOD 1

*** ORGANIZATIONAL DUNS:** Personal Info;

*** Budget Type:** ❍ Project ● Subaward/Consortium

Enter name of Organization: University of Utah

*** Start Date:** 12-01-2014 *** End Date:** 11-30-2015 **Budget Period: 1**

F. Other Direct Costs	**Funds Requested ($)**
1. Materials and Supplies	Itemized Cost
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
Total Other Direct Costs	Itemized Cost

G. Direct Costs	**Funds Requested ($)**
Total Direct Costs (A thru F)	Itemized Cost

H. Indirect Costs

Indirect Cost Type	**Indirect Cost Rate (%)**	**Indirect Cost Base ($)**	*** Funds Requested ($)**
1. Facilities and Administrative Costs		Itemized Cost	
		Total Indirect Costs	Itemized Cost

Cognizant Federal Agency

(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs	**Funds Requested ($)**
Total Direct and Indirect Institutional Costs (G + H)	Itemized Cost

J. Fee	**Funds Requested ($)**

K. * Budget Justification	File Name: 1234-BUDGET JUSTIFICATION_Utah.pdf (Only attach one file.)	Mime Type: application/pdf

RESEARCH & RELATED Budget {F-K} (Funds Requested)

Principal Investigator/Program Director (Last, first, middle): Personal Info

RESEARCH & RELATED BUDGET - SECTION A & B, BUDGET PERIOD 2

*** ORGANIZATIONAL DUNS:** Proprietary Info

*** Budget Type:** ○ Project ● Subaward/Consortium

Enter name of Organization: University of Utah

*** Start Date:** 12-01-2015 *** End Date:** 11-30-2016 **Budget Period: 2**

A. Senior/Key Person

Prefix	* First Name	Middle Name	* Last Name	Suffix	* Project Role	Base Salary ($)	Cal. Months	Acad. Months	Sum. Months	* Requested Salary ($)	* Fringe Benefits ($)	* Funds Requested ($)
1.	Personal Info				PD/PI	Institutional Base Salary	EFFORT			Itemized Cost		

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name: Mime Type:

Total Senior/Key Person Itemized Cost

B. Other Personnel

* Number of Personnel	* Project Role	Cal. Months	Acad. Months	Sum. Months	* Requested Salary ($)	* Fringe Benefits	* Funds Requested ($)
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
# OF EMPLOYEES	**Total Number Other Personnel**					**Total Other Personnel**	

Total Salary, Wages and Fringe Benefits (A+B) Itemized Cost

RESEARCH & RELATED Budget {A-B} (Funds Requested)

Tracking Number: GRANT11624079

OMB Number: 4040-0001
Expiration Date: 06/30/2011

Principal Investigator/Program Director (Last, first, middle): Personal Info

RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 2

*** ORGANIZATIONAL DUNS:** Proprietary Info

*** Budget Type:** ❍ Project ● Subaward/Consortium

Enter name of Organization: University of Utah

*** Start Date:** 12-01-2015 *** End Date:** 11-30-2016 **Budget Period: 2**

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

Equipment Item	* Funds Requested ($)

Total funds requested for all equipment listed in the attached file

Total Equipment

Additional Equipment: File Name: Mime Type:

D. Travel **Funds Requested ($)**

1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)
2. Foreign Travel Costs

Total Travel Cost

E. Participant/Trainee Support Costs **Funds Requested ($)**

1. Tuition/Fees/Health Insurance
2. Stipends
3. Travel
4. Subsistence
5. Other:

Number of Participants/Trainees **Total Participant/Trainee Support Costs**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, BUDGET PERIOD 2

*** ORGANIZATIONAL DUNS:** Proprietary Info

*** Budget Type:** ❍ Project ● Subaward/Consortium

Enter name of Organization: University of Utah

*** Start Date:** 12-01-2015 *** End Date:** 11-30-2016 **Budget Period: 2**

F. Other Direct Costs	**Funds Requested ($)**
1. Materials and Supplies	Itemized Cost
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
Total Other Direct Costs	Itemized Cost

G. Direct Costs	**Funds Requested ($)**
Total Direct Costs (A thru F)	Itemized Cost

H. Indirect Costs

Indirect Cost Type	**Indirect Cost Rate (%)**	**Indirect Cost Base ($)**	*** Funds Requested ($)**
1. Facilities and Administrative	Itemized Cost		
Total Indirect Costs			Itemized Cost

Cognizant Federal Agency

(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs	**Funds Requested ($)**
Total Direct and Indirect Institutional Costs (G + H)	Itemized Cost

J. Fee	**Funds Requested ($)**

K. * Budget Justification	File Name: 1234-BUDGET JUSTIFICATION_Utah.pdf (Only attach one file.)	Mime Type: application/pdf

RESEARCH & RELATED Budget {F-K} (Funds Requested)

RESEARCH & RELATED BUDGET - Cumulative Budget

	Totals ($)			
Section A, Senior/Key Person				Itemized Cost
Section B, Other Personnel				
Total Number Other Personnel				Itemized Cost
Total Salary, Wages and Fringe Benefits (A+B)				
Section C, Equipment				
Section D, Travel				
1. Domestic				
2. Foreign				
Section E, Participant/Trainee Support Costs				
1. Tuition/Fees/Health Insurance				
2. Stipends				
3. Travel				
4. Subsistence				
5. Other				
6. Number of Participants/Trainees				Itemized Cost
Section F, Other Direct Costs			Itemized Cost	
1. Materials and Supplies				
2. Publication Costs				
3. Consultant Services				
4. ADP/Computer Services				
5. Subawards/Consortium/Contractual Costs				
6. Equipment or Facility Rental/User Fees				
7. Alterations and Renovations				
8. Other 1				
9. Other 2				
10. Other 3				
Section G, Direct Costs (A thru F)				Itemized Cost
Section H, Indirect Costs				
Section I, Total Direct and Indirect Costs (G + H)				
Section J, Fee				

BUDGET JUSTIFICATION
University of Utah Consortium/Subaward

The total 2-year budget request is Itemized Cost

Personnel Itemized Cost

Personal Info Itemized Cost EFFORT months at a NIH maximum salary of Institutional Base Salary per year – only to be applied during the second budget period). Personal Info is the founding CSO of Recursion Pharmaceuticals and the HA and Edna Benning Endowed Professor in Medicine and Cardiology and Director of the Molecular Medicine Program. Personal Info received his graduate training in Personal Info laboratory, where they developed the drug screening platform licensed to Recursion from the University of Utah. In Personal Info Personal Info identified two known drugs that could be repurposed to treat CCM disease and performed a small set of experiments validating the ability to expand this approach to many other diseases. Personal Info will provide both scientific and management mentorship to Personal Info and Personal Info as an unpaid consultant during both years of the proposed award. Additionally, Personal Info will also oversee a subaward/consortium in which his laboratory will acquire, validate, and study relevant animal models as described in aim 3. This will require EFFORT effort from Personal Info applied exclusively during the second year of the award when the vast majority of work will be performed in Personal Info laboratory.

Fringe Itemized Cost
The University of Utah's fringe benefit rate is Itemized Cost

Other Direct Costs Itemized Cost
We request Itemized Cost for animal model experiments consistent with the proposed aim 3. Personal Info laboratory has considerable expertise developing, validating, characterizing, and studying knockout mice. We propose to acquire between five and ten murine models, and expect that the typical costs to acquire, breed, house, and study such mice will be approximately Itemized Cost per animal model. This is an estimate based on the costs associated with the use of disease-relevant animal models in the past. The expertise of Personal Info in breeding, maintaining, and studying murine models increases efficiency and reduces the associated costs.

Indirect Costs Itemized Cost
The University of Utah has a federally negotiated Facilities and Administrative Costs rate of Itemized Cost

SBIR/STTR Information

OMB Number: 4040-0001
Expiration Date: 6/30/2016

*** Program Type (select only one)**

☒ SBIR ☐ STTR

☐ Both *(See agency-specific instructions to determine whether a particular agency allows a single submission for both SBIR and STTR)*

*** SBIR/STTR Type (select only one)**

☐ Phase I ☒ Phase II

☐ Fast-Track *(See agency-specific instructions to determine whether a particular agency participates in Fast-Track)*

Questions 1-7 must be completed by all SBIR and STTR Applicants:

☒ Yes ☐ No	* 1a. Do you certify that at the time of award your organization will meet the eligibility criteria for a small business as defined in the funding opportunity announcement?
	* 1b. Anticipated Number of personnel to be employed at your organization at the time of award. # OF EMPLOYEES
☐ Yes ☒ No	* 2. Does this application include subcontracts with Federal laboratories or any other Federal Government agencies? * If yes, insert the names of the Federal laboratories/agencies:
☐ Yes ☒ No	* 3. Are you located in a HUBZone? To find out if your business is in a HUBZone, use the mapping utility provided by the Small Business Administration at its web site: http://www.sba.gov
☒ Yes ☐ No	* 4. Will all research and development on the project be performed in its entirety in the United States? If no, provide an explanation in an attached file. * Explanation: Add Attachment Delete Attachment View Attachment
☐ Yes ☒ No	* 5. Has the applicant and/or Program Director/Principal Investigator submitted proposals for essentially equivalent work under other Federal program solicitations or received other Federal awards for essentially equivalent work? * If yes, insert the names of the other Federal agencies:
☐ Yes ☒ No	* 6. Disclosure Permission Statement: If this application does not result in an award, is the Government permitted to disclose the title of your proposed project, and the name, address, telephone number and e-mail address of the official signing for the applicant organization, to organizations that may be interested in contacting you for further information (e.g., possible collaborations, investment)?
	* 7. Commercialization Plan: If you are submitting a Phase II or Phase I/Phase II Fast-Track Application, include a Commercialization Plan in accordance with the agency announcement and/or agency-specific instructions. * Attach File: 1254-CommercializationPlan_Rec Add Attachment Delete Attachment View Attachment

SBIR/STTR Information

SBIR-Specific Questions:

Questions 8 and 9 apply only to SBIR applications. If you are submitting ONLY an STTR application, leave questions 8 and 9 blank and proceed to question 10.

☐ Yes ☒ No	* 8. Have you received SBIR Phase II awards from the Federal Government? If yes, provide a company commercialization history in accordance with agency-specific instructions using this attachment. * Attach File: Add Attachment Delete Attachment View Attachment
☒ Yes ☐ No	* 9. Will the Project Director/Principal Investigator have his/her primary employment with the small business at the time of award?

STTR-Specific Questions:

Questions 10 and 11 apply only to STTR applications. If you are submitting ONLY an SBIR application, leave questions 10 and 11 blank.

☐ Yes ☐ No	* 10. Please indicate whether the answer to BOTH of the following questions is TRUE: (1) Does the Project Director/Principal Investigator have a formal appointment or commitment either with the small business directly (as an employee or a contractor) OR as an employee of the Research Institution, which in turn has made a commitment to the small business through the STTR application process; AND (2) Will the Project Director/Principal Investigator devote at least 10% effort to the proposed project?
☐ Yes ☐ No	* 11. In the joint research and development proposed in this project, does the small business perform at least 40% of the work and the research institution named in the application perform at least 30% of the work?

COMMERCIALIZATION PLAN:
Expansion of an efficient drug repurposing platform for rare genetic diseases

OPPORTUNITY OVERVIEW

Drug discovery and development has been a capital-intensive industry throughout modern times. Regardless of the method employed, vast resources have been required to identify a drug that can effectively treat a disease without undue side-effects, and increased regulatory requirements have only added to these costs. Though technology has advanced substantially over the last three decades, a massive climb in the amount of total R&D expenditures has not blossomed into a corresponding growth in the number of new drugs coming to markets. This is not to say huge advances have not been made – they have – but the cost of each new advance has steadily increased. Though it is commonly cited that it costs more than $1 Billion to bring a drug to market, more recent analyses suggest the figure could be closer to $5 Billion for the largest pharmaceutical companies[80].

There are countless reasons for these staggering costs, many of which are largely out of the control of the pharmaceutical industry. However, one contributing factor has been a logical drive toward 'blockbuster' indications; achieving the 'silver bullet' treatment of a highly prevalent disease has been at the center of most pharmaceutical company's targets. However, history has shown that certain blockbuster indications, such as Alzheimer's disease, have been plagued by high failure rates despite many billions of dollars invested[81]. The result of the focus on major indications, sometimes at any cost, has in-part led to the large increase in drug development costs. These widely-reported costs, then, feedback into the rhetoric that the only drugs worth developing are 'blockbusters'.

There have been some notable exceptions to the industry trends in recent years. Genzyme, founded in 1981, sought to take advantage of new technology in therapeutic proteins even though the early indications of such technology would find their home in the treatment of rare diseases. By 2010, Genzyme had grown to more than $4 billion in revenues and 10,000 employees while still focusing almost entirely on the treatment of rare diseases.

Recursion Pharmaceuticals, LLC, is a startup company based in Salt Lake City that seeks to follow in the footsteps of companies like Genzyme by using an innovative technology to treat rare diseases. Recursion hopes to become profitable by achieving disruptive efficiencies in the discovery and development of treatments for rare diseases, allowing healthy profits to come from relatively small markets. We aim to achieve this goal by intertwining two complementary strategies:

1) Use a drug discovery platform we have developed that is highly automated, relatively inexpensive, and able to simultaneously probe thousands of rare genetic diseases.
2) Harness the prior productivity of thousands of scientists and many billions of dollars in research and development by identifying new uses for known drugs, a strategy known as drug repurposing or repositioning.

A. VALUE, OUTCOMES, & IMPACT

Proposed technology and objectives:

Recursion Pharmaceuticals has combined a variety of cutting-edge technologies into a highly-scalable drug discovery platform. Our technology is based on modeling a large class of diseases all at once – thousands at a time. The first set of diseases we will study are 'monogenetic loss-of-function', where a mutation in a single gene causes a loss of that gene's function, leading to specific human disease. One of the most well-known diseases of this class is cystic fibrosis. Mutations in the *CFTR* gene result in a non- or poorly-functional cystic fibrosis transmembrane conductance regulator (CFTR) protein, and the loss-of-function of this protein causes the symptoms of the disease. There are several thousand monogenic loss-of-function diseases, and each can be efficiently modeled at the cellular level using a variety of genetic manipulation tools. One of these techniques, RNA interference technology (RNAi), results in elimination of most (usually 70-90%) of a specific gene's protein product[82]. This technique is easy to perform at scale, where hundreds or thousands of specific proteins can simultaneously be targeted, one in each well of a multi-well plate. In the proposed grant, we will evaluate 2,000 loss-of-function disease models using this technology.

We will conduct an in-depth examination of each of these 2,000 disease models to quantify hundreds of induced cellular changes. We will measure changes in the structure of the cells using automated microscopy, and we measure functional changes in the activity of the cells by growing them on microscopic electrodes and measuring their response to various electrical stimuli. Each disease model can then be compared to

appropriate controls, and structural and functional changes achieving thresholds of quality and significance can be used as a phenotypic fingerprint ('phenoprint') of that disease. Our preliminary data suggests that we will likely identify 200 or more diseases with a robust phenoprint.

We will then recreate each disease model at a much larger scale – thousands of wells will be filled with one disease model – and the effect of various drugs on the phenoprint will be evaluated. To further increase our ability to rapidly bring drugs to the market, we will examine only those drugs that have known human safety profiles. Those drugs that restore a disease model back to health will be prioritized for further validation.

We will next use another genetic manipulation technology, the CRISPR/Cas9 system, to validate our twenty highest-priority disease models and the drugs that rescue them. We expect to obtain at least 10 validated drug/disease combinations, and will then evaluate the potential of 5-10 of these diseases in the most relevant murine model available. We expect that at least two of these drug/disease combinations will prove efficacious at the animal level, and when combined with the known human safety profile, we will be in a position to rapidly begin human disease-specific clinical trials.

Funding of this grant would lead to a number of specific deliverables, including:

1) Quantification of phenoprints from at least 2,000 selected monogenic loss-of-function disease models from our database of many thousands.
2) Evaluation of the effects of nearly 3,000 known drugs on the phenoprint of at least 200 monogenic loss-of-function disease models.
3) Validation of the top 20 disease/drug combinations in cells using orthogonal genetic manipulation techniques (CRISPR/Cas9 knockout models).
4) Initial evaluation of the top 5-10 validated disease/drug combinations in the most relevant animal models.

SBIR Phase III:

At the conclusion of the proposed research, we expect to have identified two known drugs with potential for repurposing for the treatment of specific rare genetic diseases. In the commercialization phase of this proposal, we will file method-of-use patents, applications for orphan indication status, and preparation of investigational new drug (IND) applications to prepare for FDA clinical trials. We will also initiate discussions with any parties with rights to a drug we have identified as a repurposing candidate. Our aim in the Phase III portion of this proposal will be to work with other stakeholders to initiate human phase II clinical trials, when appropriate, and to subsequently license these drugs to larger pharmaceutical companies for further development and marketing.

Current approaches:

There are more than 7,000 rare diseases, as defined by the FDA. Though each of these diseases, by definition, typically affects fewer than 200,000 Americans, in total many millions of Americans have one of these diseases. Despite improved market and regulatory conditions over the past two decades, the vast majority of these diseases (more than 95%) do not have an approved therapy. The rare disease market, therefore, is vast and highly fragmented.

Successful approaches to addressing the rare disease market have typically been highly disease-specific. Specific drugs have been developed to treat particular diseases based on disease-specific science or mechanism. Drug repurposing has been utilized in the rare disease market, due to many of the same benefits we extoll here. Typically, however, repurposing successes in the rare disease space have been coincidental[14]. There have been more systematic attempts at repurposing drugs for the treatment of rare diseases, however these attempts have typically depended on a robust understanding of the molecular mechanisms underlying these diseases, which are often poorly understood (refs). There have been no highly efficient approaches to simultaneously exploring the potential of thousands of known drugs to be repurposed for any one of thousands of rare diseases.

Commercial Impacts:

The commercial implications of the proposed research and development are significant, and include:

1) We have already identified a drug which has potential to be repurposed to treat a hereditary stroke disorder (see Phase-I type Pilot data in Research Proposal). We are currently in negotiations to out-license or co-develop this drug with a company who has a substantial amount of pre-clinical and clinical data supporting its use in a broader indication. The proposed grant would enable us to have a total of three drugs at this stage (rather than our current one). Any one, or potentially multiple, of these drugs could by itself represent a major commercial success. Each drug we can bring forward as a repurposing candidate will

multiply the odds of generating critical early revenues that could support the growth of our company, and therefore our approach.

2) The proposed grant will provide us with the infrastructure, data/models, and validation necessary to make a compelling case for pre-negotiated deals with pharmaceutical partners to screen their safe but unmarketed drugs against our 'library' of rare disease models.
3) The proposed grant also ties in well with our approach to growing our business. Non-dilutive funding, as provided by SBIR grants, is incredibly valuable, especially when a company such as ours is relatively new. The ability to secure non-dilutive funding, and a focus on sustaining such funding as a portion of our growth strategy, will be highly attractive to investors (both professional Angels in the near-term and traditional venture capital in the medium-term).
4) While the primary outcome of this grant will be two new therapeutic candidates, another highly beneficial impact will be the generation of dozens (or even hundreds) of other leads that we could pursue as funding permits.

Phase II SBIR funding is a precious resource, that when realized, will bolster our stature in nearly all potential relationships. Our success in receiving this grant, and subsequently achieving the proposed aims, will improve our ability to partner, to secure investment, and to recruit highly effective new employees (and retain those we do have).

Societal Impact:

Rare genetic diseases affect millions of Americans, and often strike the pediatric population. Most of these diseases have no specific approved treatment, and their symptomatic treatment is incredibly costly to our healthcare system. Addressing even a single disease would have a profound impact on potentially thousands of patients and their families. Our ability to scale the proposed drug discovery system to relatively efficiently re-purpose drugs for multiple such diseases magnifies this approach with potentially profound impacts.

Educational Impact:

Our high-efficiency drug discovery platform will sometimes identify drug treatments for rare diseases with no obvious commercial viability. We will, as a rule, publish our findings of such cases in the hope that academics or not-for-profits can build off of our foundation to implement effective treatments. Unpublished Unpublished Unpublished Unpublished Unpublished Unpublished

Other Impacts:

The declining growth of the largest pharmaceutical companies has been met with an increased focus on efficiency, rare disease indications, and partnership and collaboration with small pharmaceutical companies. Though it is unlikely that Recursion's approach to drug discovery will significantly alter the course of the pharmaceutical industry, we believe our partner-centric strategy of efficient drug re-purposing for rare diseases is perfectly timed. We are confident that with a few early successes, such as we have already demonstrated in our preliminary studies underlying this proposal, we will be well-positioned to take advantage of industry trends to accelerate our growth.

Further, we are excited about the prospect of our company helping to build on a small but flourishing biotech industry in Salt Lake City, Utah. Myriad Genetics, BioFire Diagnostics (recently acquired by bioMerieux), ARUP laboratories are based within 0.5 miles of our office, with a few other notable companies such as Actavis maintaining research labs there as well. Our success would help to reinforce the success of these, and other, local companies. Salt Lake City is growing rapidly and has become a hot-spot for tech companies like Adobe, and we could imagine nothing better than to contribute to our local community by helping to make Salt Lake City a fast-growing biotech hub in the Mountain West.

B. COMPANY

Recursion Pharmaceuticals, LLC, is a start-up company based in Salt Lake City that combines innovative biological science with advanced computational algorithms to discover new therapeutic opportunities for rare genetic diseases. The company was very recently founded (November, 2013) based on technology developed by the PI of this proposal, Personal Info in the laboratory of co-founder Personal Info at the University of

Utah. A third co-founder, Personal Info with a background in computational biology and software engineering, was recruited to lead computational activities.

In the past 6 months, among other actions, Recursion pharmaceuticals became a Delaware LLC certified to operate in the state of Utah, seeded the company with a total of $130,000, licensed the underlying technology from the University of Utah, built its executive team, established relationships with vendors for experimental equipment and consumables, rented space, setup a laboratory, began conducting experiments, and recently closed a small convertible debt offering of more than $100,000 from 6 accredited angel investors. We also pitched our company at the 2014 Texas Life Science Forum at Rice University in February, and received the 'best pitch' award from among 55 companies, the majority of which were in series B or later fundraising stages. The company has received no prior federal funding of any kind. Recursion is actively recruiting its first four non-founder employees.

Recursion has in place a strong and balanced management team with business and scientific expertise. Additionally, relationships have been established with an outstanding group of business and scientific advisors and with leading research institutions. Collectively, the team is committed to achieving rapid growth based on a strong scientific rationale and shared vision for dramatically impacting the lives of individuals and families living with rare genetic diseases.

Management Team:

Personal Info *Co-Founder and CEO*

Personal Info completed his Ph.D. in Bioengineering at the University of Utah, where he developed the core technology underlying this venture while in Personal Info Personal Info played a critical role in a wide-variety of projects in Personal Info, publishing papers with at least four other research groups in high-profile journals including a co-first author article in Nature. One of his research projects was also the basis of a successful NIH R01 application, which he authored under the direction of Personal Info (2nd percentile score). Personal Info Personal Info made several invention disclosures to the University of Utah, several of which are being actively pursued through various channels for commercialization. Personal Info graduated from Rice University with a bachelor of science in bioengineering and a bachelor of arts in managerial studies. He also worked as a project manager at a medical device start-up, Medi-Screw, during his last two years of college where he gained valuable experience in both business and biotech. Personal Info recently completed an intensive residential business and entrepreneurial training program for scientists at the Stanford Business School (Stanford IGNITE).

In the past 6 months Personal Info has garnered support from the University of Utah leadership for Recursion, who granted him a flexible leave from the MD/PhD program to oversee the establishment and growth of the company. Personal Info immediately negotiated an exclusive world-wide license to the drug discovery platform from the University. He was able to reduce the University's proposed 10% stake of all revenues over $10M to a 2.5% equity position in order to incentivize the University to enable non-dilutive funding pursuits such as this proposed grant. The minority ownership of the University enabled Personal Info to negotiate preferential pricing for the use of University Core Facilities, a critical step in reducing the up-front capital costs of executing Recursion's vision. Personal Info recruited both Personal Info and Personal Info to co-found the company, and together they capitalized Recursion's founding. Personal Info subsequently secured more than $100,000 in additional funding from accredited investors. Personal Info has overseen all administrative aspects of the business to date, has recruited a number of expert advisors to join Recursion (with several additional advisors engaged in exploratory discussions), PATENT PENDING

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Personal Info will continue to administer all aspects of Recursion, while recruiting the very best possible candidates for both advisory and early employee positions.

Personal Info *Co-Founder and CSO*

Personal Info has previously co-founded two biotech companies, and has been on the cutting-edge of translational medical research at the University of Utah for more than two decades. He is the H.A. & Edna Benning Endowed Professor of Medicine and Cardiology, Director of the Molecular Medicine Program, and Vice Dean of Research at the University of Utah as well as CSO of University of Utah Health Care. He is the recipient of multiple honors including the Established Investigator Award by the American Heart Association and Clinical Scientist Award in Translation Medicine from the Burroughs Wellcome Foundation. He is a member of the American Society of Clinical Investigators. He is the author of nearly 300 manuscripts published in peer-reviewed journals including Science and Nature.

Personal Info start-up and biotech experience dates to 2001 when he co-founded Hydra Biosciences with Personal Info Personal Info (now Vice-President and Global Head of Ophthalmology at Novartis) and Personal Info was head of research and development at Hydra until the end of 2003. Hydra Biosciences is a privately held biopharmaceutical company focused on developing drugs through leveraging its expertise in ion channels and molecular regeneration. In 2006 Personal Info co-founded Navigen Pharmaceuticals with Personal Info (former CEO and co-founder of NPS Pharmaceuticals). Navigen is located in Salt Lake City and focused on the development of novel small molecules targeting the ARF6 pathway to stabilize the vasculature, as well as D-peptide based anti-viral therapeutics. Both Navigen and Hydra continue to operate, having brought in more than $25M and $75M in funding, respectively. Personal Info will use his start-up experience and vast network to help guide Recursion Pharmacuticals.

Personal Info *Co-Founder and CTO*

Personal Info attended Rice University where he studied electrical engineering. In 2005, Personal Info co-founded an e-commerce company, BuildASign.com, that has grown to more than $60 Million in annual revenues and 250 employees. Personal Info remains an owner of BuildASign.com, Personal Info Personal Info is nearing completion of a Ph.D. at UT-Austin in the laboratory of Personal Info where he is using bioinformatics approaches to elucidate the large-scale organization of protein functions. Personal Info is also a board member of the Central Texas Angel Network, the fifth most active angel investor group in the United States, through which he has gained unique insights into funding and growing start-up companies, including those in the biotech space. Personal Info has led all computational aspects of Recursion's growth, including development of a private monogenic disease database compiled by data-mining dozens of massive public databases. Personal Info also participates in the day-to-day strategic decision-making of Recursion, drawing from his successes in growing his previous company and his deep understanding of data interpretation and biology.

Resources & Advisors:

Recursion rents approximately Square Footage of laboratory space and Square Footage of office space in a full-service building adjacent to the University of Utah. Because of the proximity and affiliations with the university (through the laboratory of [ ] and through a minority ownership of the company by the University of Utah Research Foundation), Recursion has ready access to many of the core facility resources and to experts residing at the University. Beyond those resources, we also have recruited a number of renowned industry professionals to serve as an advisory board. The combined strength of our core team and advisory members is unique in a company of our size and age and speaks to the promise and excitement around our vision and technology platform. Personal Info

Consultant Info

Consultant Info

Consultant Info

Vision:

Recursion aims to be a new kind of pharmaceutical company that is modelled on robust science, but also on a belief that rather than trying to 'outsmart' biology by asking the perfect question, we can make millions of biological inquiries in an efficient manner and look for meaningful patterns in the results. This proposal is just

one of a number of early steps in our plans. Our vision is to use the same basic approach specified here to treat hundreds of diseases within ten years. We will achieve this vision in two ways:

1) We will constantly expand our set of validated rare genetic disease models. Though we've proposed here to evaluate 2,000 genes in two cell types in two assays, our vision is to query all genes in dozens of cell types in many complementary assays. We believe that this approach will allow us to identify phenoprints that can serve as the basis of chemical suppressor screens for hundreds of diseases.
2) We will partner and publish as much and as often as possible to ensure that every new drug indication we discover is rapidly delivered to patients. Our goal will be to secure a percentage of the financial success of a large number of treatments, rather than to focus on securing a large portion of a few major indications.

As we grow, our business will inevitably expand beyond monogenic loss-of-function diseases. We have envisioned variations of our technology platform for efficient drug discovery in many diverse areas including: gain-of-function genetic diseases, toxic accumulation genetic diseases, inflammation, infectious disease, and identification of novel antibiotic agents.

Achieving our Vision:

We will achieve the above stated vision by executing on a methodical growth plan, as outlined below:

Next six months: Recursion will make substantial strides forward as a young company in building out our core experimental and computational team, helping us to achieve early validation of both our platform and our first potential therapeutic, both of which will enable us to raise additional outside funding. First, Recursion will continue negotiations seeking a joint-venture to develop tempol for the treatment of CCM disease. If an agreement can be reached, we will immediately pursue an orphan indication for the use of tempol in CCM, and use our partner's data to submit an investigational new drug (IND) application to the FDA. Second, we will hire and are already recruiting for a full-time grant-writer, a full-time tissue culture technician, and a full-time scientific software developer. These positions will enable Recursion to pursue both NIH and foundation-supported grants related to rare-disease drug discovery, increase experimental throughput, and continue refining our computational analysis capabilities, respectively. Recursion has developed a list of several high-value business and scientific advisory board members, and we will actively pursue their participation during this period. Third, Recursion will continue to evaluate the phenoprint of 50 specially-selected genes in human endothelial cells, which we have funded internally. Fourth, Recursion will raise an additional $700k in convertible debt from professional angel investors in Utah, the San Francisco bay area, and Texas.

Six months to two years: Recursion will have achieved sufficient validation of our vision and approach to enable raising a large equity investment, and will expand our team to support additional grant- and foundation-related work towards clinical trials for multiple rare genetic diseases, while also pursuing high-value partnerships with large pharmaceutical companies to repurpose their FDA phase I and phase II failures. Recursion hopes to have entered into a joint venture to pursue phase II clinical trials for the use of tempol to treat cerebral cavernous malformation, and to have achieved all aims stated in this proposal. Our focus during this period will be four-fold. First, we will continue to pursue government and private foundation-sponsored research opportunities to support further research and the clinical development of candidate therapeutics. Second, we will expand our platform to up to five diverse human cell types and integrate one to two additional high-throughput assays. Third, we will use our successes to support a Series A venture capital and/or family office investment round of between $4M and $6M. Fourth, we will seek to gain the rights to screen drugs from other pharmaceutical companies which were shown to be safe in Phase I clinical trials, but failed for their intended indication for efficacy or business reasons (See 'Revenue Streams'). We would expect to employ between # OF EMPLOYEES team members at this stage.

Two years to five years: Recursion will have achieved partnerships to out-license or co-develop three or more therapeutics for orphan indications. Specifically, we would expect to have completed a phase II and phase III clinical trial (if required) for the use of tempol in the treatment of CCM. This will result in our first revenues (with the exception of up-front or milestone payments). We will also advance our drug discovery platform into additional cell types and additional diverse assays. The expansion of the discovery platform, we hope, will expand the number of genetic diseases for which we have identified a screenable phenoprint from 200 up to many hundreds or thousands. We will also repeat chemical suppressor screens for high-value disease models with additional drugs that we will have added to our library. We expect these steps to result in at least 10-15 drug repurposing candidates in our development pipeline. These goals take advantage of the current core strengths of the company without diluting our business strategy before we have a critical mass of employees

and resources. We expect that early revenues from tempol, or up-front or milestone payments for other drug candidates, will enable the proposed activities without the need for a series B or series C investment round.

Five to ten years: Because the technology platform has the potential to grow exponentially due to the number of genes, cell types, and assays that can be characterized, the longer term outlook holds great promise and growth potential. We expect to achieve revenues from multiple drugs during this period, enabling rapid growth and expansion into new markets. As our track-record of discovery is established and we build the requisite internal capabilities (medical, safety, statistics, and regulatory), we will expand our development strategy to include carrying through select high interest phase 3 projects internally, while continuing to employ high-quality contract research organizations for the majority of our clinical trial, formulation, and manufacturing needs. At this stage, we will have the ability to expand our screening platform into new disease models (or to generate or acquire other discovery platforms). We see opportunity in highly-parallel dug screening platforms in oncology, infectious disease, and patient (genotype)-specific treatments. We expect to grow to [ ] employees at this stage. Achievement of these goals could enable an initial public offering to fund additional growth. # OF EMPLOYEES

People, Growth, and Culture:

Recursion pharmaceuticals anticipates strong growth over the next ten years, and will be required to manage that growth to maintain a sustainable business entity. The most critical steps to help insure successful growth will be the identification and recruitment of the best possible early employees, managers, and advisors. On the scientific front, Recursion has already identified and retained two highly-qualified scientific advisors in anticipation of establishing a scientific advisory board composed of between five and eight individuals by the end of 2014. In addition to the individuals appointed at this time, Recursion seeks to identify and attract advisors with expertise in rare disease drug development, high-throughput screening, and drug re-purposing.

Recursion is also in the early stages of establishing a business advisory panel composed of between three and six experienced life science business leaders. This panel will serve to mentor the Recursion management team, and consult and advise on business opportunities and strategy. Recursion has entered into discussions with the former founder and CEO of a publicly traded life-science company based in Seattle to be the first member of this panel, but has not finalized an agreement at the time of submission.

As we grow, we will identify and recruit new employees who share our vision, and who bring exceptional and diverse talents to our team. We fully anticipate hiring a small number of highly-experienced managers and scientists to serve in managerial roles. However, we also plan to bring in many young, talented, and passionate employees from diverse educational backgrounds. It is our belief that a group of very diverse minds (clinicians, engineers, molecular biologists, regulatory specialists, business development, biochemists, etc) should be involved at all stages of development. We won't be able to, nor do we intend to, compete with the largest pharmaceutical companies by employing an army of scientists. Instead, we will make a niche for ourselves in the pharmaceutical market by constantly seeking out efficiency and executing on our vision. We will bring many of the practices of the tech startups of Silicon Valley to the Pharmaceutical industry, but with a uniquely 'Mountain West' feel. Our office is located just 50 feet from trailheads into the Wasatch mountain range where skiing, biking, and hiking are plentiful. We will seek passionate and hard-working employees who also value our proximity to such a wonderful outdoor resource.

C. MARKET, CUSTOMERS, and COMPETITION

Orphan Disease Market:

Large pharmaceutical companies have built their core businesses on major indications. Pfizer, for example, had five drugs with sales of more than $1 billion in 2012. One of the best performing drugs in history, LIPITOR® (Atorvastatin), was prescribed to millions of patients in 2008 and generated more than $12 billion in revenues for Pfizer that year[83].

Before 1983, only 38 drugs had been developed to treat a rare disease[84]. The Orphan Drug Act of 1982, which was signed into law in 1983, provided economic incentives for rare disease drug development. This law proved to be an important stimulus as there are now more than 400 approved orphan disease drugs on the market[84]. Since the act was passed, several companies have demonstrated an economic model for successful treatment of orphan diseases. Genzyme is perhaps the most famous of these. Today, orphan indications have become a 'hot' area in drug discovery. Drugs like GATTEX® (Teduglutide [rDNA origin]), was developed for a patient population numbering less than 1,000 in the U.S., but at a cost of more than $300,000 per patient per year. Relatively high prices may be justified in the treatment of very rare and serious disorders, and support the

notion that a successful business can be built around the treatment of very rare disorders. Despite the economic potential, the vast majority (more than 95%) of rare diseases still have no treatment[3]. The high cost of drug discovery and development, the long time from investment to expected returns, and the tremendous risk of failure means that the current model of drug discovery and development is still unlikely to meet the needs of most rare-disease patients, and the high-prices of drugs that do make it to market may put additional strain on our already faltering healthcare system.

Orphan Indications – Advantages:

Treatment of orphan indications come with certain advantages which Recursion plans to take advantage of:

1) *Seven-year market exclusivity.* Approval of an orphan drug comes with it seven years of market exclusivity independent of patent status. Further, competitors seeking similar designation must prove superiority of any treatment arriving later to the market.
2) *Tax credits for development costs.* Half of development costs can be credited under a fifteen year carry-forward provision and a three-year carry-back.
3) *Fast-track approvals and waived fees.* Orphan drug approvals at the FDA are expedited, reducing the time-to-market significantly. Additionally, application fees that can present a barrier to entry, especially for small companies, are waived for orphan drug treatments.
4) *Sparse competition.* Though rare disease treatment has become a popular new business strategy, there remain more than 5,000 untreated disorders. Though certain rare indications, such as muscular dystrophy, have become competitive indications, the majority of rare diseases are not being actively pursued by any pharmaceutical company.
5) *The potential for less costly clinical trials.* Clinical trials are extremely expensive, in part because of the large number of patients required, especially in phase III. The FDA has sometimes made provisions for much smaller clinical trials in the orphan disease space.

Orphan Indications – Disadvantages:

Treatment of orphan indications come with certain disadvantages, which Recursion will address in the following manner:

1) *Smaller markets.* This is an obvious limitation of orphan indications, although as stated above the higher prices generally supported in this market counteract the smaller patient populations. Recursion will primarily focus on developing drugs for the U.S. market, but will actively seek to expand any successful treatment to other developed markets in Europe, Australia, and the European Union to maximize the potential market size.
2) *Difficulty enrolling sufficient patients for clinical trials.* The small number of patients can make clinical trial enrollment difficult. Many rare disease patients, however, have sought care with one of a few experts for their disease, often providing a source of concentrated rare disease patients. Cerebral cavernous malformation patients, for example, often seek treatment at one of five American hospitals where particular expertise resides. Recursion will target such centers as clinical trial sites to maximize efficiency. Further, effective patient organizations exist for many rare diseases. Recursion will actively seek these organizations and their input throughout the drug development process.
3) *Potential for poor understanding of disease pathophysiology.* The mechanism of many rare diseases are poorly understood. Recursion's drug screening platform largely bypasses this issue in the case of monogenic loss-of-function diseases.

Recursion Pharmaceuticals Technology:

Recursion brings a fresh approach to drug discovery to the market that combines both highly efficient automated experimental biology and *in silico* efforts. We will differentiate ourselves by our efficiency and strategy. By simultaneously modelling thousands of diseases and rapidly evaluating the potential of known drugs to be repurposed for the treatment of these diseases, we will be able to discover a relatively large number of repurposing opportunities in a short period of time. By partnering with other pharmaceutical companies to develop many of these drugs in parallel, we will minimize the risk posed by the failure of any one drug or partnership.

Partnerships:

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In exchange, we would receive an up-front payment, milestone payments, and a portion of net profits upon successful marketing. The second potential structure is a joint venture whereby we would have joint decision-making control with our partner, be entitled to a percentage of net profits, and be required to support a corresponding percentage of an agreed-upon development budget. We would contribute a portion of our next angel investment round towards this joint venture under this secondary deal structure.

In both cases, the first step will be application for an orphan indication, followed by an IND application based on our animal data and our partner's pre-clinical data. We anticipate that these goals could be achieved during 2014. We would anticipate being allowed to proceed directly to phase II clinical trials for the prevention of hemorrhagic stroke in patients with the familial form of CCM, ideally commencing in early 2015. We would pursue an R44 SBIR grant to help fund this clinical trial (PAR-12-073, NINDS Exploratory Clinical Trials for Small Business).

Competition:

Both the rare-disease and drug re-purposing markets are rich with new entrants. There are few companies specifically focused on drug re-purposing for rare diseases, but competition nonetheless also exists from a variety of non-traditional sources. Our competition comes in the following primary forms:

1) *Large and mid-sized pharmaceutical companies.* Companies like Pfizer and Novartis have established rare-disease-focused business units and have massive resources that would be difficult to defend against. Medium-sized companies like Ultragenyx and Biomarin are nimble and focused in the rare disease space, but lack the scale of resources compared to the largest pharmaceutical companies. There have also been reports of in-house drug-repurposing efforts among the largest pharmaceutical companies. However, the principal focus of large and mid-sized pharmaceutical companies remains new chemical entities with robust intellectual property defensibility. With thousands of orphan indications, it is unlikely that we will compete directly with these companies in the majority of cases. However, our success in executing on our proposed vision could make us an attractive acquisition target for a large company with the resources to justify a new approach to repurposing all drugs under their control.
2) *Large non-profits and academic institutions.* The Broad Institute, Cures Within Reach, and the Bill and Melinda Gates Foundation are examples of diverse non-profits who have explored drug-repurposing or orphan indications. Certain of these institutions have the resources to directly compete with Recursion. Our approach will be to partner with such institutions to maximize their philanthropic goals while simultaneously accelerating our own development timeline. We have already entered into discussions with the Broad Institute about a joint CRISPR-based phenotypic screen, with a goal of applying for STTR-style funding during the summer of 2014. In such a partnership, all data generated would ultimately become public, but we would be able to help direct the research and have the opportunity to use the data in advance of our competitors. Academic centers have proven their ability to re-purpose drugs for a variety of conditions. At this time, these attempts are not systematic across many diseases, but instead focused on specific indications for which the institution or laboratory has experience.
3) *Start-up Pharmaceutical companies.* There are a number of innovative small or start-up companies focused in a similar market. Numedii and Biovista, for example, are using *in silico* approaches to repurpose drugs, though their approaches depend on a more complete understanding of mechanism that is less amenable to some rare diseases. Melior Discovery and MarcoPolo Pharmaceuticals are repurposing drugs using highly-predictive in vitro or animal models. In both cases, the number of disease models being studied is minute compared to what we propose.
4) *New technology and innovation.* Breakthrough advances in gene replacement therapy would present a substantial risk to our core business model. However, this technology has been long-promised and still has major hurdles to face. We plan to find as many orphan drug/disease combinations as possible within a few years. Our success will fuel us to expand our current platform into new disease spaces that are not threatened by this technology. Further gene replacement technology will likely face intense

regulatory hurdles and the huge number of orphan indications suggests Recursion will have some room to operate in the market.

D. INTELLECTUAL PROPERTY & DEFENSABILITY

Drug candidates:

Robust intellectual property around our drug candidates will form a core of our business. Recursion will vigorously protect this IP by all available mechanisms. By acting quickly and identifying new uses for known drugs, we can seek method of use patents, which provide some defensibility. Additionally, we will pursue orphan indication status whenever available, which provides seven years of market exclusivity regardless of IP-status. In extreme cases where, for example, we are unable to partner with a company that currently markets a drug we have discovered has a new use, we will consider pursuing generation of novel formulations and composition of matter. This approach, because it reduces the efficiency of drug development, will rarely be used, and generally only in what could be the most lucrative rare-disease indications and in the face of unwilling partners. PATENT PENDING

PATENT PENDING

PATENT PENDING

Platform technology:

Recursion has an exclusive world-wide license to our drug discovery platform from the University of Utah. As licensed from the University, this platform is difficult to defend with patents. However, Personal Info leadership of the development of the platform while at the University has enabled and will continue to enable substantial refinements and developments to the platform that are proprietary to Recursion. Continued advances to the platform in general, and specifically to software algorithms and processes developed internally to maximize our rate of discovery of rare genetic disease models and evaluate potential treatments, will give Recursion an edge against any competition. We will defend these proprietary advantages through a combination of trade secrets and patents, for which we have begun early conversations with legal experts in the area.

E. FINANCE PLAN

As mentioned previously, Recursion has been funded to a total of more than $230k through contributions of the founders and completion of a small angel round of convertible debt. In order to rapidly pursue our experimental goals and to hire several new team-members, Recursion will raise a second, larger angel round of convertible debt, targeted more broadly. We plan to raise approximately $700k from this round by mid-summer, 2014. Initial impressions from a number of angels have been favorable.

Recursion seeks to make non-dilutive government grants another important aspect of our funding model. In the immediate future, we are considering application of the following grants as time allows:

1) Exploratory clinical trials for the treatment of CCM with tempol (PAR-12-073, NINDS Exploratory Clinical Trials for Small Business). The status of this grant application will depend on our ability to execute the partnership previously described.
2) Disease-area specific drug repurposing (PAR-14-071, various institutes, Omnibus SBIR Phase I or II). We will pursue grants for the further development of drug repurposing treatments for rare-genetic diseases falling into specific therapeutic areas (neurology, metabolism, etc.). This proposed direct to Phase II grant will likely result in a number of such potential leads, which do not achieve sufficient priority to be pursued in this proposal, but could serve as the basis of additional grants.
3) Disease-specific grants via associated foundations. For each drug repurposing opportunity we identify, we will attempt to secure grants offered by private foundations related to the targeted disease that could be used to support further development.

Recursion will seek a $4M to $6M series A round from venture capital or family office sources during 2015. Traditional biotech venture capital is often weary of platform companies. We therefore believe that we will only be attractive to traditional venture capitalists when we have achieved multiple partnerships or have multiple specific drugs identified. We expect this milestone to be achieved by early 2015. We have, however, received a significant amount of investment interest from family offices. These offices sometimes do not provide as much industry-specific expertise as can be achieved through (the right) venture capital investment, however they may be willing to take larger risks because of the personal effects of rare-diseases or a desire for societal impact.

Table 1. Four-year financial plan.

($ in 000's)	2014	2015	2016	2017
Revenue	0	500	2000	5,000
Expenses	-900	-2,700	-5200	-6,000
Net Profit	-900	-2,200	-3200	-1,000
Grants (Non-dilutive)	0	900	2,000	3,000
Seed/Angel Investment	900	0	0	0
Venture Funding	0	5,000	0	0
Cashflow excl. loans	0	3,700	-1,200	2,000

F. PRODUCTION AND MARKETING PLAN

Recursion will seek to partner with contract research organizations and contract manufacturing organizations for the bulk of our development production needs. This approach will prevent the dilution of our resources towards the complex task of hiring and plant requirements associated with such tasks.

It is unlikely that Recursion will be in a position to market drugs to patients, providers and payers directly. Instead we will seek to partner with larger pharmaceutical companies to take advantage of their marketing and distribution channels. Therefore, the most important 'marketing' we will directly undertake will be the positioning of our company to potential partners. We will employ the following effective, but relatively inexpensive, steps to achieve this goal:

1) *Traditional networking*. Recursion will attend major industry events on a regular basis where we will actively network with potential partners. Recursion will continue to seek highly qualified scientific and business advisory members who can multiply and magnify the effectiveness of our networking efforts.
2) *Content marketing*. Recursion will actively publish reviews in the rare disease space, contribute to industry meetings though poster and oral presentations, and publish peer-reviewed manuscripts of those re-purposing opportunities we choose not to further pursue for economic reasons.
3) *Social Media and Online Presence*. Recursion will use its youthful and innovative approach to gain a strong following of supporters. Especially important will be outreach we make to rare-disease patient organizations. Trivial as these efforts may seem to some, they have a tremendous impact that grows every day and will improve the attractiveness of our company for partners and potential acquirers.

G. REVENUE STREAM

Recursion's revenue strategy consists of two main sources. Our initial focus lies in bringing to market, generally through development partnerships, known drugs that we discover can be repurposed as therapeutics against rare genetic diseases. In almost all envisioned situations we would receive a portion of revenues through various licensing deals, marketing deals, or through sale of an asset. As we can obtain a large number of known drugs without any specific partnerships, this approach offers a direct route to 1) rapidly impact patients in the clinic, 2) strike development partnerships that could provide some amount of early revenue, and 3) validate our approach scientifically. One concern regarding this revenue stream is the uncertainty of aligning interests and setting up intellectual property defenses with known drugs, whether they are still protected by composition-of-matter patents, or whether such patents have expired. Off-label prescribing of currently-marketed drugs makes these less attractive targets as well. However, we believe that in many cases, we will be able to strike successful partnerships, as our early negotiations regarding Tempol indicate. Further, the large number of diseases we plan to screen against supports our expectation of having a sufficient number of hits to allow for prioritization of cases where the partnership and revenue opportunity seem promising.

However, given our vision to bring to market treatments for a very large number of diseases, we see opportunity in a second revenue stream. Specifically, the validation of our science as outlined in this grant proposal will allow us to aggressively pursue partnerships with pharmaceutical companies to repurpose drug candidates shelved in phase II or phase III clinical trials. Such drugs constitute a highly compelling case, as there are fewer uncertainties related to intellectual property or off-label competition. In one form of this approach we plan to pursue, we will pre-negotiate a development revenue sharing plan with pharmaceutical companies, and at no or little upfront cost to them, screen their shelved drug candidates using our genetic disease repurposing platform. In a similar approach with a different risk-sharing structure, we may also provide a drug-screening service whereby other pharmaceutical companies could hire our team to screen larger libraries of small molecules against specific genetic disease models. Additionally, we may sell options to companies focused on specific indications, enabling them to acquire the rights to any drug we discover related

to specific disease models, or partner with such indication-focused companies in other ways to carry out screening and development. For example, a company focused on rare gastrointestinal diseases may purchase the rights to any new therapeutics we identify related to a specific set of gastrointestinal illness genes.

We believe that both of these revenue strategies will be critical for our success. It is likely that the second revenue stream will be enabled by our early successes, including grant proposals such as this one. Which of these revenue streams will ultimately become the core of our business will be dictated by where we sense the greatest opportunity lies.

CONCLUSION.

We have presented a proposal with strong preliminary data and significant potential for commercial and societal impact. We have taken the risk to start this company because of our strong belief in the potential of our approach. Our vision to build a pipeline of dozens of new rare disease treatments drives us constantly to innovate and has already attracted support from both investors and highly-sought-after advisors. The purpose of small business innovation research grants are to provide support to accelerate the commercialization of risky, but potentially impactful, technologies. Successful funding of this proposal will substantially accelerate our scientific pace and help to secure new partnerships and investments. We will work passionately and tirelessly to achieve every proposed aim and the commercial and societal impacts we have envisioned here..

PHS 398 Cover Page Supplement

OMB Number: 0925-0001

1. Project Director / Principal Investigator (PD/PI)

Prefix: Personal Info
* First Name: Personal Info
Middle Name: Personal Info
* Last Name: Personal Info
Suffix:

2. Human Subjects

Clinical Trial? ☒ No ☐ Yes

* Agency-Defined Phase III Clinical Trial? ☐ No ☐ Yes

3. Applicant Organization Contact

Person to be contacted on matters involving this application

Prefix: Personal Info
* First Name: Personal Info
Middle Name: Personal Info
* Last Name: Personal Info
Suffix:

* Phone Number: Personal Info
Fax Number: Personal Info
Email: Personal Info

* Title: Chief Executive Officer

* Street1: Personal Info
Street2:
* City: Personal Info
County/Parish:
* State: Personal Info
Province:
* Country: Personal Info
* Zip / Postal Code: Personal Info

PHS 398 Cover Page Supplement

4. Human Embryonic Stem Cells

* Does the proposed project involve human embryonic stem cells? ☒ No ☐ Yes

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: http://stemcells.nih.gov/research/registry/. Or, if a specific stem cell line cannot be referenced at this time, please check the box indicating that one from the registry will be used:

Cell Line(s): ☐ Specific stem cell line cannot be referenced at this time. One from the registry will be used.

Tracking Number:GRANT11624079 Funding Opportunity Number:PAR-14-088 Received Date:2014-04-07T17:14:41-04:00

OMB Number: 0925-0001

PHS 398 Research Plan

1. Application Type:

From SF 424 (R&R) Cover Page. The response provided on that page, regarding the type of application being submitted, is repeated for your reference, as you attach the appropriate sections of the Research Plan.

*Type of Application:

☒ New ☐ Resubmission ☐ Renewal ☐ Continuation ☐ Revision

2. Research Plan Attachments:

Please attach applicable sections of the research plan, below.

1. Introduction to Application (for RESUBMISSION or REVISION only)		Add Attachment	Delete Attachment	View Attachment
2. Specific Aims	1248-SpecificAims_Recursion_	Add Attachment	Delete Attachment	View Attachment
3. *Research Strategy	1249-ResearchStrategy_Recur	Add Attachment	Delete Attachment	View Attachment
4. Inclusion Enrollment Report		Add Attachment	Delete Attachment	View Attachment
5. Progress Report Publication List		Add Attachment	Delete Attachment	View Attachment

Human Subjects Sections

6. Protection of Human Subjects		Add Attachment	Delete Attachment	View Attachment
7. Inclusion of Women and Minorities		Add Attachment	Delete Attachment	View Attachment
8. Targeted/Planned Enrollment Table		Add Attachment	Delete Attachment	View Attachment
9. Inclusion of Children		Add Attachment	Delete Attachment	View Attachment

Other Research Plan Sections

10. Vertebrate Animals	1250-VertebrateAnimals_Recu	Add Attachment	Delete Attachment	View Attachment
11. Select Agent Research		Add Attachment	Delete Attachment	View Attachment
12. Multiple PD/PI Leadership Plan		Add Attachment	Delete Attachment	View Attachment
13. Consortium/Contractual Arrangements	1251-ConsortiumArrangements_	Add Attachment	Delete Attachment	View Attachment
14. Letters of Support	1252-LOS_Recursion_Final.pdf	Add Attachment	Delete Attachment	View Attachment
15. Resource Sharing Plan(s)	1253-ResourceSharingPlan_Re	Add Attachment	Delete Attachment	View Attachment

16. Appendix Add Attachments | Remove Attachments | View Attachments

List of Research Plan Attachments

SPECIFIC AIMS: Expansion of an efficient drug repurposing platform for rare genetic diseases.

More than 6,600 of the more than 7,000 orphan diseases have no approved treatment; at the current rate, it will take at least 500 years to develop treatments for all of them. Therefore, new approaches are needed to expedite the drug development process for these diseases, which are limited in prevalence (< 200,000 of the US population) or commercial opportunity. One potential strategy to accelerate discovery of orphan disease therapeutics is drug repositioning/repurposing. However, this strategy has thus far not been applied to rare diseases in a comprehensive manner. **Thus, there is an urgent need for an efficient drug-repurposing platform that can be systematically and efficiently applied to many rare diseases.**

Our company, Recursion Pharmaceuticals, has developed a drug discovery platform for rapidly and efficiently bringing drugs to market for rare genetic diseases. Our platform assesses the potential of drugs of known safety to treat monogenic diseases using human cellular models via the following approach:

1. Induce loss-of-function of specific genes associated with human disease in primary human cells.
2. Use multiparametric immunofluorescence imaging and transcellular resistance assays to probe the presence of structural or functional phenotypes.
3. For phenotypes that can be reliably induced and quantified, perform chemical suppressor screens using libraries of known drugs.

The feasibility of this approach has already been demonstrated in SBIR Phase-I type research (funded through non-SBIR sources), for a selected model monogenic rare disease, the hereditary stroke syndrome cerebral cavernous malformation (CCM). By screening a library of known drugs, we succeeded in identifying two compounds that suppressed phenotypes induced by small interfering RNA (siRNA) targeted against a CCM gene, *CCM2,* as well as demonstrated efficacy in a murine model of CCM disease. We are currently in negotiations to co-develop one of these compounds for the treatment of CCM (which currently has no approved therapy), in collaboration with a pharmaceutical company that has generated extensive pre-clinical and clinical data for this compound for a distinct indication.

Based on this success, this Direct-to-Phase II grant seeks to expand our drug-screening platform to evaluate at least 2,000 additional monogenic loss-of-function diseases as follows:

Aim 1: Identify phenotypes resulting from knock-down of 2,000 genes for which loss-of-function mutations are known to cause human disease. We will identify the subset of candidate genes that yield (A) ***structural*** (morphological) phenotypes and (B) ***functional*** (activity) phenotypes upon knock-down in primary human endothelial cells and primary human epithelial cells using immunofluorescence imaging and transcellular resistance.

Criteria for success: identification of at least 200 genes associated with human diseases, for which knockdown induces a gene-specific structural phenotype in at least one cell type.

Aim 2: Identify known drugs that ameliorate structural and functional phenotypes associated with knockdown of disease-associated genes. We will accomplish this by: (A) screening at least 2,727 known drugs against the 200 phenotypes identified in Aim 1; (B) evaluating and prioritizing all hits for scientific and commercial potential; and (C) validating the top 20 drug/disease combinations by generating stable knockout cell lines using the gene editing technology, CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats).

Criteria for success: identification of known drugs that ameliorate structural and/or functional, phenotypes for at least 10 CRISPR-validated *in vitro* disease models.

Aim 3: Demonstrate efficacy of identified drugs in relevant animal models of disease. We will acquire and validate relevant murine models of disease, then evaluate each drug's efficacy in its respective model.

Criteria for success: identification of known drugs that rescue at least two clinically relevant animal models of disease.

Our **overall criteria for success** for this SBIR Phase II grant is to identify at least two viable drugs, each of which can be repurposed to treat a unique orphan disease. The results of the studies proposed here will be combined with public data (or in some cases proprietary data acquired through partnership with relevant pharmaceutical companies) to pursue FDA orphan designations and 505(b)(2) IND applications for direct to FDA Phase II clinical trial studies in humans for each of the drug disease/combinations. Method of use patents, protections afforded by orphan designation, and decreased time and cost to commercialization, will serve to attract partners and investors to fund human clinical trials and SBIR phase III commercialization.

RESEARCH STRATEGY

A. SIGNIFICANCE

This application is in response to PAR-14-088: Direct Phase II SBIR Grants to Support Biomedical Technology Development and is directed at the National Center for Advancing Translational Sciences (NCATS). **The primary interest of NCATS for SBIR proposals, (PHS 2014-2), is: "the development [of] innovative tools, technologies, and intervention[s] (drug, device, [and] diagnostic) platforms that would support the creation of novel therapeutics and/or diagnostics, especially for rare and neglected diseases."**

Here we propose a drug discovery platform and drug development strategy to efficiently repurpose known drugs for the treatment of rare genetic diseases. We provide Phase I-type research data demonstrating a proof-of-principle screen of approximately 2,100 compounds for a selected rare monogenic disease that has yielded two new therapeutic candidates. This grant will support the exploration and expansion of our screening platform with a stated goal of directly probing more than 2,000 rare disease models and advancing at least two drugs directly to FDA Phase 2 clinical trials for the treatment of untreated rare genetic diseases.

There are at least 7,000 diseases meeting U.S. criteria for orphan disease status (fewer than 200,000 Americans with the disease or a market likely to be insufficient for recovering costs associated with commercializing a drug)[1,2]. Collectively, these diseases affect as many as 25 million Americans and have a high cost on our healthcare system and on society[1,2]. The vast majority of these diseases have a genetic basis, strike relatively early in life, are currently without directed therapy, and are relatively severe[3,4]. The high cost of drug development combined with relatively small markets reduces commercial interest in these diseases. The Orphan Drug Act of 1983 and its subsequent amendments created regulatory and economic incentives for drug development in the rare disease space, and there have been major successes both for pharmaceutical companies and for rare-disease patients[5,6]. However, despite several hundred successes since 1983, the pace of discovery is still too slow and more than 95% of rare diseases still have no approved treatment[1].

The traditional drug discovery strategy, which typically takes 10-12 years, consists of target identification and selection, assay development, lead discovery, medicinal chemistry, in vitro studies, in vivo studies, phase-I clinical trials, phase-II clinical trials, phase-III clinical trials, and finally post-marketing surveillance[7]. This pathway has led to the identification of many life-altering and commercially successful therapeutics. However, the cost of this strategy, in both time and money, has become a burden for even the largest indications[8-10]. **Therefore, the development of drug discovery and development strategies that maximize efficiency may have a profound impact in the rare disease space where commercial viability is increasingly being recognized.**

We strongly believe in the power of two drug discovery and development strategies to attain efficiency that will enable rapid and profitable marketing of drugs for rare diseases.

1) ***Discovery Parallelization.*** The various steps of the traditional drug development strategy are highly disease or indication-specific. These target-centric approaches require customized assays for each disease. However, a major subset of rare diseases occur as a result of a mutation in a specific gene which leads to loss-of-function. Therefore, there exists a set of several thousand diseases that have a common high-level mechanism which enables parallelization of drug discovery.
2) ***Drug Repurposing.*** Knowledge of a drug's bioavailability, safety, pharmacology, manufacturing and formulation can significantly facilitate entering the clinic more quickly and at a much-reduced cost. Drug repurposing, whereby existing drugs are used for additional or alternative indications from those for which they were originally designed or intended, takes advantage of all that is known about a drug to increase efficiency[11-14]. Indeed, reinforcing the attractiveness of this approach, repositioned drugs accounted for 30% of first to market drugs in 2009[15].

As detailed in our commercialization plan, our strategy is to move drugs identified in the proposed application directly into FDA phase 2 clinical trials using publically available information, or in partnership with companies owning IND-enabling data. We will secure interest from partner companies through licensing or co-development agreements. Our commercial success will be determined by the ability to secure a portion of the profits for a large number of repurposed rare disease drugs, while minimizing the costs associated with achieving marketability.

Interest from potential partners is projected to be high due to the increasing market opportunities for rare disease drugs:

1) There is a recent trend of large pharmaceutical companies (e.g., Sanofi, Novartis, Shire), particularly those with blockbuster drugs falling off the patent cliff, repositioning away from the large disease market toward the rare disease market[14,16,17].

2) Orphan drugs have enormous revenue potential as a result of their high prices, decreased competition, and relatively strong intellectual property protections[18].
3) The worldwide orphan drug market is projected to reach $127 billion by 2018, accounting for nearly 16% of total prescription drug sales[19].
4) Fifteen of 43 (35%) new drugs approved by the FDA in 2012 were orphan drugs[19].

Indeed, we are already in negotiations with a pharmaceutical company that has generated IND and FDA phase I clinical trial data for a drug, tempol, that we have identified using our drug discovery platform as a potential treatment for a rare disease indication (see preliminary data). This company is developing tempol for another much larger indication, but is exploring with us the possibility of taking tempol to market for the orphan indication we have identified. These negotiations are ongoing, are focused on either a licensing or co-development deal, and they support our position that companies will be receptive to partnering with us to repurpose drugs for which they have some intellectual property. Under a non-disclosure agreement, we have been given copies of all pre-clinical and clinical data generated by this company.

Finally, we are encouraged by the reception to our company among investors. Though we have not yet sought a major financing round, we have received early indications of interest from venture capitalists, family offices, and professional angel investors. One of our early angel investors in a recently closed $100,000 'friends and family' round, Private Source Private Source is a venture capitalist with experience in the biotech space, and speaks to our attractiveness in an attached letter of support. We also pitched our company at the 2014 Texas Life Science Forum at Rice University in February, and received the 'best pitch' award from among 55 companies, the majority of which were in series B or later fundraising stages.

Funding of this direct to Phase II SBIR grant will have several important impacts on our company:
1) SBIR funds will provide us with critical capital required to carry out the proposed experiments at a rate exceeding what we will be able to achieve using traditional capital sources.
2) This phase II SBIR will add two indications to our development pipeline at the level of initiating late phase I or early phase II clinical trials within two years.
3) Though we will focus on the highest priority hits in this phase II SBIR grant, we will gain a very large number of leads for us to pursue in subsequent development, through both subsequent SBIR and other funding mechanisms.
4) This SBIR will help us to lay a foundation for our drug discovery platform for subsequent expansion into other disease categories, including, but not limited to: gain-of-function genetic diseases, oncology, and infectious disease, including neglected diseases.
5) Due to the typically high capital costs associated with success in the biotech industry, early investors are often 'diluted' out of meaningful returns. In addition to traditional sources of capital, we plan to make SBIR and other 'non-dilutive' sources an important component of our research funding. SBIR funds will provide investors with confidence in our resourcefulness and intent to achieve success in the most efficient way possible, increasing our ability to secure such investments.

Our success in achieving the aims stated in this proposal will have major impacts:

Commercial: This grant will directly enable commercialization of at least two new treatments for rare genetic diseases. We will immediately seek partnerships with relevant stakeholders for each drug and acquire additional data to support an orphan drug designation and an IND to move directly to phase II clinical trials. It is possible that we could realize commercial benefits from up-front payments of a licensing deal almost immediately after we complete these aims. Further, this grant will allow us to develop dozens of other potential therapeutics that we can subsequently validate and commercialize (using both additional SBIR and other funding sources).

Societal: This grant and our success in achieving the stated aims will mean new treatments for patients with orphan diseases will be much closer to the clinic. Further, this grant will help us to demonstrate the advantages of our drug screening platform, which will enable us to achieve our vision of treating many orphan diseases at an accelerated pace.

Educational: We remain dedicated to advancing the understanding and treatment of rare diseases, even in those cases where commercialization is impractical. When our findings could lead to improvements in disease understanding or treatment, but do not make a convincing case from a business perspective, we will seek to publish those data in the hope that academics or other companies could find a way to progress the work to the clinic.

B. INNOVATION

Approach: Despite the potential of discovery parallelization and drug repurposing, there has been no sustained or systematic attempt to our knowledge to screen thousands of known drugs for efficacy in thousands of disease models using complementary *in vitro* and *in silico* approaches. The majority of attempts at repurposing have been either *in silico* alone, or based on a small number of disease indications using *in vitro* or *in vivo* approaches[20].

Our approach is innovative because we can study thousands of diseases simultaneously without requiring special understanding of each disease's pathophysiology. We measure hundreds or thousands of structural (morphological) and functional (activity) changes induced in human cells by modeling loss of function of a gene, and use these changes as a phenotypic fingerprint ("phenoprint") upon which to assess the suitability of thousands of known drugs as treatments. This target-agnostic approach to drug discovery has several compelling advantages:

1) While molecular signaling pathways are increasingly understood, biology is still amazingly complex. Pursuing a drug target based on a known signaling pathway assumes that the vast majority of the 'molecular equation' is known, or that any aspects that are not understood are unimportant. However, feedback loops and compensatory mechanisms are often present, frequently poorly understood, and commonly important. Dogma in the research field also drives 'understanding' of pathways that are inaccurate or highly incomplete. Thus, target-based approaches often fail due to unanticipated cellular effects after significant resources have been expended.
2) Despite the limitations of target-driven methods, they have been highly successful in many cases, especially for those diseases in which the pathogenesis is well-understood. Rare diseases, however, are often poorly understood. They are often studied by only a few faithful labs who have generated important data, but this data is often, and expectedly, highly incomplete. Thus, target-based approaches in rare disease drug discovery have the potential to be even more difficult and risky.
3) Disease or target-specific drug discovery requires a major investment of resources at the earliest stages of the project, when the risk of failure is the greatest. Our approach allows us to study thousands of diseases, avoiding major resource utilization until a point at which we have identified a treatment for any one of those diseases.

Technology: At a high level, the key innovation of our technology platform is our **combination of big-data-driven analysis and experimental biology** in seeking treatments for rare genetic diseases, while our competitors are focused on one or the other of these methods. This combination allows us to rapidly and efficiently discover new uses for known drugs, and our platform could be rapidly transitioned to discover novel drugs. The advanced technologies we have integrated into a single platform include:

1) Genetic manipulation using highly-controlled RNA interference (RNAi) and CRISPRs enables us to rapidly and systematically model any monogenic loss of function disease in a highly cost-effective manner.
2) High-content analysis of cell morphology using high-throughput automated immunofluorescence imaging enables us to capture high-resolution images of large cell populations (1,000's of cells per well) in a rapid manner.
3) High-content analysis of cell functionality using high-throughput transcellular resistance measures enables us to acquire diverse parameters of each disease model in real-time in a label-free environment.
4) Multi-parametric quantification of cell structure and function using CellProfiler enables us to measure hundreds of diverse parameters at one time, thus identifying unexpected and critical cellular changes that can serve as a basis for a chemical suppressor screen.

Products: The proposed research will result in novel treatment candidates for two rare diseases ready to advance quickly through late-stage clinical trials. As less than 5% of rare diseases have an approved treatment, the identified drugs will very likely represent a first and only treatment for that disease. Importantly, since the identified drugs are being repositioned, their development can advance more rapidly with SBIR Phase III development costs at only a fraction of those typical for non-orphan[19].

We understand and expect that our broad approach to drug-discovery may be less sensitive on a 'per-disease' basis when compared to traditional approaches. However, focusing on cellular models and avoiding overreliance on the limited understanding of molecular mechanisms increases our likelihood of multiple successes overall. Because we will perform our assays in such a highly parallel fashion, our platform and development strategy is much more efficient than traditional drug discovery approaches.

Our target-agnostic approach is not the only innovation of our approach. We combine a variety of important advantages and strategies, detailed below, into a single comprehensive drug discovery and development process:

- *Rare disease focus*: FDA approvals of treatments for rare diseases are expedited and often require dramatically smaller and less expensive clinical trials[21].
- *Drug repositioning focus:* By screening drugs that are known to be safe in humans but are not widely available in the U.S., we can bring drugs to market more quickly at a drastically lower cost. Examples include drugs approved in

Europe or Asia, drugs that failed phase II/III trials for efficacy reasons despite strong safety profiles, and drugs that have come off patent or are no longer marketed.

- *Horizontal strategy:* Our platform has the potential to identify candidate therapies for dozens of new indications each year, spreading risk across multiple leads and leading to multiple independent revenue streams.
- *Partner-centric:* We partner our candidate therapeutic compounds and indications early, reducing development, regulatory, marketing, and distribution costs while simultaneously diluting risk to the business based on the success or failure of a single indication.

Intellectual property: Recursion has an exclusive world-wide license to our drug discovery platform from the University of Utah. Though our drug discovery platform in its first iteration is less protectable than we would desire, as its designers we have a head-start, there is substantial technical expertise required for its implementation and improvement, and we have plans to protect our further developments and discoveries in a variety of ways:

1) **Method of use patents** PATENT PENDING
PATENT PENDING
PATENT PENDING
2) We will pursue **orphan indication** status whenever available, which will provide seven years of market exclusivity regardless of other IP status. Further, achieving an orphan indication means that competitors must prove superior efficacy before marketing a drug for the same indication, providing additional defensibility.
3) We are rapidly developing **proprietary algorithms** to enhance our already powerful drug discovery platform. Our pilot work relied heavily on the open-source CellProfiler software for image analysis, but we will refine and validate distinct data mining software tools that will enhance the defensibility of our drug discovery platform.
4) Should we be unable to partner with a company that currently markets a drug of interest to us, we will consider pursuing generation of **novel formulations and composition of matter**. This approach, because it reduces the efficiency of drug development, will be considered only in what could be the most lucrative or impactful rare-disease indications and in the face of highly unwilling partners.

C. APPROACH

Unpublished

Summary of prior SBIR Phase-I type pilot studies:

Proof of concept Phase I-type research was performed by the PI, Personal Info in the lab of Personal Info at the University of Utah.

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Background: CCM is a hereditary hemorrhagic stroke syndrome characterized by vascular malformations in the central nervous system. CCM lesions are leaky and unstable, with chronic and acute bleeding leading to inflammation and stroke respectively[22]. The only treatment for CCM is neurosurgical resection[23]. CCM occurs in two forms: sporadic and familial, which together affect as many as 1 in 200 to 500 individuals in the United States[24,25]. The familial form of CCM accounts for 20% of cases, and is associated with loss-of-function mutations in one of three genes, *KRIT1*, *CCM2*, or *PDCD10*[26]. After the failure of a target-centric hypothesis-based approach to drug

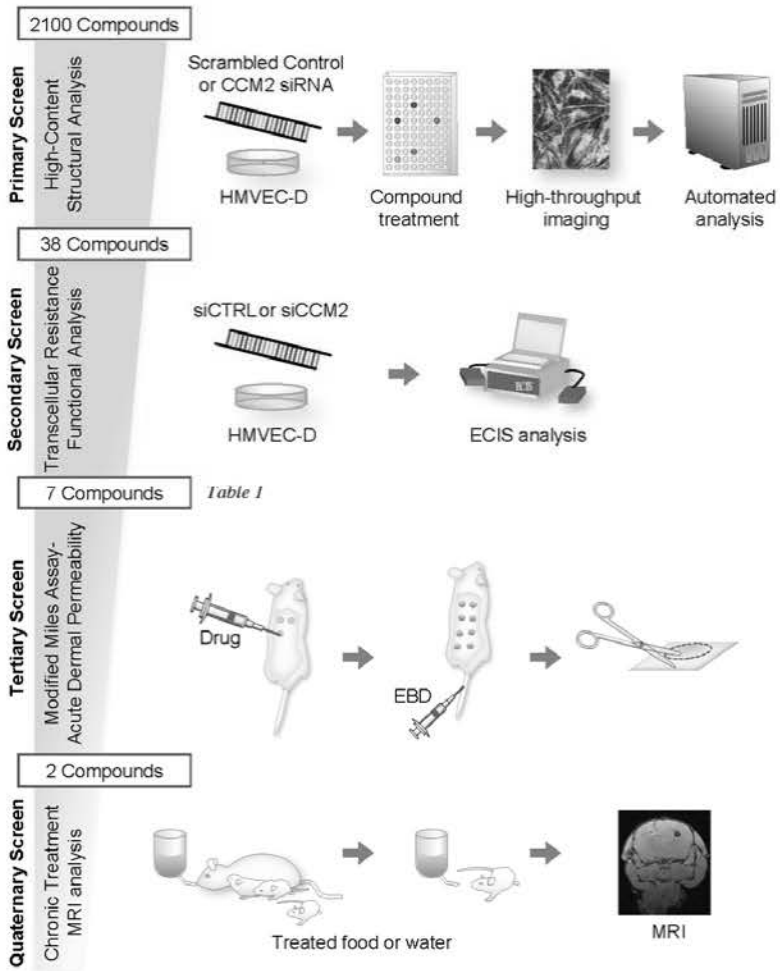


Figure 1: Overview of reported pilot drug repurposing screen.

re-purposing for CCM in Personal Info the P.I of this application, Personal Info developed an alternative approach – an unbiased target-agnostic drug discovery platform.

Phase-I type pilot - Aim 1: Quantify the structural and functional phenotypes associated with decreased CCM2 in human endothelial cells.

Criteria for Success – Development of an automated system capable of identifying CCM2 knockdown endothelial cells.

Result: Endothelial cells deficient in CCM2 have obvious structural and functional phenotypes[27] and we hypothesized that these phenotypes could be used for unbiased drug discovery. Our strategy was to develop a multi-stage screen taking advantage of *in vitro* structural phenotypes (primary screen), *in vitro* functional phenotypes (secondary screen), *acute in vivo* functional phenotypes (tertiary screen), and chronic *in vivo* disease phenotypes (quaternary screen) (Fig. 1). Fluorescent microscopy and automated cellular quantification and profiling was selected as the primary screen, transendothelial resistance (electric substrate impedance sensing - ECIS) as the secondary screen, measurement of the leakiness of dermal vasculature in a CCM mouse model as the tertiary screen, and measurement of lesion burden using small animal magnetic resonance imaging (MRI) as the quaternary and final screen. Another important aspect of our strategy was to use a library of 2,100 small molecules (Microsource Spectrum and other assorted compounds) composed of known drugs and bioactive compounds based upon our hypothesis that hits from this library could more quickly be translated to the bedside.

Primary Morphological Screen. We sought to develop a high-content imaging primary screen wherein (i) the fluorescent markers support computational recognition of cellular nuclei and cell borders, (ii) images are captured at a resolution sufficient to allow quantification of structural phenotypes, (iii) the assay is amenable to a 96 or 384-well plate format, and (iv) data are highly reproducible. To satisfy these demands, Human Dermal Microvascular Endothelial Cells (HMVEC-D) were treated with well-validated CCM2 mRNA-targeting siRNA or a scrambled control, and then seeded into 96-well imaging plates (Fig. 2A)[28-30]. Large immunofluorescence images composed of 16 adjacent fields of view stitched together automatically were captured from each well of a 96-well plate in three channels sufficient to reveal cell structure including the nucleus, actin stress fibers, and VE-cadherin cell-cell junctions (Fig. 2B). A high-throughput microscope developed for phenotypic drug discovery allowed automated imaging of an entire 96-well plate in about 60 minutes.

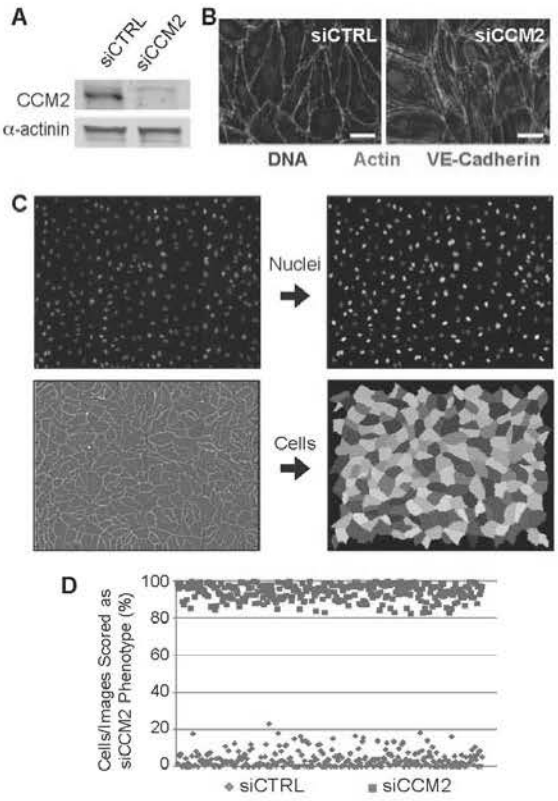


Figure 2: Primary screen - rescue of structural phenotypes associated with loss of CCM2. (**A**) Western blot analysis of siCCM2 knockdown. (**B**) Immunofluorescence images of endothelial cells treated with siCTRL or siCCM2 stained for DNA (blue), actin (green), and VE-cadherin (red). (**C**) DNA (top) and VE-cadherin (bottom) raw images segmented into nuclei and cell objects, respectively. (**D**) Result of scoring positive and negative control images using rules generated by machine-learning algorithms in CellProfiler Analyst software. Scale bars = 50 μm.

We used CellProfiler, an open-source high-content imaging analysis tool from the Broad Institute, to import images, identify the borders of each cell, and create a database of a multitude of mathematical descriptors of every cell in every image collected (Fig. 2C)[31]. We then used CellProfiler Analyst, a machine-learning tool, to develop rules that could be used to distinguish whether each cell in an image was more likely to have been treated with scrambled control siRNA or siCCM2[32,33]. **The software was able to accurately categorize images (based on the proportion of individual cells in each image scored as siCTRL or siCCM2), as 'siCTRL-treated' or 'siCCM2-treated' resulting in an assay quality score of Z'=0.7, which indicates an assay is highly amenable to high-throughput screening** (Fig. 2D)[34].

We developed a secondary orthogonal screen using trans-cellular resistance, a tool that has the capability of measuring generic changes in function (Fig. 3A)[28]. This assay employs real-time measurements of the resistance encountered when an electrical current is passed between electrodes upon which a monolayer of cells are growing[35]. We were able to reliably separate siCTRL and siCCM2 treated cells using a single aspect of this assay, the resistance achieved at a frequency of 4000 Hz in a confluent monolayer of cells. Thus we succeeded in developing an automated system capable of identifying siCCM2-treated cells, an approach we propose to perform in highly parallel fashion in Aim 1 of the

proposed grant.

The rationale for expanding this single gene approach to thousands of genes is the hypothesis that modelling many loss-of-function monogenic diseases will yield a significant number of phenotypes, which we can use as the basis for drug suppressor screening. Clearly, any particular gene knock-down may only yield a phenotype under certain experimental conditions, such as in a specific cell type, time-point, and using a particular phenotypic readout. In particular, any given gene may not be expressed in the two cell lines proposed for screening in this proposal. However, our approach does not require that all genes yield a screenable phenotype; we will focus on the subset that do. Here we describe preliminary data estimating this proportion.

We analyzed the results from a whole-genome screen of morphological phenotypes in a single cell line (HeLa cells), whose original authors identified more than 8.6% of gene knockdowns as having a significant morphological change falling into one of a certain number of defined classes, identified using automated analysis (referred to as CellMorph from this point forward)[36]. It is worth noting that the majority of these phenotypes were repeated using a second unique set of siRNA, suggesting on-target phenotypes. This percentage would suffice to achieve our proposed aims.

However, we recognized the possibility that this proportion may be higher than for human disease-related genes, because the phenotypes they scored may be disproportionately associated with essential genes in which mutations are incompatible with life. We examined this potential issue by cross-referencing the genes found to be associated with morphological changes and a list of genes associated with human disease. We found that genes known to be associated with human disease were only slightly less likely to result in morphological changes (Table 1). **From an examination set of 2,000 genetic disease genes, this translates to a conservative yield well in excess of 100 screenable disease models in a single cell-type.**

Table 1: Data supporting frequency of structural phenotypes using automated imaging.

Test Set	Total Genes	# Positive Phenoprints	% Positive Phenoprints
Whole Genome (as tested in CellMorph[36])	**21,061**	**1820**	**8.64%**
Genes associated with human disease[37]	**3,126**	**189**	**6.05%**
Excluding susceptibility-genes	**2,426**	**144**	**5.94%**
Also excluding prevalence less than 1/1,000,000	**1,412**	**88**	**6.23%**
Also excluding neonatal/infant onset	**953**	**56**	**5.88%**

***Phase-I type pilot — Aim 2*:** Identify potential treatments for CCM using a chemical suppressor screen of known drugs based on the phenotypes defined in Aim 1.

Criteria for success — Identification of at least one and fewer than 10 known drugs that ameliorate structural and functional phenotypes associated with loss of CCM2.

Result: We used the primary morphological assay as the basis of a chemical suppressor screen of 2,727 known drugs to identify those that could rescue the structural phenotype associated with loss of CCM2. We analyzed the resulting images to identify rescue using CellProfiler and CellProfiler Analyst. We selected the 38 compounds demonstrating the best rescue, and tested their ability to restore the functional defect identified using transcellular resistance, as a secondary screen. Of the 38 compounds identified using our automated machine-learning analysis, seven showed full or partial rescue of the functional phenotype (Fig. 3B). These seven include compounds from classes previously connected to CCM disease, as well as compounds without any previously described association with the disease[38-41].

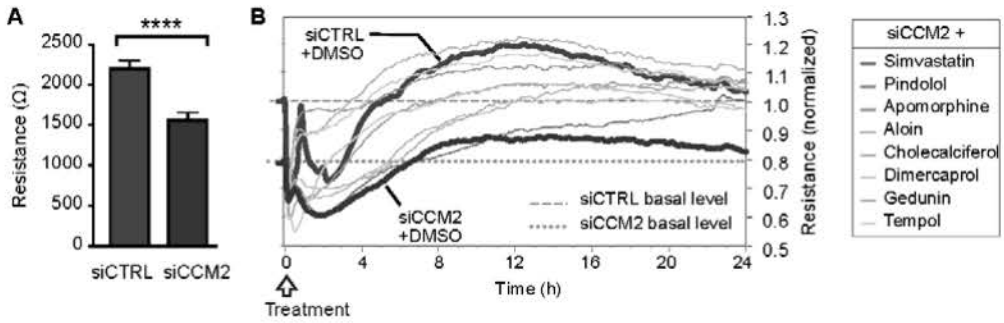


Figure 3: Secondary screen - rescue of functional phenotypes associated with loss of CCM2. (A) Baseline transendothelial resistance of unperturbed siCTRL and siCCM2 monolayers. **(B)** When added to siCCM2-treated cell monolayers, seven compounds significantly improve resistance measures after 24-hours of treatment. Graphs depict mean ± SEM.

Note: *In the pilot study, we passed compounds through the primary and secondary screens in a serial fashion due*

to a limitation in the throughput of the transcellular resistance equipment then available. In the proposed grant, all genes will be evaluated using both assays in parallel.

The rationale for expanding this single disease model approach to hundreds of disease models is the hypothesis that a significant proportion of diseases for which a phenotype can be quantified will have an effective treatment from within the realm of known drugs. This hypothesis can only be validated by the type of large-scale work we are proposing to do here. However, the large number of one-off drug repurposing reports in the literature, combined with our preliminary data in which we discovered two effective therapeutics from investigation of just 2,727 known drugs, suggests this is a rational hypothesis[42-45]. In some cases, 'off-target' mechanisms will result in efficacy for a rare disease. Many drugs are shown to have many biochemical actions beyond their intended targets, and these are sometimes the underlying cause of unexpected side-effects[46]. Statins, for example, have been reported to have many specific targets[47-59]. In other cases, the drug's intended target may play a critical, but as yet undescribed, role in a rare disease[60].

Phase-I type pilot – Aim 3: Evaluate the effect of the highest priority treatment(s) in a murine model of CCM disease.

Criteria for Success – Identification of at least one known drug that significantly reduces the number or size of lesions, as measured by magnetic resonance imaging (MRI), in a Ccm2 mouse model.

Result: Due to the time and cost associated with chronic treatment trials in our CCM mouse model, we next took advantage of a microvascular leak phenotype in our inducible endothelial-specific Ccm2 knockout mice ($Ccm2^{f/-}$; +/Tg(Pdgfb-iCreER^{T2}), hereafter referred to as Ccm2 ecKO, as a tertiary screen to prioritize hits for chronic treatment models. When we injected small intradermal wheals of a subset of our hit compounds into these mice, we found that both tempol and cholecalciferol significantly reduced peri-injection microvascular leakiness (data not shown). We do not exclude the possibility that the other compounds could be relevant therapeutic candidates for the treatment of CCM disease, but this assay allowed us to immediately prioritize tempol and cholecalciferol for further study. Next, we performed chronic treatment studies of the effects of tempol and cholecalciferol in our Ccm2 ecKO mice[27]. Nursing mothers were treated with either standard chow (1.5 IU/g cholecalciferol), an identical chow enhanced with cholecalciferol (25 IU/g), or standard chow plus tempol dissolved in drinking water (1mM) starting 5 days after delivery of their pups. After weaning, mice were fed the same diet as their mother until 5 months of age, a point at which 100% of untreated endothelial specific Ccm2 knockout mice have cerebrovascular lesions detectable by MRI (Fig. 4A). At this time, mice were evaluated for lesion status by MRI. Two reviewers with experience reading murine or human MRI were provided MRI files from all mice in the study, but were blinded to treatment. The reviewers manually outlined each lesion in every MRI, and their results were tabulated. Mice receiving the diet enriched with cholecalciferol or tempol had approximately half as many lesions compared to those receiving standard chow (Fig.

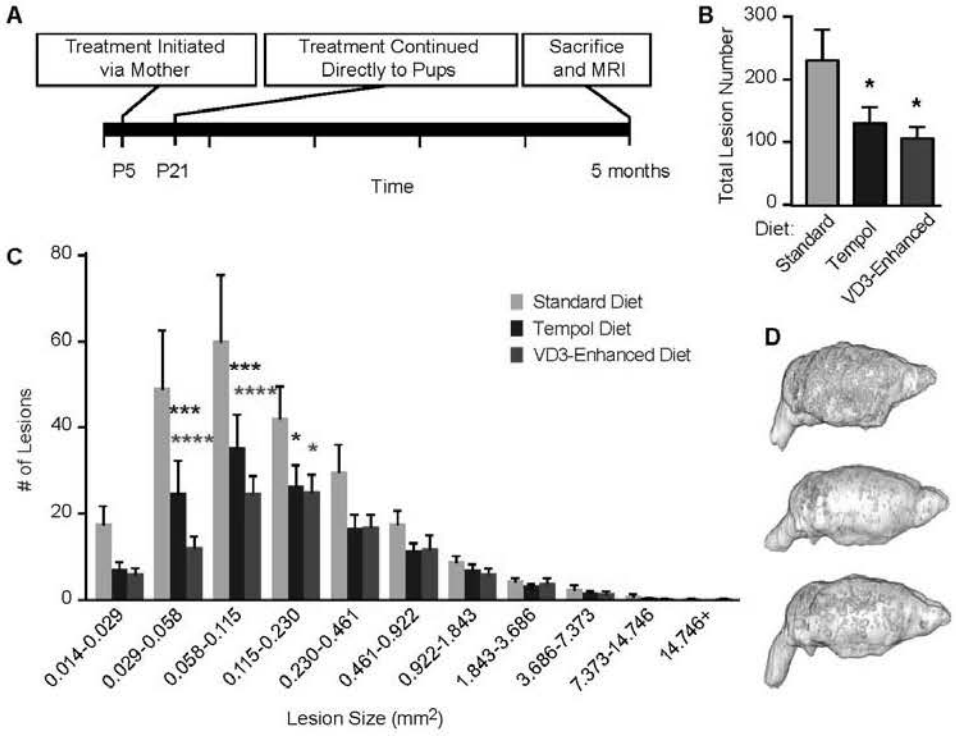
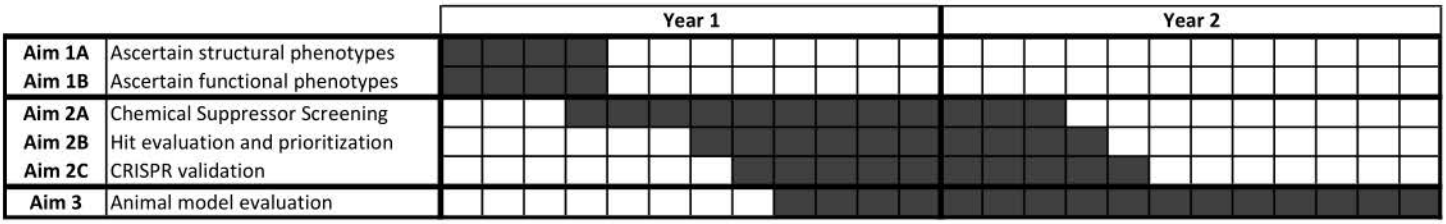


Figure 4 Quaternary screen – rescue of lesion burden in a murine model of CCM. (**A**) Timeline of treatment and analysis of cholecalciferol or tempol in Ccm2 ecKO mice. (**B**) Normalized number of CCM lesions as measured by MRI in ecKO mice. (**C**) The number of lesions of various sizes as measured by MRI in ecKO mice. (**D**) Three-dimensional reconstruction of the brain (grey) and lesions (red) from control (top), vitamin D3-treated (middle), and tempol-treated (bottom), are shown for a representative brain from each treatment arm (the mouse with the median number of lesions for each treatment group is shown). Experiment represents at least N=8 mice per group. All graphs depict mean ± SEM. * = P<0.05, ** = P<0.01, *** = P<0.001, and **** = P<0.0001.

4B). When lesion numbers were compared based on cross sectional area as quantified on MRI, both treatments decreased the numbers of both large and small lesions, though the differences among the largest lesions were not statistically significant (Fig. 4C). The effect of cholecalciferol and tempol supplementation was qualitatively obvious when comparing MRI-based three dimensional reconstructions of mouse brains (to avoid bias, the brain with the median number of lesions from each treatment group is shown) (Fig. 4D).

Conclusions. These preliminary data show that we successfully accomplished our stated Phase-I type pilot aims, as we successfully identified two new therapeutics to be investigated for the treatment of CCM. Our success was based on an unbiased screen centered on structural and functional phenotypes, as well as the generation and characterization of animal models that faithfully recapitulate the genotype and phenotype of the human disease[27,28]. We also presented data that strongly supports our hypothesis that our approach is scalable to thousands of diseases. These studies highlight the possibility that there may be a substantial number of phenotypes associated with human disease-related genes that are amenable to chemical suppressor screening in a systematic and automated manner.

PROPOSED RESEARCH APPROACH:



Proposed timeline for execution of aims. Aims 1A and 1B will begin immediately after funding and can reasonably be completed in 4 months. Aim 2A will be initiated as soon as relevant hits have been identified and will last well into year 2. Prioritization and evaluation of hits (Aim 2B) will take place on an ongoing basis starting 6 months into year 1 and continuing for just less than a year. CRISPR validation of hits (Aim 2C) will start within 9 months and will proceed for nearly 1 year. Aim 3 will start immediately upon identification of a high-priority validated drug and disease indication (~8 months into year 1) and will take up to 16 months due to the time required for breeding and/or treatment.

The specific list of deliverables for this proposal includes:

1. Multi-parametric quantification of phenotypes generated by the 2,000 highest priority gene knockdowns using siRNA-treated primary human endothelial cell and epithelial cell models.
   a. Immunofluorescence-based imaging with machine-learning algorithms for structural phenotype identification (Aim 1a).
   b. Transcellular resistance evaluation of endothelial and epithelial monolayer formation, proliferation, cell-cell interaction, and cell-substrate adhesion (Aim 1b).
2. Chemical suppressor screens of at least 2,727 known drugs against each of the 200 disease models identified in the previous step (Aim 2a).
3. Generation and evaluation of stable knockout cell lines using the CRISPR-CAS gene editing system for the 20 highest-priority disease models for which a drug of interest is identified (Aim 2b/c).
4. Evaluation of between five and ten validated hits in relevant animal models (Aim 3).

These deliverables will support a subsequent application of orphan indication for successful disease/drug combinations, followed by IND and direct to FDA phase II clinical trials (SBIR Phase III).

Aim 1: Identify phenotypes resulting from knock-down of 2,000 genes for which loss-of-function mutations are known to cause human disease. We will identify the subset of candidate genes that yield (A) ***structural*** phenotypes and (B) ***functional*** phenotypes upon knock-down in primary human endothelial cells and primary human epithelial cells using immunofluorescence imaging. Our **criteria for success** will be identification of at least 200 genes associated with human diseases, for which knockdown induces a gene-specific structural phenotype in at least one cell type.

Subaim 1A: Screen two primary cell types for structural phenotypic changes associated with knock-down of disease-related genes.

Rationale: Our preliminary data demonstrates our ability to perform siRNA and to quantify structural phenotypic changes using advanced image processing software in an automated fashion. This automation, together with additional refinements in progress, will allow us to rapidly screen for multiple structural phenotypes from more than 2000 candidate genes in parallel.

Experimental Plan: We will knockdown 2,000+ candidate genes using 3+ independent siRNA each, in two primary cell types (HUVEC and SAEC), measuring the effects on structural phenotypes by automated imaging and

analysis, using approaches we have validated (see preliminary data section).

Selection of candidate genes: There are countless online databases cataloging all manner of biological data. However, we are unaware of a database that provides comprehensive and accessible information on monogenic loss of function diseases. We have generated a proprietary comprehensive monogenic disease database that will allow us to perform siRNA studies on the maximal number of known diseases and quickly and strategically identify high-value targets in subsequent aims. Our database, generated by downloading, mining, and integrating data from many complementary public datasets, can be filtered and sorted based on an algorithm taking into account general and geographic disease prevalence, confidence of loss-of-function mechanism, availability of murine models, treatment availability, related clinical trials, geographic prevalence, and associated morbidity and mortality, among other factors. We are confident that the 2,000 highest-priority monogenic disease genes from our database will be effective for this proposal, and will continue to improve the database and algorithms as this project progresses.

Selection of cell types: All in vitro experiments will be performed using two types of primary human cells, obtained from a reputable source (Lonza Biosciences). We have significant experience handling a variety of primary human cell types, including optimization of knock-down protocols. For the proposed experiments we will use human umbilical vein endothelial cells (HUVEC) and human small airway epithelial cells (SAEC). These cells were chosen for a variety of reasons:

1) Both HUVEC and SAEC are contact-inhibited cells, meaning that under relatively broad conditions they will form a monolayer without overgrowing each other. This is a major advantage for imaging and transcellular resistance assays, as it allows for measurement of the maximum number of cells without deconvolution of the signal resulting from cell-cell overgrowth.
2) These cell types can be provided in pooled form, or can be cultured to achieve a pooled status. We have concerns about using cells from a single patient because of the possibility for patient-specific cellular phenotypes or drug rescue. By purchasing pooled cells (HUVEC), or purchasing at least five sets of cells from unique donors (SAEC), we can reduce the chance of identifying phenotypes or treatments that are not generalizable to the broader population.
3) Cancer cell lines, though useful, are widely known to harbor a large number of function-altering mutations. Given our prior success using primary cells, we strongly feel they will yield more patient-relevant results.
4) These primary human cells can be expanded through at least 7 passages. We will be able to generate a sufficient number of cells within three passages to allow for aliquot and cryopreservation. Identical sets of cells can be thawed and used for each chemical suppressor screen, reducing variations in results.

Automated imaging and analysis: Cells will be fixed and stained for multiple cytoskeletal, nuclear, mitochondrial and other structural phenotypic markers 72 hours after transfection[61]. The cells will then be imaged using a high-throughput widefield fluorescence microscope (Molecular Devices ImageXpress CLS). Our custom image-processing pipeline written in CellProfiler will then identify each cell in every image and quantify hundreds of features of each cell, depositing the measurements to a SQL database. By comparing both control and test wells against the set of all control wells for each experimental batch, we will evaluate using z-scores the significance of the perturbation for every siRNA for every structural feature measured. The composite of all significant on-target changes for each gene will be a 'phenoprint' for that gene. The strength of a phenoprint will be based on multiple factors including: the number of parameters altered in concert for all siRNA for a particular gene implying an on-target effect, the magnitude of those changes, and the uniqueness of the changes. If a large number of genes, for example, decrease cell size significantly, this aspect of any phenoprint could be de-prioritized, depending on whether this improved our outcomes, in an attempt to reduce the likelihood of identifying non-specific phenotypes.
Readout: We expect at least 200 disease models to display a significant structural phenotype.

Subaim 1B: Screen functional phenotypes in two primary cell types associated with knock-down of disease-related genes.

Rationale: Many gene knockdowns will not yield a detectable structural alteration; here, we expand the range of phenotypes detected, increasing the proportion of genes with a phenotype and strengthening the phenoprint associated with each genetic knock-down.
Experimental Plan: We will knockdown the same set of genes used in Aim 1A using at least three independent siRNA per target in two primary human cell types (HUVEC and SAEC). These cells will be seeded onto 96-well transcellular resistance assay plates and measurement of transcellular resistance will be monitored in real-time for two sets of assays. Set A will be seeded at a low density of 5,000 cells per well and followed over 72 hours to evaluate subconfluent cell mobility and proliferation. Set B will be seeded at a higher density of 30,000 cells per well and evaluated for 48 hours (with a media change at 24 hours) to evaluate cell adhesion, cell-cell junction formation, and the cellular response to a media change. All measurements will be made at 4 Hz, 400 Hz, 4,000 Hz, 10,000 Hz,

20,000 Hz and 64,000 Hz. A three-dimensional surface will be developed for each siRNA for each set (A & B) with time, resistance, and AC frequency as axes. For each experimental run, a baseline profile will be computed by averaging profiles of the control wells for that experiment. By then computing distance from the profile of each well to the baseline using Euclidean or similar distance measure, we can derive a z-score for each well in the experiment and identify those siRNA causing a significantly changed profile. For each gene in which at least two targeting siRNA result in a significant change in the surface profile, the surfaces will be compared and effects considered to be on-target if two or more of the siRNA targeting that gene show departures from baseline that are significantly positively correlated with one another when compared to correlations with controls.
Readout: Additional disease models based on functional phenotypes, plus enrichment of some of those genes' phenoprints detected in Aim 1A.

Potential Challenges. We have devised the following approaches to address potential challenges:

1) **siRNA off-target effects.** We will utilize at least three unique siRNAs for each gene target. On-target siRNA effects will be defined only as those resulting in a significant change of any given structural parameter in the same direction by at least two of the three siRNAs targeted against that gene. Structural changes in only one siRNA, or low-magnitude non-significant changes among multiple siRNA will be considered off-target effects and the use of those parameters disqualified. We will also utilize seed-sequence analysis to correct for the effects of seed-sequences. Still, some artifacts will remain, which will be filtered out in Aim 2C.
2) **Lack of expected phenotypes.** We expect more than 10% of genes to result in some measurable phenotypes (See Phase-I type pilot data). This would result in 200 disease models. If fewer than 200 disease models are identified, we will increase the number of assays (e.g. additional stains for imaging) or cell types used in our screen to achieve this.
3) **Unclear phenotypes.** We will employ at least three unique siRNA in two different primary cells types for structural and functional phenotypes for each gene of interest. Consistent structural and functional phenotypes across all three siRNAs and cell types may often not be present. For this reason, we have developed statistical analyses/algorithms to rank phenotypes based on the magnitude of each parameter change, the number of siRNAs per target demonstrating changes to a parameter in the same direction, and seed-sequence analysis among the siRNAs.

Specific Aim 2: Identify known drugs that ameliorate structural and functional phenotypes associated with knockout of disease associated genes. We will accomplish this aim by: (A) screening a library of at least 2,727 known drugs against the 200 disease models identified in Specific Aim 1; (B) evaluating and prioritizing all hits manually to ensure that drug properties are appropriate for each disease target and that a commercial opportunity exists; and (C) validating the top 20 drug/disease combinations by generating stable cell lines of each disease gene using CRISPR technology, validating the continued presence of structural and functional cell phenotypes in these lines, and reconfirming drug rescue. Our **criteria for success** will be identification of known drugs that ameliorate both structural and functional phenotypes for at least 10 CRISPR-validated *in vitro* disease models.

Subaim 2A: Chemical Suppressor Screening Using Known Drugs

Rationale: Known drugs as well as drugs that have failed clinical trials due to lack of efficacy can have therapeutic value in different settings. Using a target-agnostic approach to drug discovery and drug repurposing is an efficient method for treating diseases with no available treatments. The known polypharmacology of drugs or their off-target promiscuous effects coupled with the fact that targets identified in a particular disease can also play critical roles in other pathways or phenotypes provide further rationale for screening known drugs[47-51].
Experimental Plan: We will perform chemical suppressor screens in a staggered manner, one model per day at an overall rate of 5 per week. For each target, the cell type, assay, and siRNA shown to result in an on-target phenotype will be generated at a large scale – enough to test 2,727 compounds individually in wells for each aspect of the phenotype. To insure the homogeneity of our knockdown cells across all wells in each assay, we will perform transfection on a large quantity of cells, and subsequently seed these to each assay plate (as successfully performed by Personal Info in the phase-I type pilot studies). Due to the cost of transcellular resistance assays, for those disease models with phenotypes in both structural and functional assays, only drugs found to rescue the structural phenotype will be utilized in a subsequent functional rescue screen. 2,727 known drugs will be evaluated, with one drug per well at 10μM concentration in DMSO at a final concentration of 0.5% after 24 hours of treatment (imaging) and in real time after drug addition (functional assay).

Selection of known drug libraries: The quality of drug libraries used will have a significant effect on the success of our proposed research. We will utilize a minimum of three distinct known drug libraries: The MicroSource Spectrum Collection, the NIH Clinical Collection, and the NIH Clinical Collection II. The total number of drugs represented in

these libraries is 2,727. We are currently attempting to access additional libraries of drugs, including drugs owned by large pharmaceutical companies which achieved safety in humans but for which marketing approval was not achieved for business or efficacy reasons. We will screen additional compounds, as we acquire them, at our own cost.

Readout: Using our automated platforms for high-throughput analysis, we will identify any drugs that significantly rescue the phenotypes for a given target and consider those positive hits, and a repeat of the experiment using these hits at multiple doses will be used to confirm rescue.

Subaim 2B: Drug Development Prioritization of Confirmed Hits

Rationale: Even when a drug rescues a phenotype associated with a specific gene knock-down, drug properties may affect its efficacy in certain human diseases and their commercial potential; therefore, we will screen potential positive drug rescues identified in Subaim 2A to deprioritize drugs that are unlikely to be capable of treating the specific human disease for which they have been identified as potentially beneficial.

Experimental Plan: We expect to identify a potential drug in about 50% of phenotypes screened. This is a conservative estimate based on our prior identification of two unique drugs for the treatment of CCM (Please see Letter of Support from Consultant Info for discussion). Therefore, we expect to find 100 new drug/disease combinations. We will manually evaluate each combination based on the likelihood of efficacy and commercial potential. All publically available data for each drug hit will be studied to evaluate pharmacokinetics, safety data, proposed method of action, market availability, intellectual property status, other indications, etc. Considerations like the availability, complexity, and cost of animal models for each disease will be further considered at this stage. Together with experts in drug development and particular disease areas (including Consultant Info and additional scientific and business advisory board members), we will rank-order the drug-disease combinations.

Readout: A selection of the top 20 hits, based on likely efficacy and commercial potential, for further evaluation.

Subaim 2C: CRISPR Validation of Prioritized Drug Screen Hits

Rationale: While we will take measures (described above) to reduce the likelihood for false positives, the potential for off-target effects of RNAi convoluting our results still exists. To ensure the phenoprint and drug rescue identified in the above aims are reliable, we will use an orthogonal gene manipulation technique, CRISPR/Cas9 gene editing, to recapitulate phenotypes of the top 20 drug/disease combinations in true cellular knockout models.

Experimental Plan: We will use the CRISPR/Cas9 gene editing system to generate a stable cell line harboring a loss-of-function defect for each gene corresponding to our 20 disease models prioritized in the prior step. This technology, which is based on a bacterial immune system, has recently been employed in eukaryotic systems to knock-out specific genes in cells and in animals[62,63]. By expressing a guide RNA (gRNA) in combination with a Cas9 endonuclease in a cell, DNA double-strand breaks occur at desired genomic location followed by non-homologous recombination end joining (NHEJ) or homology-directed repair, which results in altering the DNA structure and subsequent RNA and protein expression. We will design gRNAs against specific DNA loci of our genes of interest and express them along with Cas9 in HUVEC and SAEC cells. We will design 3-4 gRNAs to create multiple knockout cell lines to ensure potential off-target CRISPR effects can be well-isolated. In addition to gRNA and Cas9, the single plasmid CRISPR system will express an antibiotic resistance vector to allow for selection of a single clone to expand and generate stable expression. We will validate the successful implementation of our cell lines using traditional approaches including PCR and western blot. Upon achieving putative knockout of the gene of interest, we will expand and freeze down the cells for both phenotype verification and chemical suppressor screening. Each cell model will then be evaluated for phenotypes using the same techniques employed in Aims 1 & 2. After validating each disease/gene 'phenoprint', we will test the drug hit for that disease (obtained in its purest form, with appropriate verification, from a new vendor) for its ability to ameliorate the CRISPR cell line phenoprint.

Readout: We expect ~50% of drug/disease combinations will be validated, yielding 10 to be moved to an animal model.

Potential Challenges. We have devised the following approaches to address potential challenges:

1) **Lack of rescuing drugs.** We expect to find a drug candidate for about 50% of siRNA-generated cell models, yielding 100 drug/disease combinations in this aim. We will identify the top 20 of these combinations for CRISPR validation. We expect about half of the drug disease combinations to validate, yielding 10 high-priority drug/disease combinations. If we fail to achieve this, we will validate more of the drug/disease combinations found in Aim 2A.
2) **CRISPR phenoprint differs from siRNA-induced phenoprint.** Due to differences in cell type and experimental techniques (complete knockout using CRISPR versus knock-down with siRNA), we may identify phenoprints using CRISPR that partially or completely differ from those induced by RNAi. If previously identified

drugs still rescue the CRISPR phenoprint, we will consider this a validated hit.

3) **CRISPR off-target effects.** The CRISPR studies will be undertaken with consultation with Consultant Info director of the University of Utah Gene Targeting Core Facility. The core has extensive background and training in designing CRISPR constructs for genetic knockouts. Though off-target effects of CRISPR-mediated knockout of gene targets have been reported, the system is generally believed to be relatively specific. Further, our use of multiple gRNAs for each gene to create multiple knockout cell lines should provide a means by which phenotypes can be cross-referenced.

Specific Aim 3: To demonstrate efficacy of prioritized hits in relevant animal models of disease. We will accomplish this aim by demonstrating efficacy of each validated hit identified in Aim 2 in its own unique murine model. Our **criteria for success** will be identification of known drugs that can be used to treat at least two orphan indications. The data generated via this grant will enable further evaluation and commercialization of each drug/disease combination in human clinical trials.

Rationale: It is imperative that efficacy be shown in an animal model of disease before entering human clinical trials, particularly since the *in vitro* phenoprint may have been identified in a cell-type unrelated to the human disease.
Experimental Plan: We will obtain relevant animal models of each disease for which we have identified a high-priority drug candidate in Aim 2 (between five and ten drug/disease combinations is expected). Personal Info through the assistance of Consultant Info has generated more than 25 knockout mouse models in the last two decades. All of these mice have been expertly evaluated and studied, and a number have served as the basis of important research manuscripts[28,64-79]. Phenotypes have been identified in a wide variety of tissues, and it is clear that Personal Info has the capacity to study many knockout mouse models. We will aggressively seek the guidance of consultants (as of yet unidentified) with specific expertise on each animal model we obtain, as well as the clinical condition for which that animal model is designed to model. These consultations will be obtained at the expense of Recursion, and are not considered a part of the proposed costs of this grant due to the inherent variability in potential costs. Therefore, it is highly likely that at least five, and potentially all ten animal models identified in Aim 2 can be generated or acquired and studied by Personal Info Drug dosing and duration will be administered based on disease model and relevant pharmacologic data known from the drugs being used. Drug safety and pharmacology will be unnecessary in animal models as drugs from Aim 2 will only be chosen if these parameters are already known. Multiple dosing and length of administration will be based on previous cited literature and safety monitoring data of the drug in addition to the observed phenotype in humans and mouse.
Readout: Animal models will be specific to each disease, and the readout will ideally be disease-specific and similar to what is found in humans.

Potential Challenges. We have devised the following approaches to address potential challenges:

1) **Lack of existing appropriate animal models.** In some cases, we may be unable to obtain an animal model or to recapitulate published defects associated with an animal model. In this case, we will use the experience of Consultant Info and Personal Info to generate new knockout mice using CRISPR-mediated deletion of the target gene (please see attached letter of support from Consultant Info
2) **Difficulty in identifying an appropriate dosing and treatment strategy.** Though prior publications highlighting each animal model and each drug may be available, it is possible our dosing and treatment strategy will need to be modified to see significant rescue since the drugs will be administered in a new disease setting. In these cases, we will perform standard dose-finding studies before proceeding to measuring efficacy in our model.

FUTURE DIRECTIONS:

We believe that this platform has the potential to scale to a large number of disease models in the rare disease space. To achieve this vision, we will initially scale our approach in two ways:

1) We will expand our study of the data obtained in this proposed study. At each stage, we will use prioritization criteria to identify the very best potential phenoprint/disease/model/drug for further study. It is likely that we will have hundreds of 'leads' available to us as a result of the proposed research. We will pursue each of these to the extent that the required resources can be justified by the potential impact (both commercial and societal).
2) We will expand this screen in subsequent iterations to the entire genome, additional human cell types, and other information-rich assays. This expansion will allow us to build a library of phenoprints for a large proportion of monogenic loss of function diseases, each of which can be used as the basis of a chemical suppressor screen. Additionally, we will build out our library of known drugs against which we screen by partnering with pharmaceutical companies to freely screen (with pre-negotiated contracts based on relevant outcomes and milestones) their drugs which succeeded in FDA phase I clinical trials but failed in phase II/III trials for efficacy or business reasons.

VERTEBRATE ANIMALS:

We propose the use of vertebrate animals (mice) in this study. These animals serve as a critical step between our careful identification of potential new uses of known drugs and their use in human clinical trials. Due to the nature of our proposal, in which we will study more than 2,000 monogenic loss of function diseases, it is difficult for us to describe how we would use each animal model. Instead, we have proposed to study between five and ten different mouse models of human disease, depending on the outcome of an in-depth validation and prioritization phase.

Given the complex task of pursuing animal work, we have partnered with the University of Utah and Personal Info to perform each animal model. Personal Info has a long history of working effectively with animal models, and understands the general protocols and serious ethical implications of this work. The Comparative Medicine Center (CMC) at the University of Utah houses a wide-variety of vertebrate animal models and is under 24-hour care by a veterinarian and a dedicated group of technicians.

We, and Personal Info, have experience in working with animals in a way that maximizes the efficiency of the research and minimizes the number of animals involved. We have extensive experience working with the University of Utah Institutional Animal Care and Use (IACUC) committee, and once our research has led to selection of a specific murine model, we will work diligently with them to develop highly rigorous protocols. This effort will be helped by our prioritization of human diseases for which animal models already exist (decreasing breeding requirements), and the use of known drugs for which a safe pharmacologic dose in mice will likely be described in the literature.

Under no circumstance will we initiate animal model work until we have IACUC authorization and contact the NIH awarding office to provide considerable more detailed answers to the questions, below.

1) **Description of Use:** As detailed above, we propose to use between five and ten strains or knockout mouse models (See Aim 3). The specifics of each strain or model will be confirmed as we conduct our chemical suppressor screens and validation experiments (See Aim 2). We will seek to minimize the number of animals required in all cases, and will provide detailed descriptions of each model and our proposed work with it before initiation of that portion of our study. We expect to be able to provide this information approximately 9 months after awarding of the grant, in budget period 1.
2) **Justification for Use:** Animals are required for these studies because we are seeking to determine whether therapeutic candidates discovered in cellular screening assays influences a mouse model of human disease. We are using these animal models to determine the potential therapeutic impact of candidate compounds for the treatment of a human diseases with significant morbidity or mortality and no approved medical treatment. Mice have been chosen because gene mutations in mice often result in clinically relevant phenotypes that can be used to model human disease. Moreover, they are readily amenable to selective gene manipulations that are more difficult to perform in other mammalian vertebrates. Because our proposal is based on drug-repurposing, these proposed animal models would potentially serve as the enabling experiments for proceeding to orphan drug designation and phase II human clinical trials. Therefore, we feel strongly that animal models are highly warranted in our proposed application.
3) **Maintenance and care facilities.** The research animal facility at the University of Utah is an AALAC approved animal facility. All animals are treated in accordance with the specifications listed in the current edition of the NIH Guide for the Care and Use of Laboratory Animals. The facility at the University of Utah is IACUC accredited. The facility provides animal holding rooms, biohazard animal holding rooms, procedure rooms, and individual, sterile surgical suites designed specifically for survival studies. The intensive care unit is staffed 24 hours-a-day, 7 days-a-week by an animal health care technician. Veterinary care is also provided on a 24 hour-a-day, 7 day-a-week basis. Automatic lighting, individual room temperature controls, and 20 air changes per hour are provided.
4) **Description of Procedures:** The specific procedures to be performed will be based on the specific animal models and human diseases required. All efforts will be made to insure minimal pain or discomfort in all cases. We will provide much more detailed information upon selection of each animal model and our proposed procedures, and in advance of initiation of such procedures.
5) **Euthanasia:** It is likely that we will be required to euthanize mice for the proposed studies. However, the exact method of euthanasia will depend on the proposed procedures and we will provide more information before commencing studies. In general, we will elect to use CO_2 for euthanasia when possible, as this method of euthanasia is consistent with the recommendations of the Panel on Euthanasia of the American Veterinary Medical Association.

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CONSORTIUM ARRANGEMENTS:

Recursion Pharmaceuticals has entered into discussions with the University of Utah and the laboratory of Personal Info Personal Info to perform the required animal experiments described in Aim 3. These discussions are documented by a **Letter of Intent to Enter Into a Sub-Contractual Agreement** (see Letters of Support, University of Utah Office of Sponsored Project).

Both Recursion Pharmaceuticals and the University of Utah (including Personal Info and Personal Info from the Office of Sponsored Projects) understand and agree with the following statement:

> *The appropriate programmatic and administrative personnel of each organization involved in this grant application are aware of the agency's consortium agreement policy and are prepared to establish the necessary inter-organizational agreement(s) consistent with that policy.*

For SBIR phase II proposals, such as this, a minimum of EFFORT of the research or analytical effort must be carried out by the small business concern (Recursion Pharmaceuticals). The respective contributions of Recursion Pharmaceuticals to this grant is Itemized Cost (see below), which is well-above the required Itemized Cost

	Direct and Indirect Cost(s)	Percent of Award
Recursion Pharmaceuticals	Itemized Cost	
University of Utah		
Total		

Letters of Support

Letters of Support

Letters of Support

Principal Investigator/Program Director (Last, first, middle): Personal Info

Letters of Support

Principal Investigator/Program Director (Last, first, middle): Personal Info

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Principal Investigator/Program Director (Last, first, middle): Personal Info

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Letters of Support

RESOURCE SHARING PLAN

Recursion Pharmaceuticals, in order to maximize commercial potential, will not share data generated under this plan for four years from the end of the award, per The Small Business Act. Recursion Pharmaceuticals, however, will make certain none-commercializable data and findings available via publication (please see a more detailed discussion in the educational impact section of the Commercialization Plan). After a period of four years, as described above, Recursion will share data with those who request it. Further, as Recursion grows, we may more broadly share databases we generate via our website or other public repository. In certain cases, we will deposit data from our screen to the PubChem database according to its procedures.

PHS 398 Checklist

OMB Number: 0925-0001

1. Application Type:

From SF 424 (R&R) Cover Page. The responses provided on the R&R cover page are repeated here for your reference, as you answer the questions that are specific to the PHS398.

* Type of Application:

☒ New ☐ Resubmission ☐ Renewal ☐ Continuation ☐ Revision

Federal Identifier: GRANT11623742

2. Change of Investigator / Change of Institution Questions

☐ Change of principal investigator / program director

Name of former principal investigator / program director:

Prefix:
* First Name:
Middle Name:
* Last Name:
Suffix:

☐ Change of Grantee Institution

* Name of former institution:

3. Inventions and Patents (For renewal applications only)

* Inventions and Patents: Yes ☐ No ☐

If the answer is "Yes" then please answer the following:

* Previously Reported: Yes ☐ No ☐

4. * Program Income

Is program income anticipated during the periods for which the grant support is requested?

☐ Yes ☒ No

If you checked "yes" above (indicating that program income is anticipated), then use the format below to reflect the amount and source(s). Otherwise, leave this section blank.

*Budget Period	*Anticipated Amount ($)	*Source(s)

5. * Disclosure Permission Statement

If this application does not result in an award, is the Government permitted to disclose the title of your proposed project, and the name, address, telephone number and e-mail address of the official signing for the applicant organization, to organizations that may be interested in contacting you for further information (e.g., possible collaborations, investment)?

☐ Yes ☒ No