



2018-2019 Crnic Grand Challenge Grant Program

Purpose

The Linda Crnic Institute for Down Syndrome is a part of the University of Colorado, housed on both the Anschutz Medical and Boulder campuses. One of its main purposes is to eliminate the ill effects of Down syndrome. The current leadership of the Institute plans to accomplish that goal by supporting research likely to aid in the understanding of the syndrome and in reducing its adverse consequences. There is no question that exciting new technologies in genomics, genetics, stem cell biology, genome editing, and advanced imaging will enable novel powerful approaches to answer key outstanding questions in the field, and should enable our Down syndrome community to make significant strides towards our goals.

Generous gifts from the Anna and John J. Sie Foundation and donors to the Global Down Syndrome Foundation, as well as significant support from the CU-Boulder and CU-Denver Chancellors' Offices, provide for seed grants to initiate research projects on the mechanisms whereby three copies of chromosome 21 lead to Down syndrome and on ways to ameliorate the ill effects in those who currently have Down syndrome. These research grants will be available to University of Colorado faculty on either campus who now study Down syndrome or who are interested in initiating projects to do so. Our purpose is to create a vibrant, exciting and active research community dedicated to solving the key issues. We will be working together, with the aim of making the University of Colorado a powerhouse in this area.

Contact

crnicgrandchallengegrant@ucdenver.edu

303-724-6599

Key Dates

Attendance at the Down Syndrome Symposium	October 24, 2017
Reply to the Email of Intent	November 7, 2017
Application Submission Due	January 5, 2018
Decisions/Results Communicated to Applicant	March 16, 2018
Funding of Successful Applicants Begins	April 2018

Eligibility

- Investigators must hold the rank of Assistant Professor, Research Assistant Professor, Instructor or higher. Adjunct and Clinical faculty are eligible, but must name a PI with regular faculty rank.
- Applicant must have attended the Crnic Down Syndrome Symposium on Tuesday, October 24, 2017.
- Applicant must have replied to the email of intent.
- The application must be relevant to Down syndrome or one of its associated conditions.
- The most successful applications will be those that directly address one or more of the "Major Challenges".
- Direct relevance of the proposals to Down syndrome is paramount.

Recipient Requirements

Those receiving a Crnic Grand Challenge Grant will be expected to become active members of the University of Colorado Down syndrome research community. Recipients will:

- participate, along with the lab members working on the research project, in the Crnic Supergroup meetings.
- self-identify as a member of the Crnic (in addition to their home department) on all publications emanating from the work resulting from this grant.
- use these funds solely to support the research described in their proposal.
- provide an annual report by March 15, 2019.
- present a report at a future Down Syndrome Symposium hosted by Crnic.
- understand that no indirect costs will be provided.

Application Requirements

All Crnic Grand Challenge Grant applications are to be submitted **no later than January 5, 2018**, and should include the following elements:

- a) a brief cover note from the PI describing the value of the project, and the expected contribution to the community of Down syndrome researchers, and a statement that all collaborators listed on the application agree with the proposal.
- b) a proposal body consisting of **no more than five pages** including figures (if any) in standard NIH grant application format. Recommended, but not required, guidelines for proposals include: specific aims, background and broader impact, and research plan. Preliminary results are not required, but should be included if they exist. (*References are not included in the five-page limit*).
- c) explanatory figures and data figures are acceptable, as are a limited number of references.
- d) a one-page budget proposal, enumerating direct costs. Please use the budget template provided on the Crnic Grand Challenge Grants Program webpage at:
<http://www.ucdenver.edu/academics/colleges/medicalschoo/institutes/lindacrnic/research/Pages/GrandChallengeGrants.aspx>
- e) NIH formatted Biosketch for the PI or PI's.

Please note that parts *a*, *b* and *c* are to be formatted as a single document in PDF format. Parts *d* and *e* are to be formatted as single documents in PDF format. These (3) PDF documents are to be submitted online at:
<http://www.ucdenver.edu/academics/colleges/medicalschoo/institutes/lindacrnic/research/Pages/GrandChallengeGrants.aspx>.

To be eligible, an email of intent to apply needs to be sent to crnicgrandchallengegrant@ucdenver.edu by **Tuesday, November 7, 2017**.

After your application submission is complete, you will receive a confirmation by email.

Please contact crnicgrandchallengegrant@ucdenver.edu if you have problems with your online submission.

Review Criteria

A peer review panel composed of faculty with a range of expertise will rank eligible applications. The primary factors in the ranking will be the scientific merit of the proposed research, its direct relevance to understanding Down syndrome and/or reducing its adverse consequences, and the long-term promise of the proposed research. Applications should make clear how the proposed research will contribute to the Down syndrome research community at the University of Colorado.

The leadership of the Crnic Institute will make award decisions based on study section ranking and programmatic needs of the Institute. All decisions will be final, and only minimal scientific critiques will be provided to applicants. Extensions of the initial one-year period of support will require the PI to apply in the next year's competition. Both success in the proposed project and participation during the previous year will be important criteria considered by the study section for renewal applications.

Budget

The awards will be for \$50,000 for the initial funding period. No indirect costs can be requested. Limited salary support, fringe benefits, and teaching buy-out are permissible, but it is expected that the majority of the budget will be for direct research support, e.g. supplies, salaries for technicians, post-docs and graduate students, necessary equipment. Grants will be made only to University of Colorado researchers, but subcontracting to collaborators elsewhere is permitted as long as it is clearly necessary to the success of the project.

When needed, additional funding of \$50,000 may be applied for. This additional funding will be dependent on scientific progress and need. Each applicant will be expected to provide written milestones, subject to approval by Crnic leadership, attainment of which will be required for additional funding. This funding will also be dependent on active participation in Crnic Supergroup meetings. To apply for this funding the PI may at any time write a progress report outlining the achievements so far and justifying the need for additional funding. In the same way, additional \$50,000 awards may be applied for as long as the milestones set at the timing of the previous award have been achieved, and both the PI and his/her lab members working on DS have been attending the DS Supergroups and symposia. Progress reports should be submitted to crnicgrandchallengegrant@ucdenver.edu.

Major Challenges

A. How does an extra copy of chromosome 21 cause the cognitive and physical differences experienced by people with Down syndrome?

1. What genes have altered mRNA expression in DS, both those on chromosome 21 and on other chromosomes?
2. What genes have altered protein expression in DS, both those on chromosome 21 and on other chromosomes?
3. Are the genes with altered expression altered in a similar manner in all tissues? Are they altered in all cells within a tissue?
4. Can cell lines be used to determine which genes are important in creating DS-related phenotypes? Can we identify cell-level markers related to the organism-level phenotypes?
5. Does overexpression of one or a few genes result in development of DS-related phenotypes?
6. Would knockdown or knockout of one or a few genes in cell lines with trisomy 21 eliminate DS-related phenotypes?
7. Do individuals with partial trisomies reveal which region or regions of chromosome 21 are critical? Is it possible to do a meta-deletion-analysis of chromosome 21 using mouse and human data to identify critical regions? Do segmental aneuploids of the same amount of genetic material as 21 of other

chromosomes have phenotypes similar to DS? Are there ways of identifying symptomless individuals with chromosome 21 segmental aneuploids? Could these be used to eliminate certain regions of 21 as critical for DS?

8. What molecular events/pathways are responsible for the developmental abnormalities of DS?
9. What molecular events/pathways are responsible for the cognitive deficits of individuals with DS?

B. How does trisomy 21 cause a novel 'disease spectrum' in the population with Down syndrome? Why is this population less likely to develop solid tumors, hypertension and angiopathies, while being highly predisposed to Alzheimer's disease, leukemia, autism, diverse autoimmune disorders (e.g. autoimmune thyroid dysfunction, type I diabetes, celiac disease), and diverse hearing and vision problems?

1. What genes or combination of genes on chromosome 21 are responsible for the protective and predisposing effects?
2. To what degree are the various co-morbidities interrelated and likely to be driven by common causal factors?
3. To what degree are the varying manifestations of the trisomy explained by inter-individual differences at the genetic, epigenetic, metabolic and physiological levels?
4. Does the appearance and severity of the various conditions correlate with transcriptome or proteome changes?
5. What is the role of the microbiome, diet and other environmental factors in the appearance of the diverse conditions?

C. How can we intervene to ameliorate/prevent the ill effects of Down syndrome?

1. What are the 'druggable' targets on chromosome 21?
2. Can NGF/BDNF therapy alleviate DS symptoms?
3. Does the gut microbiome have a role in DS? If so, would this open novel therapeutic approaches?
4. Can exercise and/or diet modify symptomology of DS?
5. Can treatments that alter epigenetic states affect DS phenotypes?
6. Can drugs alter severity of symptoms in DS mice or people with DS?
7. Can we develop molecular markers to predict symptoms before they appear and to quantitate their severity? Can we develop biomarkers for Alzheimer's disease by studying the people with Down syndrome?

D. These lists of challenges are not all inclusive. Convince us of the importance of challenges we have omitted.