



2020 Grand Challenge Grants Program

Purpose

This Request for Applications (RFA) is issued by the Linda Crnic Institute for Down Syndrome to address major research questions, or "Grand Challenges," in Down syndrome and to assist investigators in obtaining independent funding for these projects. Grand Challenge Grant applications should propose defined research projects that will further our understanding of key Down syndrome phenotypes or co-morbidities and advance the mission and vision of the Crnic Institute, as well as the larger Down syndrome research community. Applications should also be responsive to the NIH **IN**vestigation of **Co**-occurring conditions across the **L**ifespan to **U**nderstand **D**own syndrom**E** (INCLUDE) Project. Examples of Grand Challenges are attached.

Key Dates

Attendance at the Down Syndrome Research Symposium	September 25, 2019
Email of Intent to Apply due	November 15, 2019
Application Components due	January 12, 2020
Decisions communicated to applicants	March 20, 2020
Recipient funding begins	April 2020

Award Information

Awards are \$50,000 and no indirect costs are provided. 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, graduate students, and necessary equipment.

Recipients can request additional funding of \$50,000 as their project progresses. Requests for additional funding are evaluated in light of adherence to the stated Recipient Requirements (see below) and successful completion of project milestones, which would be defined and approved in collaboration with Crnic Institute leadership.

Eligibility

- PIs must hold the rank of Instructor, Research Assistant Professor, Assistant Professor, or higher at the University of Colorado. Adjunct, Clinical, and non-University of Colorado faculty may apply, but must name a co-PI with eligible rank.
- PI must have attended the Down Syndrome Research Symposium on Wednesday, September 25, 2019.
- PI must send an Email of Intent to Apply to crnicgrandchallengegrant@ucdenver.edu by November 15, 2019.
- The application must be relevant to Down syndrome or one of its associated conditions.
- The application must align and/or synergize with the NIH INCLUDE Project, whose three critical components are:
 1. High-risk, high-reward basic science studies of chromosome 21
 2. Pan-omics studies across the lifespan and among differing phenotypes/comorbidities
 3. Inclusion of people with Down syndrome in clinical research and trials

Application Instructions

- **Email of Intent to Apply** should be sent to crnicgrandchallengegrant@ucdenver.edu by November 15, 2019. The email should state the PI(s) full name, email address, and the general research area the application will address.
- **Application Components** are due at 11:59 PM MST on January 12, 2020, and include:
 - **Cover Letter** (one-page PDF). The Cover Letter should state the full title of the project, describe its expected contribution to the community of Down syndrome researchers, and how it aligns with the NIH INCLUDE Project.
 - **Abstract** (one paragraph). Succinctly summarize the project objectives and methods.
 - **Research Strategy** (6-page PDF, not counting the Bibliography). The Research Strategy should detail the proposed project with the following requirements:
 - Sections for Specific Aims, Significance, Innovation, and Approach
 - The Significance section should include a paragraph explaining how the project aligns and/or synergizes with the NIH INCLUDE Project
 - Preliminary results are not required, but should be included if they exist
 - Explanatory figures and data figures are acceptable
 - Include a Bibliography at the end of the document (citations in NIH style, not counted toward the page limit)
 - Use Arial 11-point font with 0.5-inch margins
 - **Biosketch** for the PI(s). The Biosketch should be formatted as a PDF following all NIH guidelines, which can be found online at: <https://grants.nih.gov/grants/forms/biosketch.htm>.
 - **Budget** (one-page PDF). The budget should enumerate direct costs for up to \$50,000. Please use the budget template provided online at www.crnicinstitute.org → Funding Opportunities → Grand Challenge Grants.
- Application Components must be submitted online following the instructions provided in response to your Email of Intent to Apply.

Recipient Requirements

Grand Challenge Grant recipients are expected to become active members of the University of Colorado Down syndrome research community, known as the “Crnic Supergroup.” Recipient PIs must agree to:

- attend monthly Crnic Supergroup Meetings, along with any lab members working on the project.
- present research progress reports at 1-2 Crnic Supergroup Meetings per year. Qualified lab members may also present progress reports.
- prepare a formal project presentation for a future Down Syndrome Research Symposium.
- list the Crnic Institute as an academic affiliation (in addition to their home department) on all publications emanating from the work resulting from this grant.
- use these funds solely to support the Down syndrome research described in their proposal.

Contact

crnicgrandchallengegrant@ucdenver.edu

303-724-5963

Examples of Grand Challenges

How does an extra copy of chromosome 21 cause the developmental and clinical hallmarks of Down syndrome?

- What genes have altered mRNA expression in DS, both those on chromosome 21 and on other chromosomes?
- What genes have altered protein expression in DS, both those on chromosome 21 and on other chromosomes?
- Are the genes with altered expression altered in a similar manner in all tissues? Are they altered in all cells within a tissue?
- 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?
- Does overexpression of one or a few genes result in development of DS-related phenotypes?
- Would knockdown or knockout of one or a few genes in cell lines with trisomy 21 eliminate DS-related phenotypes?
- What molecular events/pathways are responsible for the developmental abnormalities of DS?
- What molecular events/pathways are responsible for the cognitive deficits of individuals with DS?

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, autoimmune disorders, and hearing and vision problems?

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

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

- What are the 'druggable' targets on chromosome 21?
- Does the gut microbiome have a role in DS? If so, would this open novel therapeutic approaches?
- Can exercise and/or diet modify symptomology of DS?
- Can treatments that alter epigenetic states affect DS phenotypes?
- Can drugs alter severity of symptoms in DS mice or people with DS?
- 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?

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