Grant Application Information

INTRODUCTION
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, proteomics, transcriptomics, genetics, stem cell biology, gene knockouts, microscopy, etc. will enable novel powerful approaches to some age-old and important questions, and should enable our DS community to make significant strides towards our goals.

Generous gifts from the Anna and John J. Sie Foundation and the 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 CU faculty on either campus who now study DS or who are interested in initiating projects to do so. Those receiving these grants will be expected to become active members of the CU Down syndrome research community. This entails: 1) participating in supergroup meetings to be held at the LCI on the 4th floor of RC2 at the AMC. All lab members working on DS-related projects should attend these meetings; 2) self-identifying as a member of the LCI on all publications related to DS research (in addition to their home department); and 3: providing a detailed annual report at the end of each funding year. Our purpose is to create a vibrant, exciting and active research community dedicated to solving the key DS-related issues outlined below. We will be working together, with the aim of making the University of Colorado a
powerhouse in this area.

The following information describes the mechanism by which these awards will be made and the application process. A peer review panel composed of faculty with a range of expertise will be responsible for award decisions. In order to be eligible for a LCI seed grant (maximum $100,000/year) the applicant must have registered for, and attended the LCI Symposium.

CRITICAL DATES
October 19, 2012 – LCI Symposium
January 14, 2013 - Applications due
March 2, 2013 – Applications due
March 15, 2013 – Decisions made and results communicated to applicants
March 15, 2013 – Funding of successful applications

ELIGIBILITY
Investigators must hold the rank of Assistant Professor or Research Assistant Professor or higher. Adjunct and Clinical faculty are eligible. The application must be relevant to Down syndrome and/or one of its associated symptoms, including (but not limited to) Alzheimer’s disease, cognitive deficits, cancer, and developmental abnormalities. The most successful applications will be those that directly address one or more of the “major challenges” outlined below. Direct relevance of the proposals to Down syndrome is paramount.

BUDGET
The awards will be in the amount of up to $100,000 for a one-year award period. Extensions of the initial one-year period of support will be available, depending on success and participation during the first year. 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 CU researchers, but subcontracting to collaborators elsewhere is permitted as long as it is clearly necessary to the success of the project. The granted funds will be provided in two equal portions, with the second six months of funding dependent on active participation in the LCI Down Syndrome Research Group during the first six months. Awardees will remain eligible for funding in subsequent annual competitions. Funding beyond the first year will require a) having actively participated in the meetings throughout the first year; b) participation in next
year’s LCI Symposium; c) re-applying in next year’s competition; d) demonstration of some measure of success during the previous year of funding

REVIEW CRITERIA
Eligibility will be determined by the peer review panel, which will evaluate eligible applications competitively. All decisions will be final, and no scientific critiques will be provided to applicants. The primary factors in award decisions will be the merit of the proposed research and its direct relevance to understanding Down syndrome and/or reducing its adverse consequences. Applications should make clear how the proposed research will contribute to the DS research community at CU.

APPLICATION PROCESS
Seed Grant Applications are to be submitted NO LATER THAN JANUARY 14, 2013, and should include the following elements:
a) A brief cover note from the PI describing the value of the project, the expected contribution to the community of DS researchers, a statement concerning which of the major challenges listed below will be addressed by this research, and a statement that all collaborators listed on the application agree with the proposal.
b) Title of the proposed research
c) COMPLETE contact information (full name, address, affiliations, phone numbers, and email addresses) for ALL investigators
d) A proposal body consisting of no more than 5 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.
e) Explanatory figures and data figures are acceptable, as are a limited number of references.
f) A one-page budget proposal, enumerating direct costs

Applications should be sent in PDF format via email to:

Tom Blumenthal, Executive Director
Linda Crnic Institute for Down Syndrome
Thomas.Blumenthal@ucdenver.edu
If you do not receive confirmation of your application within 2 business days, please email.

ADDITIONAL INFORMATION
The investigators of each funded project will make a presentation at the 2013 LCI Symposium. Responses to the applications will be only "funded," "not funded," or "not eligible." No narrative reviews will be provided, and no appeals of the peer review panel decisions will be possible.

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 animal-level phenotypes? What type of cell? Stem cells? IPSC’s?
5. Does overexpression of one or a few genes result in development of DS-related phenotypes?
6. Would knockdown of one or a few genes in cell lines overexpressing chromosome 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. Does triplication of APP cause Alzheimer’s Disease in individuals with DS? Does APP triplication also cause other DS symptoms? Do individuals with trisomy 21 containing an APP deletion exist?

9. Set up a longitudinal study of individuals with DS, beginning at birth. Do stochastic changes occur with age? On a cell-by-cell basis?

10. Does severity of some symptoms correlate with severity of others? Do any correlate with transcriptome or proteome changes? Why do some individuals have such severe symptoms while others don’t? Do severity of symptoms in DS mice correlate with one another?

11. What molecular events/pathways are responsible for the developmental abnormalities of DS?

12. What molecular events/pathways are responsible for the cognitive deficits of individuals with DS?
13. Is regulation in cells of individuals with Down syndrome more chaotic than in unaffected individuals?

B. HOW CAN WE INTERVENE TO AMELIORATE/PREVENT THE ILL EFFECTS OF DS?

1. Could H2A macro be engineered to turn off the extra copy of chromosome 21?
2. Can NGF/BDNF therapy alleviate DS symptoms?
3. Does the gut microbiome have a role in DS?
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?

C. THESE LISTS OF CHALLENGES ARE NOT ALL INCLUSIVE. Convince us of the importance of challenges we have omitted.