Brief summaries of the projects funded by the Linda Crnic Institute for Down Syndrome in the 2013 Grand Challenge Grants Program

Total awarded: $1,300,000
Announced on 3/21/13 – World Down Syndrome Day
Contact: Tom Blumenthal, PhD, Executive Director; Tom.Blumenthal@colorado.edu

Joaquin Espinosa, PhD
Associate Professor, MCDB, Boulder
A Genetic Screen For Synthetic Lethal Pathways With Trisomy 21
The Espinosa lab will scan the human genome in search of genes whose function is essential for the survival of cells with three copies of chromosome 21, yet at the same time dispensable for cells with only two copies. The identification of these genes will illuminate the molecular processes that allow the cells of individuals with Down Syndrome to accommodate the burden of an additional chromosome. Eventually, this knowledge may enable the design of therapeutic strategies modulating the activity of these genes.

Mathew Kennedy, PhD
Associate Professor, Pharmacology, AMC Denver
Mechanisms of beta-amyloid synapse elimination
Certain features of Down syndrome brain pathology closely resemble Alzheimer’s disease. One of the hallmarks of both Down syndrome and Alzheimer's disease is the loss of neuronal contacts in the brain called synapses. Loss of synapses leads to cognitive symptoms associated with these conditions and is thought to be a result of increased production of a toxic peptide called beta-amyloid. The Kennedy lab will investigate how beta-amyloid causes synapse loss in hopes of finding targets for future therapies.

Richard Spritz, MD
Professor, Human Medical Genetics, AMC Denver
Genetic Analysis of Autoimmunity in Down Syndrome
Over half of patients with Down Syndrome develop one or more autoimmune diseases—autoimmune thyroid disease, celiac disease, vitiligo, type 1 diabetes, and rheumatoid arthritis. The Spritz lab has discovered a gene on chromosome 21, called UBASH3A, that contributes to occurrence of these diseases in non-Down Syndrome patients. They will determine whether UBASH3A causes the very high risk of autoimmune diseases in Down Syndrome. If it does, their findings will enable easy testing to identify the subgroup of Down Syndrome individuals at highest risk, who thus would benefit from intensive clinical surveillance and early treatment.
Karl Pfenninger, MD  
Professor, Pediatrics, AMC Denver
The Pfenninger group is interested in the causes of intellectual disability associated with Down syndrome (DS). They study APP, a protein that is overproduced in DS brain. APP is known to be involved in Alzheimer disease, but their primary interest is its role in brain development. Their data indicate that overproduction of APP affects the development of the brain’s circuitry and, thus, may significantly contribute to DS-associated cognitive deficits. Using genetically engineered mice and cell culture systems they will define the effects of APP over-dosage in DS on the wiring of the developing brain, with the ultimate goal of targeting APP to ameliorate DS-associated intellectual disability.

Tamim H. Shaikh, PhD  
Associate Professor, Pediatrics, AMC Denver
*Genetic Modifiers of Autism Spectrum Disorders in Patients with Down Syndrome.*  
A significant number (~10%) of children with Down Syndrome (DS) are also diagnosed with autism spectrum disorders (ASD). The underlying cause of this increased risk for ASD in DS remains to be fully understood. The Shaikh group will use state-of-the-art techniques to analyze the genomes of children with DS, both those who have ASD and those who do not, to determine if differences in their genomes contribute to the development of ASD.

James DeGregori, PhD  
Professor, Biochemistry and Molecular Genetics, AMC Denver
*Defining how adaptive hematopoietic landscapes contribute to increased leukemogenesis in Down Syndrome individuals.*  
Down Syndrome is associated with a striking increase in leukemia incidence, as well as a variety of other problems associated with blood cell production, including reduced immunity. Using mouse models, the DeGregori lab will determine whether deficiencies in blood cell production originate in the reduced function of blood stem cells. Furthermore, they will ask whether the increase in leukemias associated with Down Syndrome is actually caused by the stem cell defects: does the poor health of these stem cells enhance the evolution of leukemias? These studies could indicate mechanisms to improve blood cell function and prevent leukemias in individuals with Down Syndrome.

Rui Yi, PhD  
Assistant Professor, MCDB, Boulder
*Tissue specific analysis of transcriptional and translational landscape in Down syndrome models*  
To decipher the underlying mechanism of how an extra copy of chromosome 21 causes Down syndrome, the Yi lab will harness the power of quantitative sequencing to determine the effect of gene dosage imbalance on transcriptional and translational activity in trisomic embryonic stem cells and their disomic derivatives.
Christopher Link, PhD
Associate Professor, Integrative Physiology, Boulder

*Transcriptome analysis in paired trisomic/disomic Down syndrome cells*

The extra copy of chromosome 21 that causes Down syndrome is believed to change the expression of many genes, but exactly which genes have altered expression is not resolved. The Link lab will use cultured cells from individuals with Down syndrome that have been converted into neurons to determine which genes have altered expression when an extra copy of Chromosome 21 is present. These genes with altered expression in neurons will likely be similarly mis-expressed in the brain, and thus may underlie the intellectual disability associated with Down syndrome.

Vivek Balasubramaniam, MD
Associate Professor, Pediatrics, AMC Denver

*Endothelial Progenitor Cell Dysfunction in Down Syndrome*

Infants and children with Down Syndrome have a high incidence of obstructive sleep apnea. In addition, they have impaired growth and function of their circulating vascular stem cells. There is a link between sleep apnea and increased cardiovascular disease in adults, which is related to dysfunction of circulating vascular stem cells. There have been no studies to date looking at the effect of obstructive sleep apnea on number or function of circulating vascular stem cells in Down Syndrome. The Balasubramanian group will examine the effect of sleep apnea on vascular stem cells in individuals with Down Syndrome.

Kevin Jones, PhD
Associate Professor, MCDB, Boulder

*BDNF augmentation as a therapeutic treatment for Down Syndrome*

There is evidence that reduced signaling between neurons mediated by growth factors, a class of signaling proteins that influence the health and function of cells, may be a significant contributor to the intellectual disability that occurs in Down syndrome. The Jones lab will test whether increasing the abundance of one specific growth factor can prevent Down syndrome pathology in a mouse model. They will screen for drugs that increase the abundance of this growth factor with the ultimate goal of developing therapeutic drugs for the treatment of Down syndrome.

Michael Yeager, PhD
Assistant Professor, Pediatric Critical Care, AMC Denver

*Depressed AIRE Expression Causes Immune Cell Dysfunction & Autoimmunity in Down Syndrome*

Immune system disturbances experienced by individuals with Down syndrome account for an enormous disease burden ranging from quality of life issues (hair loss), to more serious health issues (thyroid disease), to life-threatening issues (leukemia, respiratory tract infections). The Yeager lab will shed light on why the immune system does this. Their goal is to drive the development of newer therapies to help individuals with Down Syndrome in several aspects of their immune health care, from improved self-image to longer, more productive and happier lives.
Robin Dowell, PhD
Assistant Professor, MCDB and Biofrontiers Institute, Boulder

Genetically encoded suppressors of the deleterious Down syndrome phenotypes

Gene expression, the first step in interpreting the information encoded in the genome, is altered in Down Syndrome. The Dowell lab goal is to understand how an extra copy of chromosome 21 affects the behavior of key proteins involved in regulating expression. Ultimately this knowledge will be critical to the development of therapeutics targeted at mitigating aberrant gene expression.

Francis Hickey, MD
Sie Center Medical Director
Professor, Pediatrics, AMC Denver

The pharmacokinetics of morphine in post-operative cardiac patients with Down syndrome

This study will use blood samples from children with and without Down syndrome undergoing cardiac surgery. The study will provide information to improve the management of post-operative pain and sedation in children with Down syndrome and congenital heart disease, as well as all children with Down syndrome in their pain management. Knowledge about the metabolism of morphine in these patients will guide dosing and therefore limit the risks and side effects that these patients are exposed to in all clinical situations where pain control is needed.

Ding Xue, PhD
Professor, MCDB, Boulder

Presenilin and Ubiquilin and their roles in Down Syndrome treatments

Down syndrome (DS) patients are at high risk of developing Alzheimer’s disease (AD). Mutations in two genes, presenilin and ubiquilin, are associated with AD, and have been shown to cause apoptosis, a major form of neurodegeneration in AD. The Xue lab will use *C. elegans* as a model to study the mechanisms and signaling pathways of presenilin and ubiquilin and to identify treatments that can ameliorate the ill effects of DS and AD.