Collins Medical Trust

Medical Research and Education in Oregon

2021 Annual Report

Founded in 1956 by Truman Collins, Sr.

Collins Medical Trust

2021 Annual Report

Purpose and History

"The principal and income of the trust fund shall be used (a) to aid, further, promote, develop, encourage and sponsor research, experiment and work in the cause, cure and treatment of human diseases or in any field of medical research, and (b) to aid, further and promote medical education."

The Collins Medical Trust was founded by Truman Collins Sr. in the fall of 1956. He was interested in the medical field and wanted to set up a trust that would contribute to medical research and education taking place in Oregon. Contributions were made to the trust over the next ten years or so. Its assets have grown significantly since that time, largely due to the wise investment decisions of the financial adviser, Jim Miller, over the first forty years of the Trust's existence.

We value and fund a range of health-related research, including basic laboratory science, clinical research, and public health investigations. Because the Trust makes relatively small grants—typically in the $20,000 to $30,000 range—our focus for research has primarily been seed funding for projects that, if successful, will go on to apply to the NIH or to other large funders for later-stage funding. We also like to support researchers at a stage where they are gaining their independence in a supportive environment.

Since its inception, the Collins Medical Trust has made grants totaling about $10.0 million.

Trustees and Staff

Truman Collins Jr., Trustee (1990 – present) Dr. Elizabeth Eckstrom, Trustee (2003 – 2021) Dr. Virginia Tilden, Trustee (2017-present) Dr. John Nutt, Trustee (2020 - present) Ryan Luria, Trustee (2020 - present)	Loree LePaige, Administrator (2022 – present) Cody Hohenshelt, Administrator (2021 – 2022) Shannon Osieczanek, Administrator (2016-2021) Timothy R. Bishop, Treasurer (1990 – present)

Financial Statements (Fiscal year ending September 30, 2021)[1]

Assets and Liabilities

Assets:	2020	2021
Cash	$806,000	$758,000
Stocks	$7,515,000	$10,530,000
Total Assets	$8,321,000	$11,288,000
Liabilities	$59,000	$99,000
Net Assets	$8,262,000	$11,189,000

Revenue and Expenses

Income:	2020	2021
Income (Interest & Dividends)	$247,000	$225,000
Realized Gains	$804,000	$634,000
Unrealized Gains	($968,000)	$2,582,000
Total Income	$83,000	$3,441,000
Taxes & Investment Expense	($11,000)	($12,000)
Net Investment Income	$72,000	$3,429,000
Grants - Net	($495,000)	($500,000)
Charitable Purpose Expense	($2,000)	($2,000)
Net Revenue	($425,000)	$2,927,000

[1] Rounded to the nearest thousand

2021 Grants (October 1, 2020 – September 30, 2021)

Research

Sarah Andres, PhD. OHSU Foundation $30,000
Examining the Impact of Human Digestion on Human Milk Extracellular Vesicle miRNA Cargo for Necrotizing Enterocolitis Prevention

Stephen Bowden, MD. OHSU Foundation $30,000
Enumerating Circulating Hybrid Cells to Discriminate Tumor Grade in Adult Human Glioma

Karina Nakayama, PhD. OHSU Foundation $29,999
Regenerative skeletal muscle engineering using patterned scaffolds to promote healing of adjacent bone

Andrea Stroud, MD, MS, FACS. OHSU Foundation $30,000
Relationship of Weight Loss and Serum Biomarkers on Breast Cancer Incidence in Women with Obesity: Analysis of the Longitudinal Assessment of Bariatric Surgery Cohort

Isabelle Logan, PhD. Oregon State University $30,000
Cell-surface nitrated proteins as novel tumor-selective immunological targets

Michael Brasino, PhD. OHSU Foundation $30,000
The Development of Commensal Bacteria as Non-Invasive, Cancer-Sensing Probes

Alexandra Dimitrova, MA, MCR, MD. OHSU Foundation $29,992
Electrophysiologic Study of Acupuncture's Temporal Effect on Nociception in Chronic Pain Patients

Renee Ryals, PhD. OHSU Foundation $30,000
Optimizing a low-protein diet to elicit retinal neuroprotection

Deena Walker, PhD. OHSU Foundation $30,000
A novel role for thyroid hormone signaling in the regulation of sex differences in addiction

Wesley Yu, MD. OHSU Foundation $30,000
Preventing Metastasis of Genetically High Risk Melanoma

Ana Paula Piovezan Fugolin, DDS, MS, PhD. OHSU Foundation $30,000
Enzyme-Responsive Nanoparticles for Dentin Collagen Preservation

Zachary Working, MD. OHSU Foundation $30,000
Role of single-dose intravenous iron therapy for the treatment of anemia in the setting of orthopaedic trauma: a pilot study

Jonathon Reeder, PhD. University of Oregon $20,000
Thermal Management of Implantable Nerve Coolers for Cooling-Induced Local Analgesia

Tammy Weissman, PhD. Lewis and Clark College $30,000
A new *in vivo* model to study alpha-synuclein aggregation in Parkinson's Disease

Michael Espiritu, PhD. Pacific University $30,000
Determination of the structure-activity relationship of the conotoxin MIIIB: a novel inhibitor of voltage gated potassium channels.

Total Research: $439,991

Education:

Nursing Education Fund	Providence Community Health Foundation	$30,000
Paquet Scholarship Fund (50% Scholarship - 50% Endowment)	Linfield School of Nursing	$30,000
Total Education:		**$60,000**

Total Grants Approved in 2021: $499,991

Illustrative Prior Grant Recipients:
Text by Sarah Carratt, Ph.D. & Jonathon Pruneda, Ph.D, OHSU

"Targeted therapies for SETBP1-mutant Chronic Neutrophilic Leukemia"
Sarah Carratt, Ph.D.
Oregon Health & Science University
$30,000 awarded in January 2020

Myeloproliferative neoplasms are a class of blood cancer in which genetic mutations drive an increased production of white blood cells. Prior research by OHSU clinical investigators, including Dr. Brian Druker, has shown that targeting the mutations that cause the white blood cells to proliferate is an effective therapeutic strategy.

In chronic neutrophilic leukemia (CNL), the majority of patients have *CSF3R* mutations. Discovery of these mutations led to the use of ruxolitinib to target signaling driven by the *CSF3R* mutation. In 2020, the first clinical trial for CNL reported a 54% overall response rate with ruxolitinib in those patients with mutant *CSF3R*. To improve response rates in more of these patients, it is likely that we will need efficacious and safe combination therapeutic strategies. As an early-stage investigator, Dr. Carratt wants to transform molecular biomarkers of poor prognosis into opportunities for targeted therapies.

In 2020, the Collins Medical Trust provided funding to Dr. Carratt to investigate strategies for overcoming resistance to ruxolitinib in CNL. The goal of this project was to identify novel therapeutic targets for drug-resistant leukemia. Dr. Carratt investigated a new strategy to target a second mutation in a gene called *SETBP1* that is recurrently mutated in leukemia and is associated with poor prognosis.

SETBP1 mutations drive poor outcomes in atypical chronic myeloid leukemia (aCML), juvenile myelomonocytic leukemia (JMML), chronic myelomonocytic leukemia (CMML), myelodysplastic syndromes (MDS), myelodysplasia/myeloproliferative neoplasm overlap syndrome (MPN/MDS), and secondary acute myeloid leukemia (sAML). *SETBP1* overexpression occurs in about 28% of AML cases as a result of a translocation near the *SETBP1* gene, and leads to shorter overall survival. Therapeutic strategies that eliminate *SETBP1*-driven clonal populations, or sensitize these cells to other agents, would improve long-term therapeutic responses by targeting a biomarker of aggressive, often refractory, leukemia cells.

One of the barriers to therapeutic development for *SETBP1*-mutant leukemias is a lack of appropriate model systems. Dr. Carratt developed a new CNL mouse model where she could evaluate the role of *SETBP1* in leukemia progression, and found that *SETBP1* accelerates leukemia progression by more than nine months. It has been difficult to understand why *SETBP1* causes worse outcomes in patients with leukemia, but using this mouse model and novel cell lines, Dr. Carratt was able to show that *SETBP1* upregulates known drivers of proliferation. Using leukemia cell lines and patient samples, she found that cells with *SETBP1* mutations are susceptible to drugs that target a protein called LSD1. She then showed that these inhibitors reversed SETBP1-driven upregulation of proliferation-associated pathways.

Using two different leukemia mouse models that she developed, Dr. Carratt tested LSD1 inhibitors alone in combination with ruxolitinib. In one model, mice are resistant to ruxolitinib. In the other, mice are sensitive to ruxolitinib, but the treatment does not produce a durable response. Dr. Carratt found that using the combination of these two drugs lengthened survival in both models.

Support from the Collins Medical Trust has fundamentally advanced Dr. Carratt's career in medical research by providing seed funding for an independent research project. She used this data to apply for an NCI K99/R00 Pathway to Independence award, "Targeting oncogenic SETBP1-driven programs to improve outcomes in leukemia," which was submitted in February 2021 and resubmitted in November 2021 (currently pending). These data were also used to successfully apply for a $50,000 American Society of Hematology award, which will fund the investigation of additional therapeutic targets.

Data funded by the Collins Medical Trust are presented in a manuscript that is undergoing peer review at *Blood*, and are available as a preprint on *BioRxiv* (https://doi.org/10.1101/2021.11.04.467367). These data are exciting because they provide preclinical evidence for a combination therapeutic strategy that could be used in a number of difficult-to-treat leukemias.

"Prediction of bacterial effectors targeting the host ubiquitin signaling response"
Jonathan Pruneda, Ph.D.
Oregon Health & Science University
$30,000 awarded in November 2019

A healthy immune response to infection requires rapid and robust signaling following the detection of an invading pathogen. Regulation of these signaling pathways is controlled by post-translational modifications, i.e., changes made to cellular proteins (the workers of the cell) that act as earmarks for directing events like recruitment or activation. One of the most versatile post-translational modifiers used by humans is ubiquitin, which itself is a small protein that is attached to other proteins through a process called ubiquitination. Protein ubiquitination controls many different processes throughout the cell, including degradation of the protein substrate, recruitment of repair machinery following DNA damage, as well as immune signaling following infection. The reason that ubiquitination can control so many different cellular outcomes is that, as a protein in and of itself, ubiquitin can be further post-translationally modified. In fact, ubiquitin can be in turn ubiquitinated, creating an array of ubiquitin chains that differ in the way they are linked together. Each of these unique ubiquitin chain types serve as distinct earmarks that direct an appropriate response. For example, while one type of ubiquitin chain may signal for degradation, another will trigger the DNA damage response. We don't fully understand what each ubiquitin signal means or does in a cellular context, but we do know that the process of ubiquitination is very tightly regulated, and breakdown of this regulation can cause diseases

such as cancer, neurodegeneration, and autoimmunity. The process is so tightly regulated that in some types of signaling, such as the immune response to infection, multiple types of ubiquitin chains are used in sequence to activate a retort. Due to the complexity of this system, we often refer to it as "the ubiquitin code," which reflects the specificity of the signaling language as well as the mystery surrounding the remaining ubiquitin chain types that have yet to be cracked. The ubiquitin code is regulated by 'writers' that assemble it (E1, E2, E3), 'readers' that translate it into a biological outcome (Ubiquitin Binding Domains, UBDs), and 'erasers' that remove it (Deubiquitinases, DUBs).

The ubiquitin system is unique to eukaryotic organisms and thus is absent in things like bacteria. Interestingly (and unfortunately for us), despite not having a ubiquitin system themselves, some disease-causing bacteria have evolved enzymes (proteins that perform a job) that regulate ubiquitination for the specific purpose of altering our signaling responses during infection. These enzymes are transferred into human cells during infection through syringe-like machines called secretion systems. By delivering these enzymes into the host cell, the bacteria are able to manipulate our signaling in order to invade, replicate, and shut down our immune responses. Bacterial enzymes can perturb ubiquitin signaling in many different ways, including redirection, inhibition, or elimination.

In 2019, the Collins Medical Trust provided funding to Dr. Pruneda to explore the methods employed by pathogenic bacteria to remove host ubiquitin signals. **The primary goal of this proposal was to develop computational approaches to predict bacterial DUBs that contribute to infectious diseases**. The first part of this work completed a study of predicted bacterial DUBs, which had been identified through similarity of their amino acid sequence (the building blocks of a protein) to analogous human enzymes. Following from this work, Dr. Pruneda proposed to develop and apply a more sophisticated computational prediction method with the goal of identifying even more examples of bacterial DUBs across diverse species.

As proposed, in 2020 Dr. Pruneda and his team completed their biochemical study of the first group of predicted bacterial DUBs. This work validated DUB activities in human pathogens such as *Legionella pneumophila* and *Burkholderia ambifaria*, as well as in the mosquito endosymbiont *Wolbachia pipientis*. Biochemical experiments narrowed down the type of ubiquitin signal targeted by these bacterial DUBs, which may inform future work on their functions during infection. By determining the molecular structure of several examples, Dr. Pruneda's group was able to identify certain commonalities and differences among the bacterial and related human DUBs, the latter being key for future efforts to therapeutically inhibit these bacterial enzymes. **This work was presented at the Northwest Branch Meeting of the American Society of Microbiology in November of 2019, as well as an international conference on ubiquitin signaling called *Ubiquitin and Friends* that was held virtually in May of 2020**. A manuscript describing this work was deposited as a preprint to the *BioRxiv* server in March of 2020 for immediate dissemination, and following peer-review **was subsequently published in *The EMBO Journal***.

The second aspect of this proposal outlined Dr. Pruneda's plans to improve future efforts to predict bacterial DUBs by developing a more sophisticated computational approach. The group's findings from the initial study on bacterial DUBs showed a surprising diversity in protein sequence, structure, and mechanism. To account for these largescale differences that have arisen through bacterial evolution, Dr. Pruneda's group opted to train a computer algorithm to recognize small underlying features that are common among known DUBs. After the computer algorithm is trained and tested on known DUBs, the next step will be to use the model to predict new examples from a database of pathogenic bacteria. Top scoring predictions will then be selected for follow-up studies that seek to validate DUB activity using

established biochemical assays. If successful, this approach could dramatically change the way virulence factors contributing to bacterial infection and disease are identified. This work formed the Master's thesis project for Justine Nguyen, who has since completed and successfully defended her thesis. **Dr. Pruneda expects to continue this work over the coming year, after which he will disseminate his findings to the public through scientific presentations and peer-reviewed publication.**

This Collins Medical Trust award allowed Dr. Pruneda's laboratory to quickly establish a publication track record and make significant advances toward developing new methods that will feed many new areas of research. **Both of these outcomes contributed greatly to his recent funding applications, including a proposal that was recently funded by the R35 MIRA program at the NIH.** This award is considerable ($250,000 in direct research costs per year) and will fuel Dr. Pruneda's research on bacterial manipulation of host ubiquitin signaling for five years (7/1/2021 – 5/31/2026).

Policies and Procedures

Current submission guidelines are available at http://www.collinsmedicaltrust.org/

Replies to Applications
The Trustees meet three times a year, in January, May and September. Requests should be submitted by the last business day of the month preceding these months to receive timely consideration. It is not possible to react to emergency requests for crash programs. When an application has finally been acted upon by the Trustees, it will be accepted or rejected in writing sent to the mailing address of the applicant by the first week in the following month.

Reports

The organization receiving a grant from the Collins Medical Trust has a responsibility to report on the use of the funds granted. Unless otherwise indicated at the time disbursement is made, reports are requested to be made annually until the entire grant has been expended and the full impact of the grant is realized. These reports should cover not only progress, but also evaluate the results being achieved.

Additionally, throughout the duration of the project, any substantial changes in scope, personnel, or funds that are re-directed from the original purpose, should be reported to the Administrator of the Collins Medical Trust for approval by the Trustees at their next regularly scheduled meeting.

Lastly, the Collins Medical Trust appreciates acknowledgment, primarily in scientific publications, for their contribution in support of the project.

Trustee Biographies

Truman W. Collins, Jr.
Truman is a son of the founder of the Collins Medical Trust (Truman W. Collins, Sr.), and has been a trustee since 1990. Truman earned his undergraduate degree from Willamette University in 1986 and his Master's degree in Computer Science from Stanford University in 1987. In addition to serving as Trustee of the Collins Medical Trust, Truman is the President of The Collins Foundation, and a board member of The Collins Companies. He serves as a trustee of Willamette University, and is a board member of Foundations for Better Oregon.

Elizabeth Eckstrom, MD, MPH
Elizabeth is a geriatrician who specializes in promoting a healthy lifestyle in older adults and in educating all health professionals to be competent in the care of older adults. She is Professor of Medicine and Chief of Geriatrics in the Division of General Internal Medicine & Geriatrics at Oregon Health & Science University in Portland, Oregon. She Co-Directs OHSU's Healthy Aging Alliance.

Her research has focused on interprofessional education, tai chi to improve health in older adults, and fall prevention. She also studies the effectiveness of training primary care faculty in geriatrics, and speaks regionally and nationally on strategies to optimally care for older patients in primary care practice. Personal interests include travel, windsurfing, telemark skiing, gardening, and piano.
Dr. Eckstrom stepped down as a trustee in 2021. The Collins Medical Trust would like to thank her for her 18 years of thoughtful, insightful, and dedicated service as a trustee.

Virginia Tilden, Ph.D, RN, FAAN
Virginia Tilden is professor emerita in the School of Nursing at Oregon Health & Science University. She served as Senior Associate Dean for Research in the School, 1999-2003 and 2012-2021, and as Dean of the College of Nursing at the University of Nebraska Medical Center, Omaha, Nebraska, 2003-2011. She was principal investigator of five NIH funded studies and PI or co-investigator of numerous foundation and professional organization research grants spanning a 40-year research career. She is the author or co-author of 110 scholarly publications primarily focused on improving end-of-life care, clinical teamwork, and interprofessional education. To accelerate the national agenda on collaborative care, she served on boards and advisory committees at the American Board of Internal Medicine Foundation, the American College of Physicians, Primary Care Progress, the American Academy of Nursing, and the Society for General Internal Medicine. She earned her bachelor of science degree from Georgetown University, her master's and PhD degrees from the University of California San Francisco, and her postdoctoral certificate in clinical bioethics from the University of Washington.

John Nutt, MD
John G. Nutt, MD, is a professor of neurology and physiology/pharmacology at Oregon Health and Science University, and director emeritus of the OHSU Parkinson Center and of the Portland VA Parkinson's Disease Research, Educational and Clinical Center.

Dr. Nutt's interests are in motor control and the treatment of Parkinson's disease. His work in experimental therapeutics has been seminal in understanding the intricacies of levodopa actions in Parkinson's and in exploring other symptomatic and disease-modifying therapies for the disease. Another major interest is in gait and balance. He developed a classification system for these disorders that has influenced all subsequent work in this area. Other studies focus on the mobility problems in

Parkinson's disease including understanding the pathophysiology of "freezing," developing methods to measure gait and balance for interventional clinical studies, and treatment of balance and walking problems. Dr. Nutt is a widely recognized movement disorder clinician, included in Best Doctors for the past 11 years.

Ryan Luria, MSW

Ryan Luria is a member of the Collins family in the third generation since the Collins Medical Trust's founding. He graduated from Pomona College with a BA in English and earned an MSW from Portland State University. He has worked as a case manager and mental health therapist. In addition to serving as a Trustee of the Collins Medical Trust, Ryan serves as a Trustee of The Collins Foundation. He also sits on the boards of Catlin Gabel School and the Quest Center for Integrative Health. He lives in Portland with his wife, Sacha, and their three children.