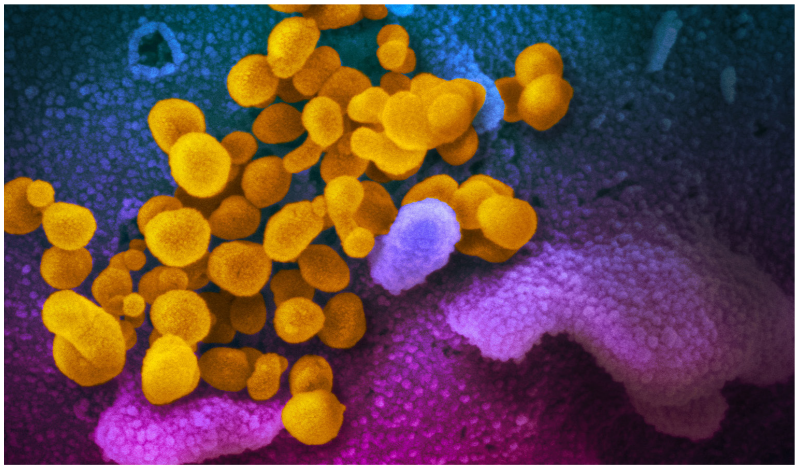
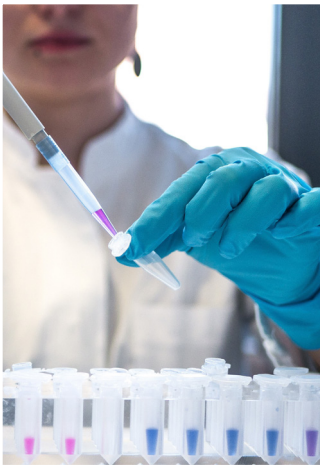
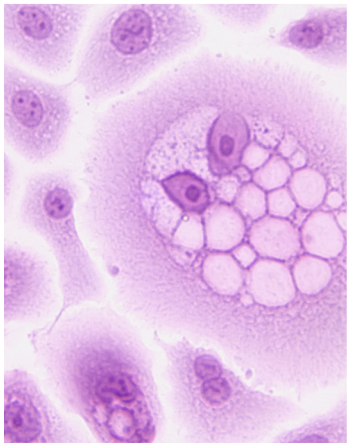
Siebel Stem Cell Institute

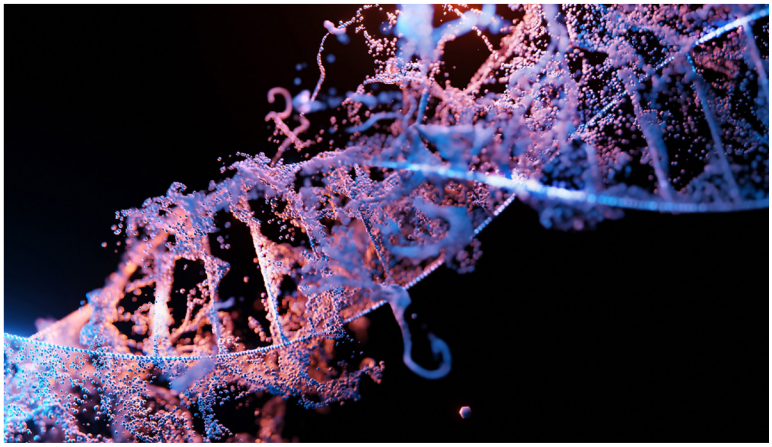
ANNUAL REPORT

2021









A COLLABORATION BETWEEN

UNIVERSITY OF CALIFORNIA, BERKELEY

AND STANFORD UNIVERSITY

CONTENTS

INTRODUCTION

With deep gratitude to Tom and Stacey Siebel and the Thomas and Stacey Siebel Foundation, we are pleased to share the 2021 annual report on the Siebel Stem Cell Institute. Since the Institute's founding at UC Berkeley and Stanford University in 2008, affiliated researchers have made meaningful progress toward leveraging the enormous therapeutic potential of stem cells to improve human health and wellbeing. This report features an overview of the work and potential real-world applications of the Siebel Stem Cell Institute's community of scientists who are pioneering this critical line of research.

Throughout 2021, the Institute continued to sustain a select group of the two universities' established and early-career biologists, physician-scientists, geneticists, computer scientists, and engineers in their efforts to make substantive advances in regenerative medicine. In this report, we share these findings, which include new insights into the artificial growth of organs, the usage of stem cells to treat sickle cell disease, and the understanding of gene expression to create better-targeted treatments for obesity and the diseases it can cause.

The research conducted with Siebel Stem Cell Institute support has tremendous potential for addressing human conditions and diseases such as Alzheimer's, autism spectrum disorders, cancer, sickle cell disease, Parkinson's, PTSD, vision loss, and degenerative changes associated with aging.

Here are some highlights of the research pursued by the Siebel Stem Cell Institute community in 2021:

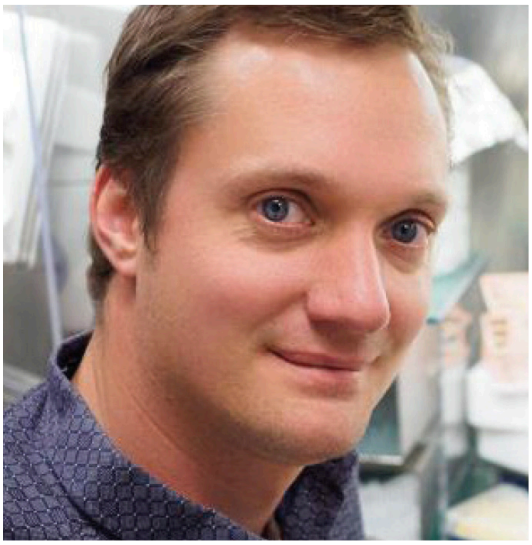
- Berkeley Siebel Fellow Andrew Modzelewski and Thomas and Stacey Siebel Distinguished Chair Lin He discovered a remarkable early embryonic role for retroviruses that have been evolutionarily incorporated into mammalian genomes and used retrovirus expression to illuminate the gene regulatory network responsible for specifying embryonic and extraembryonic tissues critical to the healthy early development of mammalian embryos. Their fundamental work could have implications for human infertility, and is helping to uncover the diverse and surprising functions of genetic "dark matter."

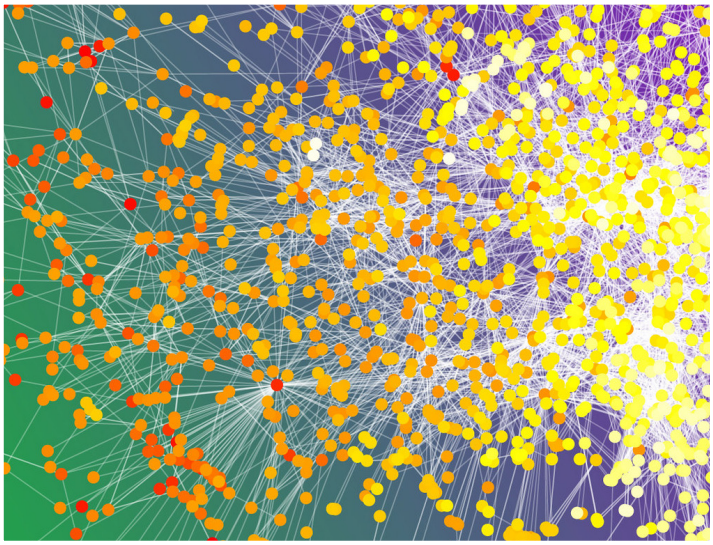
- Siebel Investigator Lay Teng Ang's lab at Stanford Medicine demonstrated that embryonic stem cell-derived human liver progenitors can engraft the injured mouse liver, regenerate human liver tissue in vivo, and partially improve survival. With the generation of pure populations of human liver cells from induced pluripotent stem cells, we hope to provide a source of liver cells for transplantation into patients in need.
- Working in collaboration with Dr. Mark Walters at UCSF and other Berkeley investigators at the Innovative Genome Institute (IGI), former Berkeley Siebel Institute Postdoctoral Fellow Mark DeWitt initiated an NIH- and CIRM-funded clinical trial using CRISPR-based gene editing to work toward a cure for sickle cell disease.
- The Ang lab at Stanford also generated pure populations of human artery and vein endothelial cells from embryonic and induced pluripotent stem cells. A large supply of human endothelial cells could drive diverse applications, such as modeling of cardiovascular diseases and vascularizing organoids or tissues for regenerative medicine. In collaboration, the Ang and Loh labs used the generated arterial stem cells to study the effects of the Nipah and Hendra viruses. These viruses, like Ebola, are hemorrhagic diseases that are highly infectious and kill more than half the people they infect with little or no effective treatment options currently available.

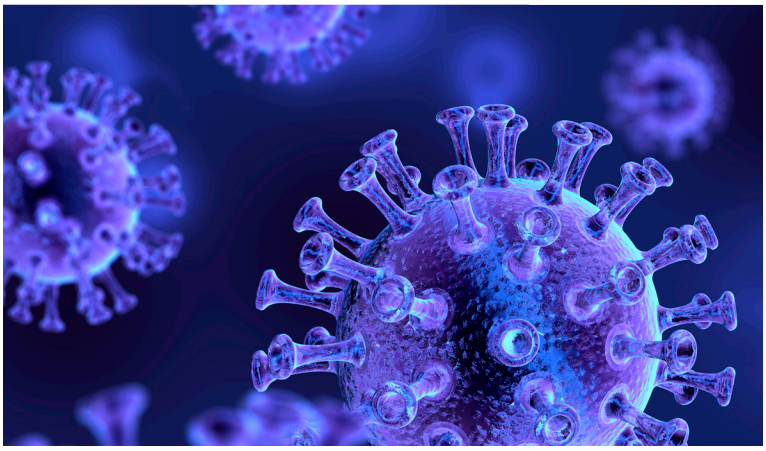
- Berkeley Professor of Bioengineering Kevin Healy and 2018–19 Siebel Scholar Verena Charwat engineered a stem cell-derived 3D micro physiological heart and liver cell "dual organ on a chip" and demonstrated its ability to predict toxic drug interactions. This major innovation enables the screening of cardiac drug candidates to predict unsafe interactions.

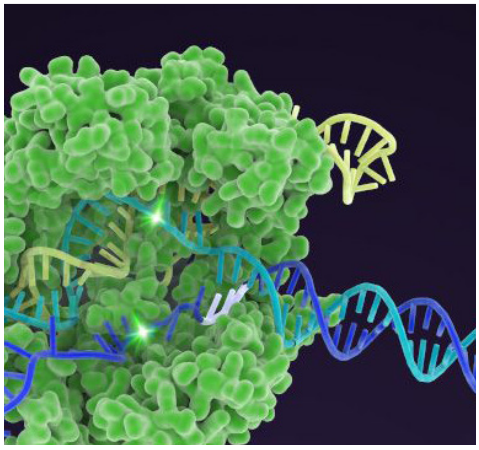
As this remarkable enterprise continues to grow and evolve, we remain committed to the founding principles of the Siebel Stem Cell Institute — to leverage the therapeutic potential of stem cells to improve human health. It is with tremendous thanks to Tom and Stacey Siebel and the Thomas and Stacey Siebel Foundation that we share the following overview of our work from 2021 and the promising and exciting new directions we're pursuing in regenerative medicine.


ENGINEERING









SIEBEL STEM CELL INSTITUTE: BERKELEY

"The Siebel Stem Cell Institute is a proven stepping stone for researchers studying and applying stem cell and gene therapy," says Berkeley Stem Cell Center Director Dirk Hockemeyer. "This science has profound implications in the real world and ongoing investments by the Siebel Stem Cell Institute have made it possible to bring together the best minds in the field."

In 2021, the postdoctoral Siebel Scholars at the UC Berkeley Siebel Stem Cell Institute continued to advance critical research that aims to reveal the underlying causes of a wide array of diseases and challenges to human health. Their work makes a vital contribution toward developing therapeutics and strategies that improve lives and increase longevity.

Selected for the promise of their research, these Siebel Scholars made advances toward realizing the goal of transforming insights in stem cell science into effective technologies and treatments. Siebel Scholars worked in concert with other researchers at the Berkeley Stem Cell Center to identify and harness the extraordinary potential of stem cells to prevent and cure disease.

The outstanding research by the investigators associated with the Siebel Institute was instrumental to director Dirk Hockemeyer's successful proposal of a $5 million five-year training grant awarded by the California Institute of Regenerative Medicine in 2020. This training grant has enabled the Siebel Stem Cell Institute at Berkeley to resume awarding seed grants that support research efforts with tremendous potential before they are developed adequately for consideration by external funding agencies, while continuing to support early career scientists.

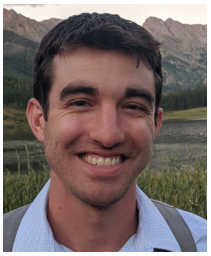
SIEBEL SCHOLARS

Benjamin Fellows

PH.D. MATERIALS SCIENCE AND ENGINEERING
CLEMSON UNIVERSITY
STEVEN CONOLLY LABORATORY

Tracking the fate of transplanted stem cells

Benjamin Fellows and faculty mentor Steven Conolly are working toward using high-resolution magnetic particle imaging (MPI) to track and monitor the engraftment of Cas9 edited hematopoietic stem cells used to treat sickle cell disease. MPI is potentially an ideal imaging modality to track the fate of transplanted cells because the magnetic tracer stays bright indefinitely, and each cell provides an identical signal anywhere in the body with zero depth attenuation. As a Siebel postdoc, he achieved reproducibly efficient synthesis of new "super ferromagnetic" tracers that will improve current resolution by an order of magnitude and progressed towards the challenging goal of encapsulating them in biocompatible materials without reducing their essential ability to reversibly interact within a magnetic field. Their goal is for MPI is to become an essential imaging tool in achieving stem cell-based cures for hematopoietic diseases.

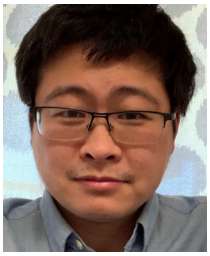


Jake Flood

PH.D. CELL/CELLULAR AND MOLECULAR BIOLOGY
UNIVERSITY OF COLORADO, BOULDER
JOHN DUEBER AND DAVID SCHAFFER LABORATORIES

Investigating cell lineage tracing to further understanding of human organ development

Recent advancements in cell culture technologies have enabled the development of artificially grown organs including the liver, kidney, and brain. These 3D cultures, called organoids, facilitate the study of organ development and a wide variety of human diseases. Flood's research improves upon a tool newly developed in the John Dueber lab, EvolvR, that enables investigators to apply cell lineage tracing to better understand human organ development. By studying how EvolvR interacts with host DNA repair factors, he was able to engineer improvements which resulted in a 1000-fold increase in EolvR's efficiency. This method is now being employed in the lab to better understand stem cell differentiation in developing organoids and may contribute to the ability to grow replacement tissues and organs in the laboratory.



Hanquin Li

PH.D. NEUROSCIENCE
STATE UNIVERSITY OF NEW YORK AT BUFFALO
DIRK HOCKEMEYER LABORATORY

Engineering a novel system to study the functional significance of human genetic variation

Millions of genetic variants have been identified in the human population. Many of these are predicted to be associated with diseases, but methods for testing these predictions are lacking. Li and faculty mentor Dirk Hockemeyer devised a high throughput CRISPR-based method of reproducing genetic variants of interest and examining their functional significance by deleting one copy of the gene of interest and introducing specific genetic changes to the remaining gene copy. As proof of principle, Li and collaborators generated human embryonic stem cell lines containing mutations corresponding to the top two variants predicted to affect the levels of fatty acid desaturases (FADS), enzymes that control fatty acid production, and demonstrated that these variants led to altered levels of FADS expression. This method enables rapid and efficient testing of the functional significance of observed genetic variants and may be used to guide the design of genome engineering-based corrective therapies.

Andrew Modzelewski

PH.D. GENETICS, GENOMICS AND DEVELOPMENT
CORNELL UNIVERSITY
SIEBEL STEM CELL INSTITUTE FELLOW
LIN HE LABORATORY

An unexpected role for retroviruses in normal mammalian embryogenesis

Andrew Modzelewski's research in the laboratory of faculty mentor Lin He, Siebel Distinguished Chair in Stem Cell Biology, targets the initial development of the fertilized egg into cells that will comprise the embryo or its supporting tissues. It has long been recognized that mammalian genomes include DNA originally derived from retroviruses. Originally considered inert "junk," these sequences of viral origin have more recently been recognized to be actively expressed to generate RNA. The early embryo is a particularly rich site of endogenous retrovirus gene expression, but why? Modzelewski demonstrated for the first time that co-option of retroviral gene expression is an essential contributor to the normal program of mammalian embryogenesis. During a precise 24-hour period in mouse preimplantation development, retroviral gene MT2B2 is spliced to a cell cycle regulating gene to create a hybrid protein required for embryos to properly implant in the uterus. He then showed that remarkably, other placental mammals including primates have co-opted unrelated retroviral genes in this same way to ensure proper embryonic implantation. This work was published in the prestigious journal *Cell*.

Lin Qi

PH.D. BIOMEDICAL/MEDICAL ENGINEERING
OHIO STATE UNIVERSITY
ANDREAS STAHL LABORATORY

Developing a platform to understand adipose metabolism and reduce the prevalence of obesity

Obesity is widespread worldwide, and greatly increases the risk and severity of diseases ranging from type-2 diabetes mellitus, fatty liver disease, and kidney dysfunction. A critical feature of these obesity-driven diseases is insulin resistance in skeletal muscle and white adipose tissue (WAT). To facilitate the rapid screening of pharmacological and environmental compounds for beneficial or detrimental effects on insulin sensitivity, Qi optimized a protocol to efficiently differentiate human induced pluripotent stem cells to WAT, functionally comparable to primary cells, in a micro-sized platform, and established three independent on-chip assays to assess insulin sensitivity. As a proof-of-concept, this device was used to successfully screen known insulin sensitizing and desensitizing compounds, showing its potential in pharmacological applications to combat obesity and its consequences.

Nike Walther

PH.D. BIOPHYSICS AND MOLECULAR AND CELL BIOLOGY
HEIDELBERG UNIVERSITY
ROBERT TJIAN/XAVIER DARZACQ LABORATORY

Applying leading-edge imaging technology to understand intestinal tissue formation

Throughout organ formation and adult tissue renewal, genes must be turned on and off at the correct time and at the correct location within a tissue. The self-renewing mammalian intestinal epithelium provides a unique model to study gene regulation since differentiation progresses linearly from stem to mature cell types within only a few days. Using intestinal organoids that reconstitute this behavior in the dish, Walther applies quantitative live imaging methods to understand how 3D genome organization affects gene expression as cells differentiate. As a Siebel postdoc, Walther has developed the molecular tools required for these studies and have acquired proof-of-principle imaging data. When completed, these studies will enable Walther and others to derive mechanistic models of how cell fate decisions and cell type transitions are controlled in the small intestine in health and disease.

SIEBEL DISTINGUISHED CHAIR

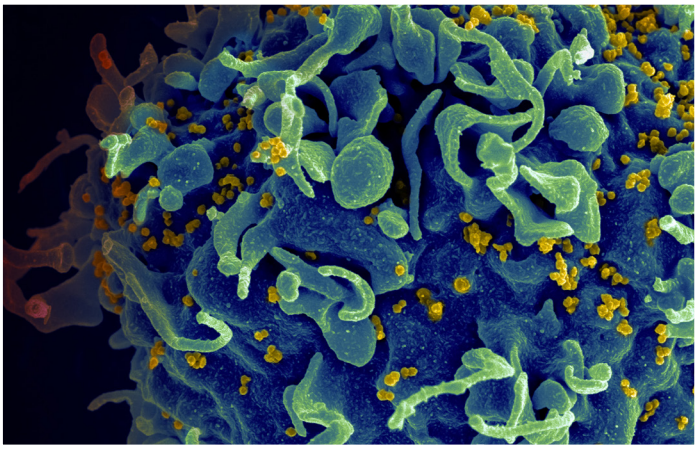
The Siebel Distinguished Chair was established at UC Berkeley in 2007 with funding from the Siebel Foundation in order to honor outstanding stem cell researchers and to enable them to pursue high-risk, potentially transformative new ideas.

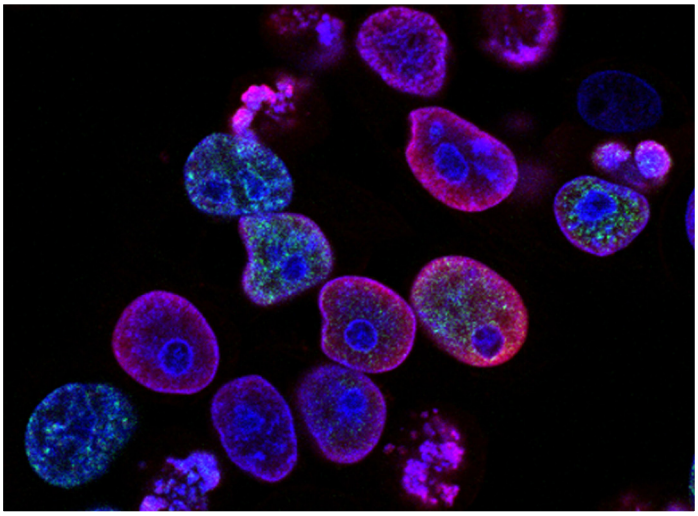
Lin He

THOMAS AND STACEY SIEBEL DISTINGUISHED CHAIR IN STEM CELL RESEARCH
PROFESSOR OF CELL AND DEVELOPMENTAL BIOLOGY

Revealing the behavior and function of noncoding RNAs

Thomas and Stacey Siebel Distinguished Chair in Stem Cell Research Lin He studies the functional importance of noncoding RNAs in development and disease, combining mammalian genetics, genomics, cell, and molecular biology approaches. The focus of He's lab is to understand the biological functions of the regulation of various non-coding elements, in order to dissect the functional interplay between protein-coding genes and non-coding elements in development and disease, specifically involving preimplantation embryos, cilia biology, cancer biology, and stem cells. A key event in early embryogenesis is the establishment of two distinct lineages, one for cells that will become the embryo proper and one that will form the extra embryonic tissues such as the placenta. Blastomere cells that are still able to follow either lineage are termed bipotent. Extending their previous studies identifying noncoding RNAs as key markers of bipotent cells, the He group recently identified the gene regulatory network that controls this essential step in mammalian development. Their study, published in *Cell Reports*, showed that the transcription factors Klf5 and Klf4 are essential in this process, and demonstrated that by experimentally increasing Klf5 levels mouse embryonic stem cells can be returned to the earlier, bipotent cell fate.





BERKELEY SIEBEL STEM CELL INSTITUTE NEWS

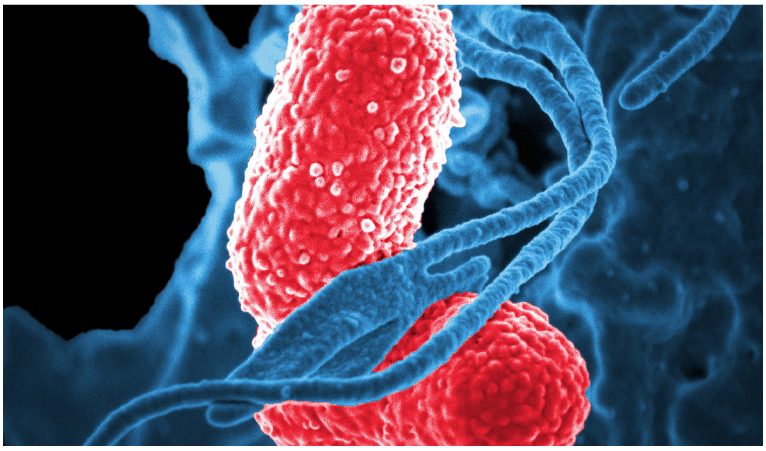
Postdoctoral Fellow **Verena Charwat**, her mentor Kevin Healy and colleagues have created three-dimensional, stem-cell-derived "organs" cultured in small microfluidic devices, enabling the simultaneous testing of numerous tiny cell cultures. In a major innovation published in *Frontiers in Pharmacology*, they developed a microfluidic device containing both heart and liver cells differentiated from genetically identical induced pluripotent stem cells. This device enables the screening of cardiac drug candidates for potentially toxic or inactivating chemical modifications by the liver, as well as cardiotoxicity testing of drugs in a wide range of human genetic backgrounds before embarking on a clinical trial.

Mark Walters, Jordan Family Director of Hematology and Oncology at UCSF Benioff Children's Hospital and collaborators at UC Berkeley's IGI and UCLA School of Medicine received FDA approval for an NIH and CIRM-funded human clinical trial aimed at curing sickle cell disease. The trial will use CRISPR-based genome editing of patients' own blood forming stem cells to correct the single nucleotide error in the hemoglobin gene that is responsible for the debilitating and life threatening effects of this genetic condition. Gene edited stem cells will be returned to the patient's bone marrow where they are expected to engraft and produce red blood cells with correctly functioning hemoglobin, preventing sickling behavior and its pathological consequences. The genome editing aspect of this project was initiated at the IGI by former Siebel Postdoctoral Fellow **Mark DeWitt**, in collaboration with his mentor, Jacob Corn and Dr. Walters. Dr. DeWitt is now instrumental to the UCLA portion of this collaboration as scientific project manager. Researchers are recruiting patients for treatment in Oakland and Los Angeles, beginning with up to six adults with sickle cell disease. If found to be safe and effective, it will expand to enroll three adolescents aged 12 to 17 years old. Seven patients are expected to be treated in Oakland and two at UCLA.

David Schaffer, professor of chemical and biomolecular engineering, bioengineering, and neuroscience and previous director of the Berkeley Stem Cell Center, has been named a fellow of the National Academy of Inventors, the highest professional distinction accorded solely to academic inventors. He was honored for his groundbreaking body of work in pioneering the use of engineered viruses to deliver gene therapies. Schaffer's leading-edge work has significantly furthered the development of novel gene and cell therapies to treat currently incurable human diseases.

Upon completing his appointment as a 2021 Siebel Fellow, **Andrew Modzelewski** joined the faculty of the University of Pennsylvania School of Veterinary Medicine, where he will continue his research into the role of retrotransposon reactivation in mammalian preimplantation development, reproduction, and disease.


Cell



SIEBEL CELL INSTITUTE AT STANFORD

Support from the Thomas and Stacey Siebel Foundation continues to encourage bold and creative stem cell and regenerative medicine research at Stanford. In 2021, the Siebel Stem Cell Institute at Stanford was fully transitioned to the Siebel Investigator model, supporting promising early career investigators, their trainees, and staff. "We remain deeply grateful to the Thomas and Stacey Siebel Foundation for their philanthropic investment in young scientists through this model," says Dr. Weissman. "It's giving early career researchers a reliable funding platform for themselves and their lab teams from which they can investigate novel ideas and pathways that will impact human health."

The payoff from early support is often measured in decades rather than years. Dr. Weissman remembers "The early programs of Charles Chan, Mike Longaker, and me on the origin and transplantation of mouse, then human bone and cartilage stem cells in health and disease seemed to be filled with barriers. But in the past few years year these bone stem cells, cartilage stem cells, and the skeletal stem cell that gives rise to them have been isolated and proven to be regenerative on their own or with the help of known growth factor cytokines. And the early work on leukemia stem cells by me and Ravi Majeti and our students Siddhartha Jaiswal, Mark Chao, and postdoctoral fellow Catriona Jamieson at the beginning of Siebel support have evolved to identify 'Don't eat me' signals on the cancers which, when blocked, have by now led to therapeutic monoclonal antibodies in late stage clinical trials that treat formerly incurable acute leukemias, preleukemic age related myelodysplasia, and therapy resistant aggressive lymphomas" says Dr. Weissman.

Dr. Majeti recently stepped down from being chief of hematology at Stanford Medicine to succeed Dr. Weissman as the director of the Stanford Institute of Stem Cell Biology and Regenerative Medicine; Dr. Jamieson is director of the UCSD Sanford Stem Cell Clinical Center and deputy director of its Moores Cancer Center and brought forward new therapies for myeloproliferative diseases; Dr. Jaiswal co-discovered with Dr. Ben Ebert at Harvard that as we age, single blood stem cells that acquire single mutations [shown by Majeti, Weissman, and team to also be the first step in the development of acute myelogenous leukemia] that leads to the development of daughter cell clones that predispose the individuals to all of the above blood diseases as well as atherosclerosis and more; and Dr. Chao led the clinical development

of magrolimab, the blocker of don't eat me signal CD47 at Forty Seven, Inc and Gilead, and is now CEO at a new company founded by Jaiswal.

And, this past year investigator Lay Teng Ang and the Ang Lab advanced new research demonstrating that the efficient and rapid generation of stem-cells could be used in critical research on deadly hemorrhagic viruses. "Support from the Siebel foundation is an inspiration for my entire lab team," says Dr. Ang. "It's a wonderful foundation from which we can build and grow a premier research lab at Stanford."

SIEBEL INVESTIGATOR PROGRAM

Ang Laboratory

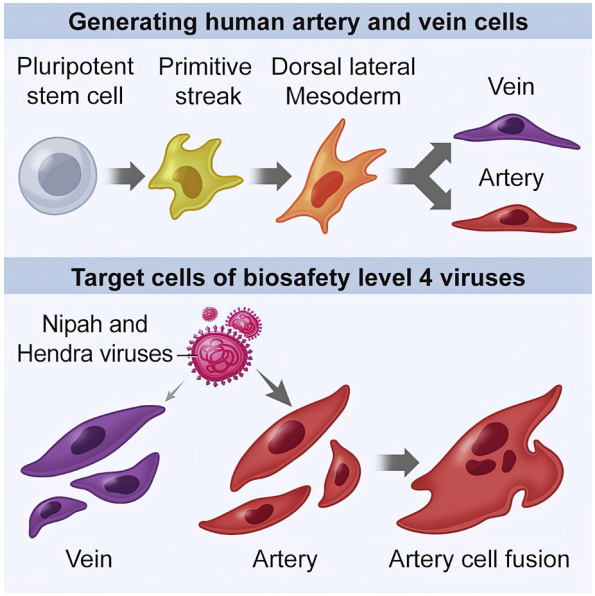
LAY TENG ANG
ASSISTANT PROFESSOR, DEPARTMENT OF DEVELOPMENTAL BIOLOGY
INSTITUTE FOR STEM CELL BIOLOGY AND REGENERATIVE MEDICINE

Generating artificial human blood vessels to study deadly viruses

Dr. Ang has received support from the Siebel Stem Cell Institute since 2018, enabling her to establish and expand her stem cell and regenerative focused research lab. Recently, this support enabled Dr. Ang and her team to create artificial human blood vessels in a Petri dish, and to study the Nipah virus — one of the world's deadliest — which attacks blood vessels.

The ability to generate highly pure blood vessel cells (such as artery and vein cells) from human embryonic stem cells is fundamentally important. Blood vessels pervade every organ of the human body and play key roles in health and disease. Human embryonic stem cells are attractive sources of artery and vein cells since they can be grown in large numbers in a Petri dish.

However, one bottleneck is that embryonic stem cells can also make non-blood vessel cell-types and hence efforts to make artery and vein cells often result in impure cell mixtures. The Ang lab addressed this challenge by discovering the combinations of signals, which need to be precisely activated or inhibited within short spans of time, to generate artery and vein cells. Together, this enabled the Ang lab to generate human artery and vein cells with unprecedented purity (>90%) and speed (within three to four days).



Generating human artery and vein cells.

Dr. Ang then exploited these artery and vein cells to study viruses that attack blood vessels. In collaboration with Dr. Kyle Loh, a previous Siebel awardee, Dr. Ang examined the Nipah and Hendra viruses. Both are in the same virus family as Ebola. While Hendra virus infections in humans are rare, Nipah is a highly infectious hemorrhagic disease that kills more than 59% of infected individuals. Devastatingly, the Nipah virus is spread by air between humans and no treatments or vaccines exist. Nipah virus is listed by the World Health Organization (WHO) as one of the top nine pathogens around the world that could cause a pandemic.

In studying a normal virus, a pathologist might take samples after a patient's death and examine them under a microscope to see how the cells have been disrupted. But Nipah, classified as a biosafety level four (BSL4) virus, can only be studied in highly secure, negative pressure BSL4 labs where scientists must wear full-body "space suits" to protect themselves at all times. By contrast, the coronavirus that causes COVID-19 is a BSL3 virus.

Dr. Ang working in the biosafety level 4 (BSL4) lab

Dr. Ang collaborated with Dr. Joseph Prescott, a BSL4 virologist at the Robert Koch Institute, to apply the stem cell-derived artery and vein cells to study Nipah virus. Together, they demonstrated that Nipah virus preferentially attacks artery (rather than vein) cells. This was a surprising outcome, since scientists previously thought that viruses attacked all blood vessels equally. The virus induced individual artery cells to fuse together into gargantuan, swollen "super cells" containing the contents of 23 individual cells, which then rapidly died. Unexpectedly, as they were infected and killed by Nipah virus, artery cells were almost completely unaware that they were virally infected and failed to turn on alarm bells or antiviral defenses.

Dr. Ang's research was the first to demonstrate the power of stem-cell-derived cell types as toolkits to study the effects of deadly BSL4 viruses in a dish. In June 2022, the research results from these studies were published in the journal *Cell*. Key takeaways from the published article include:

- Efficient, rapid generation of >90% pure human artery and vein cells in three to four days
- Precisely inducing artery cells by blocking vein-specifying cues and vice versa

- Nipah and Hendra viruses preferentially infect artery (rather than vein) cells
- Human pluripotent stem cells provide a new platform for BSL4 virology

This work would not have been accomplished without generous support from the Thomas and Stacey Siebel Foundation.

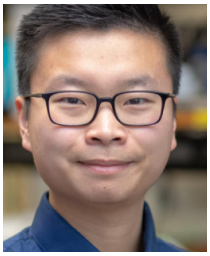
THE ANG LAB FELLOWS AND TRAINEES

The Stanford Siebel investigator program provides comprehensive support for the lab of an early career faculty member. Several talented young researchers and continuing trainees worked in the Ang lab this year. Dr. Ang has also been a champion of her trainees; over the past four years, she has mentored several young trainees including Kevin Liu and Alana Nguyen. Both of whom have gone on to pursue doctorate programs, at Stanford and UC Davis, respectively. They are also co-first authors of the recently published *Cell* article.

Jun Jiang

PH.D., PEKING UNIVERSITY

Jun Jiang, a postdoctoral fellow, obtained his Ph.D. from Peking University. There, he focused on how different branches of the cellular signaling pathway corporate to respond to different levels of the ER (endoplasmic reticulum) stress and how to utilize it to induce cancer cell apoptosis. He discovered that the IRE1 branch and the PERK branch show different sensitivities to the ER stress. He is now interested in liver regeneration and immune mechanisms of viral infection. He hopes to develop the disease model based on stem cells and discover basic underlying mechanisms.



Kevin Liu

M.S., UNIVERSITY OF SOUTHERN CALIFORNIA

Kevin Liu is interested in using stem cells to derive bladder epithelial progenitors for cell replacement therapy in patients with bladder cancer. In addition, he is interested in the mechanism behind how stem cells differentiate into pure liver cells for liver transplantation and effective drug testing. He hopes to learn more about the mechanism behind how stem cells differentiate into pure liver cells for liver transplantation and effective drug testing. Liu is a current Ph.D. candidate at the Stanford School of Medicine.

Alana Nguyen

M.S., SAN JOSE STATE UNIVERSITY

Alana Nguyen, San Jose State University, has worked on projects seeking signaling pathways and markers distinguishing vein vs. arteries in endothelial-derived hESCs as well as the formation of HSCs from hESCs. As a CIRM Scholar at Stanford University, she explored the generation of human T cells from embryonic stem cells for potential cancer immunotherapy. Alana is currently an integrative pathobiology Ph.D. candidate at UC Davis.

CONCLUSION

In 2021, the Siebel Stem Cell Institute at Berkeley and Stanford continued to advance the wide array of research endeavors aimed at unleashing the therapeutic potential of stem cells. By creating and sustaining the Institute, the Thomas and Stacey Siebel Foundation ensures that talented scientists at all stages of their careers can develop new insights as they work to address some of the most intractable challenges to human health and longevity. Thanks to the Siebel Foundation's steadfast support, this community of trailblazing scholars is helping to bring the extraordinary potential of regenerative medicine to the service of those in need and advancing the Institute's highest goals by cultivating a healthier human future.

APPENDICES

APPENDIX A: MAKENA CAPITAL MANAGEMENT Q4 FUND REPORT

Partner Information	
Investment:	**Makena Endowment Portfolio - Makena Capital Associates (U.S.), L.P.**
Investor name:	The University of California Berkeley Foundation The Siebel Stem Cell Institute
Investor number:	2249
Quarter ending:	December 31, 2021

Performance

	Q3 2021 Final	Q4 2021 Preliminary[3]	Year-to-date Preliminary[3]
Net return[1]	2.50%	0.08%	13.85%
Projection[2]		*0.9% to 2.4%*	*14.6% to 16.2%*
% Reported[3]	*100%*	*61%*	*61%*

Estimated Capital Account Activity

	Current Quarter	Year-to-date
Preliminary capital balance as of September 30, 2021	$ 5,125,978	
Valuation adjustments	96,292	
Final capital balance, beginning of period	$ 5,222,270	$ 4,590,832
Contribution	-	-
Distributions and withdrawals	(1,000,000)	(1,000,000)
Tax withdrawals	(54)	(78)
Transfers and assignments	-	-
Rebalance Transactions	-	-
Net capital activity	4,222,216	3,590,754
Income (loss)	21,503	680,126
Management fee	(3,186)	(10,819)
Priority allocation	(13,958)	(13,958)
Net income (loss)	4,358	655,349
Incentive fee	(131)	(19,660)
Preliminary capital balance as of December 31, 2021	$ 4,226,443	$ 4,226,443
Fee waiver, subject to contingent reallocation	-	-
Preliminary balance as of December 31, 2021, net of fee waiver	$ 4,226,443	$ 4,226,443

Disclosures

[1] Net of all fees except fee waiver.

[2] Projected performance is based on projections for each unreported asset class. Projections are calculated for each asset class using a variety of sources including, but not limited to, manager estimates and public markets. Projected performance is shown net of all fees.

[3] % Reported represents the actual valuations received from managers at the time of the publication of this capital statement. Remaining values will be updated in the following quarter capital statement.

The net returns and the capital account balance set forth above are preliminary, estimated and unaudited. The net performance estimates reflect the deduction of all expenses including estimated incentive fees. Final reported capital account balance and performance may vary considerably from these estimates. Additionally, a significant percentage of our portfolio has not reported results for the period covered by this report. Past performance is not indicative of future results, which may vary.

The information contained herein has been prepared solely for informational purposes and does not constitute an offer to sell or the solicitation of an offer to buy any security; it is neither a prospectus nor an advertisement, and no offering is being made to the public. Investments in the fund are subject to significant risks (including risk of total loss) and should be carefully reviewed.

Please contact Rossella Curci of Makena Capital Management at (650) 926-0510 or clientoperations@makenacap.com with any questions or inquiries.

Totals may not sum due to rounding.

APPENDIX B: FUND ACCOUNT AND SUMMARY REPORT

OCTOBER 1, 2020 TO SEPTEMBER 30, 2021

Account Balance History	Berkeley	Stanford
Beginning Balance (October 1, 2020)	$954,212	$1,043,622
Fund distribution Berkeley (January 27, 2021) Stanford (January 31, 2021)	$500,000	$500,000
Expenditures		
Scholar Support	$411,492	$313,280
Seed Grant Collaborations, Equipment and Supplies	$21,306	$213,569
Operational Support	$21,851	$139,592
Total Expenditures	$454,649	$666,440
Ending Balance (September 30, 2020)	$999,563	$877,181