

THE UNIVERSITY OF MICHIGAN Center for Organogenesis

ORGANOGENESIS



STEM CELLS & REGENERATIVE MEDICINE

TRAINEE HANDBOOK

**For NIH and Non-Traditional
Fellowships**

2016-2017

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I. MESSAGE FROM THE PROGRAM DIRECTOR

Welcome to the Center for Organogenesis (CFO). We are happy to have you join our Research Training Program. Our goal is to help you prepare for an independent research career in the clinical, applied or basic sciences. We know that your individual progress is essential to the continued success of our research program itself. The maintenance of an environment that enriches your scholarly growth is of the utmost importance to us. We encourage you to take advantage of all that is available here. Also, we welcome your input; please suggest ways that we can improve our program.

As Project Director, I have overall responsibility for the Organogenesis Training Grant Program. Dr. Linda Samuelson serves as the Associate Director of the Training Program. Dr. Ivan Maillard will serve as Director of Clinical Co-mentorships, an optional opportunity described further in this handbook. Your faculty mentor will supervise your day-to-day activities. Scott Barolo, Ph.D. serves as faculty ombudsperson.

We hope that you will find this orientation booklet helpful in acquainting yourself with the resources available through the CFO. Retain it for future reference. It includes brief summaries of our research programs, as well as introductions to other trainees. In addition, there are descriptions of facilities and administrative procedures at CFO.

With all best wishes for a rewarding year.

A handwritten signature in black ink, appearing to read "Deneen Wellik". The signature is fluid and cursive, with a large initial "D" and "W".

Deneen Wellik, Ph.D.
Director, Organogenesis Training Program
Professor, Internal Medicine and Cell & Developmental Biology
Director, Center for Organogenesis

II. CFO RESEARCH TRAINING PROGRAM

"Organogenesis" unites research in the clinical, basic and applied sciences, translational science and applied arenas with a common goal:

To understand the basic mechanisms by which organs and tissues are formed and maintained, and to use this knowledge to create long-lasting artificial organs, improved stem cell therapies and effective organ transplantation systems that will correct acquired and genetic human diseases.

Advances in organogenesis will demand fluent interdisciplinary cross-talk among basic, applied and clinical scientists. Importantly, such cross-talk will accelerate the speed at which important findings in basic research are translated into therapeutic advances in the clinic. At the same time, the constant exchange of information between basic and applied scientists will trigger important improvements in *in vitro* models for the study of organ development, function and disease.

These are exciting times, as the genome projects are providing vast opportunities for functional analysis of genes. It has been estimated that 50% of the genome is devoted to sequences that encode molecules required during processes of organogenesis. But for the vast majority of genes, function has yet to be assigned. Moreover, it is clear that single genes can give rise to multiple protein isoforms, which in many cases have distinct functions. Thus, discovery of the signaling networks that control development and homeostasis of any single organ is a major challenge for the future. Research in model organisms will provide important clues. Already, work in the fly has correctly identified many of the genes required to make a human heart; work in the frog has led to an understanding of how the embryo knows anterior from posterior and dorsal from ventral; the genetic basis of apoptosis was first identified in the worm; plants are now providing clues to innate immunity; and through the study of mutations in zebrafish, genes have been identified that lead to organ malformation or dysfunction and the human counterparts of these same genes cause similar human diseases and birth defects. The assignment of gene function and the clarification of regulatory networks will continue to benefit from our ability to explore and exploit such model systems.

We are also beginning to see the clinical possibilities afforded by several of the secreted molecules discovered in various developmental systems. Such molecules are now being used to promote the growth of blood vessels in diseased hearts, to allow the culture and amplification of bone marrow stem cells for transplantation, and to create prosthetic bone grafts that will promote local generation of new healthy bone. The study of secreted factors used during development in the embryo (e.g., the Wnt and Hedgehog proteins) are providing new information on the cellular pathways that lead to cancer. Past the gene level, research in tissue engineering is leading to development of new strategies for maintaining, expanding and differentiating stem cells in culture, for healing difficult fractures, for correcting major skeletal defects, and for developing artificial eyes, ears, teeth, kidneys, livers and intestines.

As we look to a future in which the importance of interdisciplinary work in the biomedical sciences is increasingly stressed, it is important to identify strategies to help the next generation of scientists to successfully navigate an increasingly complex research landscape. The training program in Organogenesis was therefore initiated with two major objectives:

- * To provide intellectual and technical training in the field of organogenesis.
- * To promote interdisciplinary thinking by exposing trainees to research that crosses boundaries between the clinical, basic and applied sciences.

The training program in Organogenesis operates within the context of the richly interactive environment provided by the CFO. The activities of the Center are designed to foster the training program and promote the intersection and involvement of trainees with all aspects of Center functions.

Training faculty are chosen from among the >120 faculty members of the CFO from the following schools and colleges, and disciplinary units:

- * **College of Engineering:** Departments of Biomedical Engineering, Chemical Engineering Mechanical Engineering, and Macromolecular Science and Engineering.
- * **College of Literature, Science and the Arts:** Department of Molecular, Cellular and Developmental Biology
- **Medical School:** Departments of Internal Medicine, Dermatology, Biological Chemistry, Surgery, Cell and Developmental Biology, Human Genetics, Ophthalmology and Visual Sciences, Pathology, Pediatrics and Communicable Diseases, Pharmacology, Molecular & Integrative Physiology.
- * **School of Dentistry:** Departments of Periodontics and Oral Medicine, Biologic and Materials Sciences, Orthodontics and Pediatric Dentistry and Cariology, Restorative Sciences and Endodontics
- * **School of Public Health:** Environmental Health Sciences (Toxicology)

See Appendix for a list of current participating faculty mentors and research activities of other trainees.

A. Trainee Activities

All predoctoral and postdoctoral trainees are expected to engage in the activities listed below.

1. **Research Project.** The primary activity for each trainee in the program is a research project that is directly related to organogenesis and to the research of the mentor(s), and is supervised by your mentors during the entire period of the training. For predoctoral trainees, this project will relate directly to the dissertation. Postdoctoral trainees will be expected to design a research project that may be an outgrowth of their dissertation research, but will represent a new research direction.
2. **Monthly Trainee Meetings.** Held once monthly (September-May). The monthly trainee meeting provides trainees with a forum to meet together as a small group to discuss a variety of topics including trainee research, new technology, ethics, job markets, and grant writing. Lunch is provided to all attendees.
3. **Seminar Series.** Held on Monday afternoons at 4:00 pm during the academic year, the CFO sponsors a seminar series (held in the BSRB Seminar Rooms). All trainees are expected to attend all seminars (excused absences are required). As part of the seminar series, training grant fellows will also be encouraged to host certain seminar speakers for lunch. Any expenses incurred by an individual for these activities will be reimbursed by the CFO.
4. **Additional Formal Educational Training.** The graduate course entitled “Organogenesis: Stem Cells to Regenerative Biology – CDB 582/583” is the centerpiece of this training program. The course is offered during the Winter term and will focus on understanding the biology of stem cells, how stem and progenitor cells are important for organ formation during development, maintenance during adult life, how perturbations in these cells can lead to disease, and how tissue engineers are learning to harness these cells to replace damaged tissues and organs. The course is team-taught by faculty with clinical or research expertise in the topic. All trainees are expected to attend and participate in this course.
5. **International Symposium on Organogenesis.** The CFO sponsors a series of International Symposia on Organogenesis. These symposia are designed to expose the faculty, students and

postdoctoral fellows at the University of Michigan to exciting new ideas and expertise in the area of organogenesis. During the symposium, 5-6 internationally recognized experts present their current research. A poster session provides opportunities for faculty, fellows and students to display their research. Prizes are awarded to the best student and best postdoctoral poster. All trainees are required to attend the symposium and to present a poster at the poster session. The symposium happens approximately every two years.

7. Clinical Co-mentorship opportunity. This component is optional and will be coordinated by Drs. Wellik, Samuelson and Maillard. The objective of the clinical co-mentorship is to provide opportunities for trainees in the basic sciences to engage with clinical problems and activities. Our leadership will help any trainee identify clinical faculty who are willing to work with the trainee to provide information, opportunities for rounding, shadowing, notification of grand rounds or the like.

8. Participation at Scientific Meetings. Whenever possible, each trainee will be encouraged to present his/her research at a scientific meeting. The Organogenesis training program provides NIH trainees with \$500 per year for this purpose. You must seek approval from the CFO prior to your travel and explain the purpose of the meeting. Additional travel support is available through the Organogenesis BioArtography fund (see below).

9. BioArtography. Students, postdocs, faculty and staff are encouraged to submit digital images of tissues and cells to the CFO. These images include muscle, fat, ovary, testes, skin, bone, kidneys, sperm, neurons and both human and mouse embryonic stem cells. A panel will select the best images to be matted, framed and sold at the Ann Arbor Art Fair and on the BioArtography website (www.bioartography.com). Since 2005, the BioArtography sales have grossed around \$130,000 and over sixty travel grants have been awarded to students and postdocs. The success of this adventure has been outstanding and enthusiasm is high for continuation. Trainees are expected to volunteer for one 4-hour booth shift or for matting and framing duty during the Ann Arbor Art Fair.

10. Responsible Conduct of Research. The NIH mandates that all pre and postdoctoral trainees on institutional research training grants, attend training in the Responsible Conduct of Research a minimum of eight hours of formal training at least once during each career stage and at least every 4 years. To fulfill this NIH requirement, all trainees are asked to attend "PIBS 503 "Research Responsibility and Ethics". PIBS 503 is in session every fall term from September to December. Course materials including case studies and podcast lectures are available online through CTools, and discussion will take place in small group sessions offered at many different times throughout the semester. Graduate students should register for PIBS 503 (1 credit) in Wolverine Access. Postdoctoral fellows should contact the course administrator Kierstin Fiscus to request a spot in the course (kfiscus@umich.edu). Deadline for 2016 enrollment is October 18, 2016.

It is also suggested that trainees take advantage of the University's Research Ethics and Compliance Program (www.research-compliance.umich.edu/), which covers a broad range of activity from general guidelines about conducting research responsibility to specific regulations governing a type of research. The Program for Education and Evaluation in Responsible Research and Scholarship (PEERRS) is a web-based foundational instruction and certification program for members of the University community engaged in or associated with research. <http://my.research.umich.edu/peerrs/>. For some faculty, staff and students, PEERRS certification is required, which is obtained by passing a short quiz for each required topic area. All UM faculty, staff and students are invited to use the modules and certification tests to improve their knowledge and awareness of responsible research practices.

B. Evaluation Procedure/Progress Report

NIH trainees are required to submit a progress report after one year in the *Training Program*. This report is evaluated by the *Training Program Directors*, before the trainee receives continued fellowship support. Evaluation of each trainee will be based on written evaluations submitted by the trainee and mentors, written reports from the mentoring committee (for postdoctoral fellows only) as well as feedback from the trainee presentation. Participation by the trainee in the CFO seminars, Organogenesis graduate course, monthly trainee meetings, trainee research presentations, and other activities, are also a part of the Progress Report. Trainees and mentors will receive notice approximately 6 weeks before the end of the first year of funding to submit the Progress Report to the CFO. Non-traditional trainees are typically appointed for one year and are not required to submit a progress report.

C. Grievance Procedure

All trainees initially are expected to resolve any emerging difficulties by direct interaction with the assigned mentor who will adhere to the principles of scientific ethics in effect in his or her departmental home, as well as at the CFO. In the event that resolution is not possible at this level, then the trainee should approach the faculty ombudsperson (Dr. Scott Barolo). If a resolution is not possible at this level, then the trainee may choose to approach the Training Grant Director (Deneen Wellik). If resolution still is not possible, the trainee shall next file a written statement to the Training Grant Director stating the problem, the facts which support the allegations, and the disposition of the matter at prior informal stages. In the case of grievances directly involving the *Training Program*, the Training Grant Director may seek advice from the *Training Program Operating Committee* and/or the *CFO Advisory Committee* or establish an *ad hoc* committee for advice on the matter. Before the Director decides a case, she will consult the Office of the General Counsel to assure correct and consistent interpretation of ethical facts. When the Director decides on a matter, the reasons for the decision will be given in writing.

III. CFO ADMINISTRATION AND MISCELLANEOUS PROCEDURES

A. Center for Organogenesis Office and Staff

The CFO office is located on the 2nd floor of BSRB (2058C). Amalia DiRita serves as Administrator to both the Center and Training Program. Please contact Amalia for questions regarding your appointment in the Training Program.

B. Tuition

The Training Grant provides funding to cover tuition and mandatory registration fees for predoctoral fellows. Other student related fees (student assembly, legal services, and school and college government) cannot be paid by this training grant, and are the trainee's responsibility.

C. Health Care Benefits

All NIH-paid trainees are eligible for health care benefits through the Organogenesis Training Grant. Please note - when a funding change has been made in the trainee's appointment, it often causes a lapse in health care coverage. It is the trainee's responsibility to check with the Benefits Office on a regular basis regarding coverage. Please contact Amalia DiRita if you have any questions or problems regarding your health insurance coverage.

D. Stipend Checks and Withholding Taxes

Stipend checks are issued monthly. If you have a discrepancy in your check, please contact Amalia DiRita. As an NIH research fellow, Federal and State income taxes will not be withheld from monthly stipend checks. However, the stipend is considered taxable income. It is the responsibility of the trainee

to file estimated taxes quarterly, or to make other arrangements regarding withholding taxes. The trainee will not receive a W-2 statement from the University of Michigan.

E. Hosting and Travel Reimbursements

Hosting and travel reimbursements will be made to trainees for research-related expenses. Approved travel can be reimbursed if all expenses are documented with receipts. Research-related purchases and all travel requests must be approved by the Training Grant Director in advance and must be documented with receipts. Amalia DiRita will handle all reimbursements. Travel advances are not permitted.

IV. APPENDIX

A. Research Activities of Current and Recent Trainees

Predoctoral Fellows

Devika Bagchi, Department of Molecular & Integrative Physiology, Mentor: Ormond MacDougald, Ph.D. **“Investigating the dynamic and selective regulation of phosphatidylcholine metabolism by β -adrenergic receptor stimulation in adipose tissue biology.”** Adipose tissue plays a key role in whole body metabolic function. With either obesity or lipodystrophy, white adipose tissue (WAT) storage capacity is exceeded and circulating lipids are stored ectopically, particularly in the liver and skeletal muscle, leading to insulin resistance and metabolic dysfunction. Phospholipids (PL) are essential components of cell membranes and key signaling cascades. Alterations in the PL composition of plasma membranes can have dramatic effects on cellular function by modifying cell structure, interactions of extracellular ligands with receptors in the cell membrane, or intracellular signal transduction cascades. Adipocytes store excess lipids by packaging them into cytosolic lipid droplets (LD). Phosphatidylcholine (PC) is the major PL present in eukaryotic cell membranes and is a vital component of the monolayer surrounding LDs. While the biochemistry underlying de novo PC synthesis via the Kennedy pathway has been well characterized, a potential role for PCs in adipose function has only recently been uncovered. Patients diagnosed with congenital lipodystrophy have identified loss-of-function mutations in the gene encoding phosphate cytidyltransferase 1 alpha (PCYT1A), the enzyme that catalyzes a key step in PC synthesis. These patients demonstrate markedly lower PCYT1A expression and significantly reduced synthesis of PC. Additionally, siRNA knockdown of PCYT1A in cultured 3T3-L1 pre-adipocytes impairs adipogenesis⁶. Taken together, these data suggest an important role for PC in adipose tissue development and function. Understanding the physiological regulation of PC synthesis and turnover during adipogenesis will provide important insights into the mechanisms underlying adipose tissue development and function.

Emily Bowers, Department of Cell & Developmental Biology, Mentor: Daniel Lucas-Alcaraz, Ph.D.

“Role of Bone Marrow Granulocytes in Regulating Vascular Homeostasis and Regeneration”

Hematopoietic stem cells (HSC) are the cells responsible for blood cell production through the life of the individual. HSC transplant (HSCT) is the only curative procedure for patients suffering from diverse hematological disorders including leukemia, myelodysplastic syndrome, and aplastic anemia. However, HSCT is still considered a last resort therapy due to the risk of life-threatening complications. An example is reduced blood cell production by the transplanted HSC leading to severe neutropenia, anemia, and thrombocytopenia, increasing the risk of infection, internal bleeding, and death. Prior to HSCT, a patient must undergo exposure to γ -irradiation or chemotherapy to remove the diseased hematopoietic system and allow for engraftment of the transplanted cells. However, these treatments also severely injure the bone marrow (BM) vasculature. Vascular regeneration is a necessary first step for successful HSCT, yet the mechanisms that drive vascular recovery are not well established. We have discovered that adoptive transfer of BM granulocytes dramatically accelerates vascular and hematopoietic regeneration after

HSCT via TNF α . My goal is to further elucidate how BM granulocyte-derived TNF α acts on endothelial cells during regeneration and to uncover the role of BM granulocytes in endothelial homeostasis.

Kyriel Pineault, Department of Cellular & Developmental Biology, Mentor: Deneen Wellik, Ph.D. **“Measuring the progenitor potential of Hox11-expressing skeletal mesenchymal cells using a novel Hoxa11CreER² allele.”** The posterior Hox genes (Hox9-13) have critical functions in proximodistal patterning of the limb skeleton during development and Hox11 genes specifically pattern the zeugopod (radius/ulna and tibia/fibula). Using a Hoxa11eGFP reporter, we have reported that Hox11 is not expressed in differentiated cell types and is instead expressed in undifferentiated mesenchymal cells surrounding the developing skeletal elements[1]. We recently demonstrated that Hox11 genes continue to be expressed regionally through adult stages, and identified Hox11-expressing cells as a sub-population of skeletal mesenchymal stem/progenitor cells (MSCs) that express markers PDGFR α and CD51 and possess the ability to differentiate into chondrocytes, osteoblasts, adipocytes. The origin of skeletal MSCs is unknown, but our preliminary data shows that embryonic Hox11-expressing cells co-express the same progenitor markers observed in adulthood. Collectively, these data lead us to hypothesize that Hox11-expressing cells represent a progenitor population in the embryo that give rise to chondrocyte and osteoblast lineages during development and may be the origin of adult skeletal stem cells. Using our newly generated Hoxa11-CreERT2 allele, I will test this hypothesis via the following specific aims:

Aim 1: Determine the contribution of Hox11-expressing cells to the skeletal lineages during development. Lineage tracing of Hox11-expressing cells will be performed at embryonic and adult stages using a newly generated Hoxa11-CreERT2 allele.

Aim 2: Assess the requirement for Hox11-expressing progenitors. Hox11-expressing cells will be ablated at embryonic and adult stages using Hoxa11-CreERT2 crossed with Rosa-DTA. Resulting phenotypes will be examined histologically. The function of adult Hox11 MSCs will be tested in an ulnar fracture model after Hoxa11-CreERT2; Rosa-DTA cell ablation.

Kunal Rambhia, Department of Biomedical Engineering, Mentor: Peter Ma, Ph.D. **“Regeneration of vascularized bone on novel, injectable nanofibrous spongy microspheres.”** Every year, more than one million Americans experience critical size, non-healing bone injuries caused by trauma, infection, surgical resection, or disease.[1,2] Current clinical treatment options include surgical fixation, bone grafting, and osteogenic growth factors. However, there are drawbacks and inefficiencies to each of these methods. Surgical methods are invasive and increase risk of infection. Autografts result in donor site morbidity and are inherently limited in shape, size, and amount of bone available for transplant. Allografts and xenografts introduce a risk of immunogenic response or disease transmission. While the half-lives of osteogenic growth factors such as bone morphogenetic proteins (BMPs) are brief in vivo, current therapies cannot support sustained delivery of growth factors over a sustained amount of time. Supraphysiological high dose treatments of growth factors are required to compensate for these limitations, which can have unwanted and potentially harmful side effects including nonspecific bone growth or tumor development. Regeneration of bone through tissue engineering is therefore a desired solution to critical size defects.

Michael Scales, Department of Cell & Developmental Biology, Mentor: Benjamin Allen, Ph.D. **“Investigating GLI function during pancreas homeostasis and neoplasia.”** Pancreatic Ductal Adenocarcinoma (PDAC) has one of the lowest survival rates among malignant diseases¹. PDAC frequently features inappropriate regulation of the Hedgehog (HH) signaling pathway, a key developmental pathway implicated in a variety of human diseases. However, the exact contribution of HH signaling to PDAC progression is controversial, and therapeutic attempts to target this pathway have failed. In PDAC, tumor-derived HH ligands signal in a paracrine manner to surrounding stromal fibroblasts. Cellular responses to HH are mediated by the GLI family of transcription factors (GLI1-3); however, the role of GLI proteins in the context of pancreatic cancer remains largely unexplored. I hypothesize that misregulation of GLI activity enhances stromal recruitment, vascularization, and metastasis during PDAC progression. To test this hypothesis, I propose the following specific aims:

Aim 1: Characterize Gli expression in the healthy pancreas and in PDAC. I will utilize Gli_{lacZ} reporter mice crossed with genetically engineered mouse models of pancreatic cancer to study Gli expression in the healthy (Aim 1A) and neoplastic (Aim 1B) pancreas.

Aim 2: Investigate stromal GLI function in PDAC. I will determine how modulating GLI transcriptional activity in pancreatic fibroblasts affects PDAC progression. I will utilize both dominant active and dominant negative Gli2 alleles to modulate stromal GLI activity in pancreatic fibroblasts, and evaluate the resulting PDAC phenotypes with chicken chorioallantoic membrane (CAM) tumor growth assays (Aim 2A) and genetic mouse models (Aim 2B).

Postdoctoral Fellows

Michael Chung, M.D., Ph.D., Department of Surgery, Mentor: Benjamin Levi, M.D. Ph.D. **“Targeting inflammation and TGF-beta signaling in chondroprogenitor cells of heterotopic ossification.”**

Heterotopic ossification (HO) leads to bone deposition in extra-skeletal sites severely restricting range of motion, limiting prosthetic use and causing chronic pain and wounds. Given the lack of therapeutics and suboptimal outcomes with excision, there is a need to elucidate the mechanism and develop cell specific HO prophylactic strategies.

Aim 1: To define the role of macrophage recruitment and macrophage-specific TGF- β production on HO. Our preliminary data demonstrate that macrophage depletion with clodronate eliminates pre-HO ectopic cartilage *in vivo*. We hypothesize that TGF- β produced by macrophage is critical for ectopic chondrogenic differentiation of mesenchymal cells. First, we will eliminate macrophages using (1) *LysM-cre/iDTRfl/fl* mice and (2) FDA-approved trabectedin treatment.

Aim 2: To demonstrate that novel microparticles can be used to silence genes specifically in macrophages. Our preliminary data show that microparticles composed of poly-L-lactic acid/poly-glycolic acid (PLGA) can be engineered for macrophage uptake. Due to the role of macrophages in pathologies including but not limited to HO, a novel microparticle delivery system presents the potential for widespread therapeutic use. We will utilize newly developed microparticles designed for macrophage-specific uptake to deliver *Tgfb1* siRNA for HO prevention. The development of a macrophage-specific delivery system represents a valuable advance to test candidate siRNAs in macrophage-related pathologies. This proposal will elucidate the role of macrophage-specific TGF- β 1 in the generation of HO, and validate a novel cell-specific therapeutic delivery strategy. To determine the effect of macrophages on ectopic cartilage and HO using our proven mouse HO model. To demonstrate a critical involvement of TGF β 1 produced by macrophages, we will use macrophage-specific *Tgfb1* cKO mice (*LysM-cre/Tgfb1fl/fl*, shared by Dr. Laurie McCauley) to evaluate the impact on ectopic cartilage and the osseous lesion using our mouse model.

Elizabeth Mills, Ph.D., Department of Molecular & Behavioral Neurosciences, Mentor: Daniel Goldman, Ph.D. **“Strategies for stimulating CNS repair in fish and mammals”**. Muller glia (MG) in the zebrafish (zf) retina and radial glia (RG) in the brain responds to injury by dividing and generating stem cells for tissue repair. Inhibition of glycogen synthase kinase (GSK3) is sufficient to drive zfMG reprogramming, however, the underlying mechanism remains unknown. Several other signaling pathways, including *Ascl1a*, *Lin28*, and *Stat3* are also necessary for zfMG reprogramming and our preliminary data suggests they may act in a synergistic fashion. We will test whether these synergistic combinations can also drive reprogramming in zfRG and mammalian MG.

Aim 1: Test the hypothesis that β -catenin and/or mTOR are sufficient to drive zfMG proliferation in the uninjured retina. GSK3 inhibition stimulates MG proliferation in the uninjured and injured fish retina. GSK3 inhibition stabilizes β -catenin and stimulates mTOR activity in MG and RG-derived stem cells in retina and brain, respectively. Therefore, β -catenin and mTOR are good candidates for mediating the proliferative effects of GSK3 inhibition.

Aim 2: Test the hypothesis that signaling components necessary for MG reprogramming synergize with each other to enhance regeneration in the zfCNS. Injury-dependent induction of *Ascl1a*, *Lin28*, and *Stat3*, along with GSK3 inhibition, are necessary for MG reprogramming and proliferation in the injured fish retina. *Ascl1a* and *Lin28* can synergize, and we will test whether additional signaling molecules can

further enhance MG reprogramming. The most effective combinations will be tested on zfRG stem cell formation in brain to assess universality.

Aim 3: Test the hypothesis that signaling components that enhance regeneration in fish will stimulate MG reprogramming in the mouse retina. Manipulation of pathways/genes, which regulate regeneration in the fish is hypothesized as a strategy to enhance mammalian regeneration. Data from recent studies forcing *Ascl1a*/*Lin28* expression in the mouse retina supports this approach (Fig. 2). Addition of GSK/ β -catenin/mTOR and Jak/Stat3 pathways may further stimulate mammalian MG reprogramming in the injured retina.

B. List of Training Grant Faculty

Benjamin Allen, Ph.D.

Assistant Professor, Department of Cell and Developmental Biology

Scott Barolo, Ph.D.

Associate Professor, Department of Cell and Developmental Biology

Susan Brooks-Herzog

Professor of Molecular and Integrative Physiology, Professor of Biomedical Engineering

Kenneth Cadigan, Ph.D.

Associate Professor, Department of Molecular, Cellular and Developmental Biology

Sally Camper, Ph.D.

Professor and Chair, Department of Human Genetics; Professor of Internal Medicine

Rhima Coleman, Ph.D.

Assistant Professor of Biomedical Engineering, Assistant Professor of Mechanical Engineering

Andrzej Dlugosz, M.D.

Poth Professor of Cutaneous Oncology, Comprehensive Cancer Center, Professor of Dermatology and Cell and Developmental Biology

Gregory Dressler, Ph.D.

Collegiate Professor of Pathology

Renny T. Franceschi, Ph.D.

Professor, Department of Periodontics and Oral Medicine, Dental School; Professor, Department of Biological Chemistry and Biomedical Engineering

Roman Giger, Ph.D.

Associate Professor, Department of Cell and Developmental Biology and Department of Neurology

Daniel Goldman, Ph.D.

Bernard W Agranoff Collegiate Professor of Neuroscience, Interim Chair, Department of Biological Chemistry, Professor of Biological Chemistry and Research Professor, Molecular and Behavioral Neuroscience Institute

Deborah Gumucio, Ph.D.

Professor and Interim Chair, Department of Cell and Developmental Biology, Professor, Computational Medicine and Bioinformatics

Gary Hammer, M.D., Ph.D.

Millie Schembechler Professor of Adrenal Cancer, Associate Professor of Internal Medicine, Division of Metabolism, Endocrinology & Diabetes, Associate Professor, Department of Molecular and Integrative Physiology, Director of the Endocrine Oncology Program – Comprehensive Cancer Center and Director of the Center for Organogenesis

Patrick Hu, M.D., Ph.D.

Research Associate Professor, Institute of Gerontology, Associate Professor of Internal Medicine, Associate Professor of Cell and Developmental Biology

Lori Isom, Ph.D.

Professor and Interim Chair, Department of Pharmacology, Professor, Molecular and Integrative Physiology

John Kim, Ph.D.

Frederick C Neidhardt Collegiate Professor of Life Sciences, Research Associate Professor, Life Sciences Institute, Associate Professor of Human Genetics

David Kohn, Ph.D.

Professor of Dentistry, Department of Biologic and Materials Science, Professor of Biomedical Engineering

Paul H. Krebsbach, D.D.S., Ph.D.

Professor and Chair, Biologic & Materials Sciences; Roy H. Roberts Professor of Dentistry and Professor of Biomedical Engineering.

Lisa Larkin, Ph.D.

Associate Professor of Molecular and Integrative Physiology, Research Associate Professor, Associate Professor of Biomedical Engineering

Benjamin Levi, M.D., Ph.D.

Assistant Professor, Surgery

Daniel Lucas-Alcaraz, Ph.D.

Assistant Professor, Cell & Developmental Biology

Peter X. Ma, Ph.D.

Professor, Departments of Biologic and Materials Sciences, Biomedical Engineering, Macromolecular Science and Engineering

Ormond A. MacDougald, Ph.D.

John A. Faulkner Collegiate Professor, Department of Molecular and Integrative Physiology, Professor of Internal Medicine

Ivan Maillard, M.D., Ph.D.

Jeffrey M Leiden Collegiate Professor of Life Sciences, Research Associate Professor of the Life Sciences Institute, Associate Professor of Internal Medicine and Cell & Developmental Biology

Laurie K. McCauley, D.D.S., Ph.D.

Professor and Dean, School of Dentistry; William K. and Mary Anne Najjar Professor, Department of Periodontics and Oral Medicine

Miriam Meisler, Ph.D.

Myron Levine Distinguished University Professor of Human Genetics, Professor of Human Genetics and Neurology

Juanita Merchant, M.D., Ph.D.

H Marvin Pollard Professor of Gastrointestinal Sciences, Professor, Internal Medicine, Division of Gastroenterology, and Molecular & Integrative Physiology

Yuji Mishina, Ph.D.

Professor of Dentistry, Department of Biologic and Materials Sciences

Charlotte Mistretta, Ph.D.

William R Mann Professor of Dentistry, Department of Biologic and Materials Sciences, Associate Dean for Research and PhD Training, School of Dentistry

Jack Parent, M.D.

William J Herdman Professor of Neurology and Professor of Neurology

Marina Pasca Di Magliano, Ph.D.

Assistant Professor, General Surgery and Cell & Developmental Biology

Linda Samuelson, Ph.D.

John A. Williams Collegiate Professor of Gastrointestinal Physiology; Professor, Departments of Molecular & Integrative Physiology and Internal Medicine, Associate Director of the Center for Organogenesis

Ernestina Schipani, M.D., Ph.D.

Professor of Orthopaedic Surgery, Professor of Internal Medicine, and Professor of Cell and Developmental Biology

Lonnie Shea, Ph.D.

William and Valerie Hall Department Chair of Biomedical Engineering, Professor of Biomedical Engineering, Chair; Department of Biomedical Engineering, Professor of Chemical Engineering

Jason Spence, Ph.D.

Assistant Professor of Internal Medicine and Assistant Professor of Cell and Developmental Biology

Deneen Wellik, Ph.D.

Director, Organogenesis Training Program

Associate Professor, Department of Internal Medicine, Division of Molecular Medicine & Genetics; Department of Cell and Developmental Biology, Assistant Director, Center for Organogenesis

Trisha Wittkopp, Ph.D.

Assistant Professor, Molecular, Cellular and Developmental Biology

Sunny Wong, Ph.D.

Assistant Professor of Dermatology and Assistant Professor of Cell and Developmental Biology

Jun Wu, Ph.D.

Research Assistant Professor, Life Sciences Institute, Assistant Professor of Molecular and Integrative Physiology

Yukiko Yamashita, Ph.D.

James Playfair McMurrich Collegiate Professor of the Life Sciences, Research Associate Professor, Life Sciences Institute, Associate Professor of Cell and Developmental Biology

Please Direct Your Inquiries To:

Amalia DiRita
Center for Organogenesis
The University of Michigan
109 Zina Pitcher Place, 2058 BSRB
Ann Arbor, MI 48109-2200
Phone: (734) 936-2499; Fax: (734) 763-2162
Email: amdirita@umich.edu
CFO Web: <http://www.organo.med.umich.edu>