On The Cutting Edge
Message from the Chair

Mackenzie Professor and Chair Ken Azarow, M.D., F.A.C.S., F.A.A.P.

As we enter a new academic year, I’m able to report an undeniable sense of pride in the investment and return the department has experienced in our research program. Since the hiring of our Vice Chair of Research Jonathan Brody, Ph.D., we have seen scholarly advances in every division. This issue of *On the Cutting Edge* serves to bring you, our department, alumni, and friends, updates on the research progress, and accomplishments of the department this past year, all of which have been remarkable.

First let me bring your attention to the artwork that covers this issue of *On the Cutting Edge*. It is a piece of art that currently hangs in the center of our Department of Surgery Hallway in Mac Hall. The work is entitled “Women in Surgery” and the artist, Ameya Okamoto, has devoted her work to the cross section of art and social justice for all. This reinforces the Department's commitment to diversity, equity, and inclusion across all of our missions. Next, to highlight the importance of scientific advance in surgery and in surgical education, we have highlighted the role of our Vice Chair for Research and instituted the new Jonathan Brody Award for Research. This award is given annually to the resident with the greatest research impact during the academic year, with Ranish Patel, M.D., as this year's inaugural recipient.

In this issue of *On the Cutting Edge*, please note a common theme: team science. Whether you are working at a bench, developing new approaches to direct a patient's own immune system to recognize and destroy cancer cells, or examining a database looking at clinical outcomes, there is an emphasis on collaboration and diversity of opinions to yield the most innovative and scientifically sound advances to the medical community. Almost all of our research endeavors involve either surgical residents, graduate students in scientific disciplines, or medical students emphasizing the role research has in one's overall medical education.

Just a few additional notes from the chair as you get ready to dive into this issue. The department began housing a research center 2 years ago, The Donald D. Trunkey Center for Combat and Civilian Casualty Care. The center has truly been a hub for trauma research here at home and across the nation. The center is home to one of the largest prehospital blood treatment studies in existence and has been successful at giving our seed grants to local investigators. Our surgical scientists program continues to flourish as well, and this issue will not only highlight the work of Robert Eil, M.D., but will introduce a one-of-a-kind surgical informatics science lab: the “surgical decision-making science lab,” with Ruchi Thanawala, M.D., M.S., as director. As you read these and several other highlight articles you will recognize the enormous effort that has gone into this program. With that said it is my pleasure to present to you this issue of *On the Cutting Edge*.
The Eil Lab

Dramatic change is needed in our approach to treating metastatic cancer.

Despite multi-agent chemotherapy regimens, oncogenomics, precision medicine, and cancer screening programs, the rate of death from cancer in the United States has not changed significantly since the 1950s. Over the same period of time, the rate of death from heart disease decreased by two-thirds due to medical advances. Current standard-of-care treatments for metastatic solid cancer produce durable complete responses in less than 1 percent of patients.

The Eil Lab focuses on developing new approaches to direct a patient’s own immune system to recognize and destroy cancer cells.

T lymphocytes, a type of immune cell that emigrates out of the thymus, can recognize and kill cancer cells. Recent medical advances have led to the development of cancer treatments based on the antitumor activity of T cells (checkpoint blockade and the adoptive transfer of tumor-specific T cells). These revolutionary therapies have produced dramatic clearance of widespread cancer in some patients. However, in most cases while T cells can be found infiltrating cancers, their function is often constrained within tumors – allowing immune evasion and cancer progression.

While the successes achieved with T cell based therapies demonstrate the promise of a new era of cancer treatment, disease progression currently remains the most common outcome owing to tumor-induced immune evasion and T cell dysfunction.

To achieve meaningful progress in the application of T cell therapies for solid cancers, two remaining barriers must be overcome:

1) There are limited safe and effective T cell targets that distinguish the cancer from normal tissues.  
2) The hostile environment of tumors deploys effective tools to prevent the function of T cells that do recognize cancer cells.

While there remains a critical need to augment T cell antitumor function within cancers, those features of the intratumoral microenvironment that drive immune evasion remain unclear.

This topic remains an area of intense investigation, with many investigators focusing on cytokines (TGFβ), co-inhibitory signals (CTLA-4, PDL-1), and cell-cell interactions (regulatory T cells & myeloid derived suppressor cells) as mechanisms of tumor induced immune suppression. However, tissue and biochemical characteristics specific to tumors may also be important for T cell function.

Simply put, a high abundance of cell death characterizes many tumors and is associated with poor prognosis.

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In current efforts, the Eil Lab uses genetic engineering strategies with viral (retro and lentiviral transduction) and non-viral (CRISPR-Cas9) techniques, pre-clinical models adoptive T cell transfer for cancer treatment, and human samples to develop new therapies. We aim to immediately translate our findings to patients with metastatic cancers, with an emphasis on those involving the liver and pancreas. As a surgeon-scientist, Dr. Eil has a unique perspective and platform, allowing us to extend our studies to clinical and research specimens as well as prospective clinical trials treating patients with cancers involving the liver, bile ducts, and pancreas.
The research conducted in each of our divisions is multifaceted and ultimately strengthened by communication and overlap with other programs, departments, institutions and organizations.

Surgical oncology research is often particularly cross-disciplinary and is a prime example of the collaborative efforts our department undertakes to further surgical research and advancements. Take a look!

Just a few of the programs, departments and resources our surgical oncologists utilize to help advance discovery

- Department of Surgery Vice Chair of Research Jonathan Brody, Ph.D.
- OHSU School of Nursing - quality of life
- OHSU Department of Neurology - assessment of peripheral neuropathy
- OHSU Department of Radiology - liver volumetrics
- OHSU Department of Nuclear Medicine - functional liver assessment
- OHSU Division of Hematology Oncology - rectal cancer and colon cancer, pancreatic cancer, GIST, gallbladder cancer, sarcoma, cholangiocarcinomas, and more
- OHSU Division of Gastroenterology - multiple projects in pancreatic cancer and HCC
- OHSU Department of Interventional Radiology - liver hypertrophy and hepatic arterial infusion
- OHSU Department of Cell, Developmental, and Cancer Biology
- International collaborations with the Hepatic Arterial Infusion Research Network (HCNR) for hepatic arterial infusion trials
- International collaborations with the USCD and Rotterdam Cancer Center in The Netherlands for GIST
- International Cholangiocarcinoma Research Network (ICRN) to support cholangiocarcinoma
- OHSU Knight TIL working Group
- Sentinel Lymph Node working group
- Castle BioSciences
- SWOG
- Rahul Roychoudhuri, Ph.D., University of Cambridge
- Lyell Immunopharma
- BCC Translational Research Fellowship

Research Resources:
- Research technicians
- Post Doctoral scholars
- Graduate students
- Surgical residents in lab years
- Medical students
- Research assistants through the Knight Clinical Trials structure
- Radiology research residents
- Interventional radiology fellows and residents
- Knight Biostatistical Shared Resource core
- Department of Surgery statistical support
- SRO Division Research Assistants – Data, IRB Management
- Department of Surgery Grant Coordinator
Our pediatric craniofacial and reconstructive surgical team has a focused research interest on how social determinants of health can affect access to care and surgical outcomes for underserved populations. As an example of this, faculty within our division recently published a study investigating American Indian Alaska Native (AIAN) access to comprehensive cleft care.\textsuperscript{1} We believe not addressing orofacial clefts in a timely manner with quality comprehensive care can lead to worsened outcomes and further marginalization of these children. Additionally, in recognition that access to care within reasonable travel distances functions as such a barrier, the CMF team has also established multiple outreach clinics in Oregon to better serve these populations. By doing so, we hope to not only explore the issues through research, but implement real time solutions targeting these concerns.

Vascular Surgery welcomed new Division Head Sherene Shalhub, M.D., M.P.H., in February - she brings her expertise and role as lead investigator for the Aortic Dissection Collaborative which is federally funded by the Patient Centered Outcomes Research Institute (PCORI). This 1-year contract titled “Community-Led Research Development in the Aortic Dissection Collaborative” is aimed at:

- Understanding current patient-reported outcomes used in aortic dissection research and making recommendations for future research
- Identifying patient barriers to participating in randomized clinical trials
- Collaborating on including patient-centered outcomes and patient-reported outcomes in major national registries, including the Vascular Quality Initiative (VQI) and the Society for Thoracic Surgeons (STS) registry

Dr. Shalhub also serves as the Chair of the National Registry of Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions (GenTAC) Alliance Science working group. She is member of the Society for Vascular Surgery, the Professional advisory board for the Marfan Foundation, and the Ehlers-Danlos Society medical and scientific board.

INDUSTRY-SPONSORED TRIALS

**TRIOMPHE**: A Multi-arm, Multi-Center, Non-Randomized, Prospective, Clinical Study to Evaluate the Safety and Effectiveness of the NEXUS™ Aortic Arch Stent Graft System in Treating Thoracic Aortic Lesions Involving the Aortic Arch. (Endospan Ltd.)

PI: Cherrie Abraham, M.D.

**Zenith p-Branch Pivotal Study**: The Zenith® p-Branch® Pivotal Study is a clinical trial approved by FDA to study the safety and effectiveness of the Zenith® p-Branch® endovascular graft in combination with the Atrium iCAST™ covered stents in the treatment of abdominal aortic aneurysms. (Cook Research Inc.)

PI: Cherrie Abraham, M.D.

**Gore TBE Trial**: Evaluation of the GORE® TAG® Thoracic Branch Endoprosthesis (TBE Device) in the Treatment of Lesions of the Aortic Arch and Descending Thoracic Aorta. (W. L. Gore & Associates, Inc.)

PI: Cherrie Abraham, M.D.

**Fibrillin Surveillance**: Use of plasma-detected fibrillin peptide fragments for pre- and post-operative aortic aneurysm and dissection surveillance. (Virogenomics BioDevelopment Inc., NHLBI Grant Funded.)

PI: Cherrie Abraham, M.D.

**Jaguar Trial**: Objective Analysis to Gauge EVAR Outcomes Through Randomization in a Real World Population. Comparison of ALTO Abdominal Stent Graft System to comparator group (2:1). (Endologix)

PI: Cherrie Abraham, M.D.

**Terumo TREO Post Market Registry**: A post-market registry with prospective and retrospective analysis of results of Terumo Treo Abdominal Aortic Stent Graft System. (Terumo sponsored registry.)

PI: Amani Politano, M.D., M.S.
Our basic research, led by Fred Tibayan, M.D., is focused on the developmental origins of cardiovascular disease. Specifically, we are looking at how altered mechanical loading conditions such as fetal blood pressure change gene expression and extracellular matrix composition in the developing valves and aorta. This develops in ways that predispose them to disease in adulthood. Recently, we have been using advanced spectroscopy to quantify lipidomics and myocardial fibrosis in human heart failure.

BETTER SYSTEMS OF CARE

Castiglione Bhamidipati, D.O., Ph.D., M.Sc., is a cardiac surgeon in our division clinically focused on treating adult patients with congenital heart disease and patients with complex aortic pathologies. He is interested in understanding and developing better systems of care for these patients using the databases. He is involved with the STS adult congenital heart disease workforce and congenital heart surgery database task force to better understand how these patients can be served. Dr. Bhamidipati’s recent work includes examining the relationship between race and patients with adult congenital heart diseases. He is the PI of several local and regional registries, as well as a clinical cardiac surgery trial around aortic dissection.

INFORMATICS AND EDUCATION

Ruchi Thanawala, M.D., M.S., (pictured left) as an informatician and surgical education researcher, is leveraging the power of data science, technology, and machine learning to pursue research in multiple realms. She is exploring and outlining the complexity of learning science within surgical education. She is the lead scientist in a multi-institution team applying advanced modeling techniques, such as Bayesian modeling, and machine learning to understand how we learn in the operating room during surgical training. Dr. Thanawala’s work also focuses on using informatics tools to improve the completeness and depth of quantitative surgical education data. Last fall, her work was presented on the development of a model to predict the entrustability of a surgical resident using surgical process mapping at the ACS Clinical Congress. She is presenting at the upcoming APDS meeting on the complexity of self-assessment of skill in surgical residents and the need to develop this metacognition skill in training. Dr. Thanawala has ongoing research in the creation of an ontology of surgical case components to measure the relatedness of operations. This work will inform quantification of technical skill acquisition, maintenance and loss. She has an active study, in collaboration with DMICE, on the use of natural language processing applied to operative notes to identify resident level cognitive understanding of an operation.

3-D PRINTED AORTIC VALVES

Yoshi Otaki, M.D., pediatric and congenital cardiac surgeon, specializes in implanting hand-crafted valved ePTFE conduits for select conditions. Together with Ashok Muraidaran, M.D., they are investigating the mid- and long-term outcomes of this implant. Dr. Muraidaran, section head of pediatric cardiothoracic surgery, is the primary investigator in a few studies including the incidence and recovery vocal fold dysfunction in infant cardiac surgery, pulmonary function tests in newborns with critical congenital heart disease and is collaborating with researchers to design a 3-D printed, personalized aortic valve based on 4D flow MRI studies in animal models.
The Donald D. Trunkey Center for Civilian and Combat Casualty Care continues to orchestrate collaborative researcher across the Pacific Northwest. The Center, which was established in 2020, is directed by Martin Schreiber, M.D., Professor and Head of Trauma, Critical Care and Acute Care Surgery. It embodies the deep connection between trauma care at OHSU and service in the U.S. military.

A centerpiece and catalyst for growth has been the Trunkey Center’s seminar series, bringing together around 100 researchers each month and working across all trauma-related disciplines. The seminars highlight cutting edge research in the field, and serve as a focal point for new collaborations. Speakers include basic scientists, clinicians, engineers, epidemiologists, and public health experts, many of whom were brought together for the first time by the Trunkey Center. The series has a central role to play as the Center continues to grow and amplify research in trauma by fostering interdisciplinary collaboration, increasing research funding, and accelerating bench-to-bedside discoveries.

Most notably, the Trunkey Center recently received $15.4M in research funding from the Department of Defense to study the effect of Prehospital Kcentra for Trauma Patients with Hemorrhagic Shock. And in 2022, the Center was able to extend a $20,000 Trunkey Center Research and Innovation Award to Dominic Siler, M.D., Ph.D., for his ongoing work in Neurotrauma Research here at OHSU.

**CURRENT ACTIVE STUDIES INVOLVING PATIENTS INCLUDE:**

- Brain Oxygen Optimization in Severe Traumatic Brain Injury – Phase 3 (BOOST-3)
- Implementing Best-Practice, Patient-Centered Venous Thromboembolism (VTE) Prevention in Trauma Center
- In Hospital and Prehospital Kcentra for Hemorrhagic Shock
- Prehospital Airway Control Trial (PACT)
- Use of Hypertonic Saline after Damage Control Laparotomy to Improve Early Primary Fascial Closure
- Allogeneic Bone Marrow-derived human Mesenchymal Stromal Cells for the Treatment of Acute Respiratory Distress Syndrome after Trauma
- Use of Whole Blood for Massive Transfusions
- Use of Virtual Reality as a Distraction Technique to Limit Opiate Use in Traumatic and Surgical Wound Dressing Management
- Strategy to Avoid Excessive Oxygen for Critically Ill Trauma Patients (SAVE-O2)
- Predictors of Low-Risk Phenotypes after Traumatic Brain Injury Incorporating Proteomic Biomarker Signatures (PROTIPS)
- Blood volume, components and capillary leaks in SARS-CoV-2 and bacterial infections: A prospective, observational study

**CURRENT FUNDING SOURCES WITHIN THE DIVISION OF TRAUMA, CRITICAL CARE AND ACUTE CARE SURGERY: 32 FUNDED PROJECTS WORTH APPROXIMATELY $18 MILLION**
In our Division of Pediatric Surgery, there are 9 faculty across two tertiary children's hospitals with diverse research interests and expertise. We partner with faculty in other departments (including neonatology, pediatric gastroenterology and the biomedical sciences) to collaborate on clinical and translational research. Our group currently has more than 50 active studies, at various stages of development, enrollment and publication. Many of these are multi-institutional prospective and retrospective studies within three national research consortia.

Clinical outcomes research represents a large focus of our effort. For example, our “Minimizing Variance in Pediatric Surgery” program investigates the effectiveness of evidence-based protocols for the management of common pediatric surgical diseases ranging from perianal abscesses to gastrochisis. Additional studies include those investigating congenital anomalies, pediatric solid tumors, and global health. Pediatric trauma research results from work at the two Level 1 Pediatric Trauma Centers in Oregon including 15 current studies. Basic science efforts include building a biobank of patient serum, stool and surgical tissue specimens (with Brian Scottoline, M.D., Neonatology), and we are now conducting microbiome-based and stem cell-based experimental research into pediatric inflammatory intestinal diseases such as necrotizing enterocolitis. Additionally, grant-funded research includes large national clinical studies related to congenital diaphragmatic hernia (DHREAMS), pediatric inflammatory bowel disease (ENRICH-US), and pediatric disaster management (WRAP-EM) as well as institutional studies focused on hypercoagulability in injured children.

Our faculty are proud to mentor students, residents and pediatric surgery fellows during their clinical and/or dedicated research time. We offer a pediatric surgery research fellowship to interested residents, for 1 or 2 years. As our division’s director of research, Mubeen Jafri, M.D., leads our effort and welcomes new ideas for collaboration. The breadth of pediatric surgery offers limitless research opportunities, and we strive to make a meaningful difference in the care of our patients.
C. Kristian Enestvedt, M.D., has a particular interest and expertise in liver transplantation. He has most recently established a National Liver Transplant GVHD Registry and studies via collaborations with the OHSU Bone Marrow Transplant Team. His work has helped demonstrate the incidence of donor-derived clonal hematopoiesis mutations and association with inflammatory outcomes after liver transplantation. Dr. Enestvedt also studies circulating cell-free DNA in cirrhotic patients in early disease detection of hepatocellular carcinoma (HCC) and those with existing HCC, post locoregional treatment or liver transplantation, in order to assess treatment response and recurrence.

Abdominal Transplant Surgery

Davy Woodland, M.D.’s work has been focused on human auto-islet transplant with the OHSU Brenden-Colson Center for Pancreatic Care developing institutional protocols for optimal cell isolation and participation in IRB for expanded patient criteria. Working with his colleagues in GI, Pathology, and Surgery, he has helped develop plans for a clinical trial of TPAIT for IPMN.

In addition, springing from the opioid reduction initiative, Dr. Woodland has gathered data on a series of 60 consecutive kidney transplant cases, including phone polling of usage after discharge, followed by meetings with pharmacy and anesthesia for planning interventions. These efforts are in the planning phase for trackable intervention and manuscript preparation for which data has already been gathered.

A Unique Veteran Experience

The current work of newly-appointed division head Erin Maynard, M.D. (pictured above), is an examination of HCV treatment failures in kidney transplant recipients who are HCV negative and receive HCV positive donor organs – a unique Veteran experience. The IRB submission was done with Chris Connelly, M.D., and a funding application is planned.

Dr. Maynard, together with Ruchi Thanawala, M.D., M.S., and John Stowers, D.O., is also in the midst of putting together EPA for transplant fellows to then track along with Firefly. Their goal is to submit this to other transplant institutions that utilize Firefly so fellows can see how they are progressing compared to their peers.

Organ Usage Following UNOS Liver Allocation Policy

Past-division head of 15 years and the Inaugural Rabkin Professor, Susan Orloff, M.D., remains highly active in research with a look at cost analysis and liver organ usage pre- and post- implementation of the February 2020 UNOS liver allocation policy. Her study of portal hypertension and outcomes after surgical portacaval shunts is ongoing.

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Oregon Health & Science University is a nationally prominent research university and Oregon’s only public academic health center. It educates health professionals and scientists and provides leading-edge patient care, community service and biomedical research.

Change can’t happen if we see things just one way. That’s why diversity is so important to OHSU.