BIOGRAPHICAL SKETCH

NAME: Tridu Huynh

eRA COMMONS USER NAME: thuynhuy

POSITION TITLE: Clinical Assistant Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Start Date MM/YYYY	Completion Date MM/YYYY	FIELD OF STUDY
University of California – Los Angeles, Los Angeles, CA	BS	09/2009	06/2013	Molecular Cell and Developmental Biology; Biomedical Research
University of Vermont – College of Medicine, Burlington, VT	MD	08/2014	06/2018	Medicine
Scripps Clinic/Green Hospital, La Jolla, CA	N/A	07/2018	06/2022	Internal Medicine/Physician-Scientist Track
University of California – San Diego, San Diego, CA	N/A	07/2022	04/2024	Hematology/Oncology Fellowship

A. Personal Statement

I have spent my training years developing a foundation in basic science and clinical knowledge/skills to best allow me to conduct translational research with a focus in immunology across health and disease.

As an undergraduate researcher in the Department of Medicine – Cardiology at UCLA, I learned and applied basic, broadly applicable molecular biology techniques to study the inflammatory interaction between oxidized phospholipids and endothelial proteins contributing to atherosclerosis. I then went on to the La Jolla Institute for Immunology where I developed my understanding and skills in the field of immunology while assisting in the study of nuclear receptor NR4A1's role in CD8 T-cells' development and effector function. Subsequently, I completed a medical degree to obtain the pathophysiological insight necessary to perform translational research.

I then entered an ABIM research-track residency program as a KL2 scholar at Scripps Green/The Scripps Translational Research Institute. My two main projects there included the study of tumor-infiltrating lymphocytes (specifically natural killer cells and T-cells) in a patient-derived xenograft mouse model of human lung adenocarcinoma treated with a novel combination immunotherapy of an interleukin-15 superagonist and PD-1 blockade. The second project was a study of SARS-CoV-2 infected patients' peripheral blood through massive parallel cytometry and downstream machine-learning assisted analysis. Finally, as a hematology/oncology fellow, I gained first-hand clinical hematological/oncological knowledge, as well as designed two clinical trials of immunotherapies in lung cancer and Kaposi sarcoma.

My goal continues to work in translational research in immunology across health and disease with an interest in leveraging machine-learning capabilities.

B. Positions and Honors

Positions and Employment

2009 - 2011 Research Assistant, Department of Molecular & Medical Pharmacology, University of California, Los Angeles, CA
2013 - 2014 Research Associate, Division of Inflammation Biology, La Jolla Institute for Immunology, San Diego, CA
2018 - 2020 Internal Medicine Resident Physician, Scripps Clinic, La Jolla, CA
2020 - 2022 KL2 Clinical Scholar, The Scripps Research Institute/Scripps Research Translational Institute/Scripps Clinic, La Jolla, CA
2022 - 2024 Hematology Oncology Fellow, University of California – San Diego, San Diego, CA
2024 - Clinical Assistant Professor, Department of Medicine, Division of Hospital Medicine, Stanford Medicine, Stanford, CA

Other Experience and Professional Memberships

2018 - 2022 Member, American College of Physicians (ACP)
2018 - Member, American Society for Clinical Oncology (ASCO)
2019 - 2022 Board Member, Graduate Medical Education Research Subcommittee at Scripps Clinic
2020 - Member, Society for Immunotherapy of Cancer (SITC)
2021 - Society for Immunotherapy of Cancer – Ad Hoc Reviewer

Clinical Honors

2017-2018 Clinical Honors in Internal Medicine, Intensive Care Medicine, Hematology/Oncology, Family Medicine, Neurology, Urology, Anesthesiology
2018 The Michael J. Moynihan, Sr. Award for Excellence in Internal Medicine

Research Honors

2016 National Institute of Diabetes and Digestive and Kidney Disease (NIDDK) Medical Student Research Grant
2018 KL2 Award, Scripps Research Translational Institute/The Scripps Research Institute
2019 Scripps Clinic Medical Group (SCMG) Research Award
2022 NIH NCI Loan Repayment Program Grant Recipient
2024 University of California Lung Cancer Consortium Nanostring WTA Grant

C. Contributions to Science

1. Natural Killer Cells and Cytotoxic Tumor-Infiltrating Lymphocytes a Patient-Derived Xenograft Model

Existing patient-derived xenograft (PDX) mouse models of solid tumors lack a fully tumor donor-matched, syngeneic, and functional immune system. We developed a model that overcomes these limitations by engrafting lymphopenic recipient mice with a fresh, undisrupted piece of solid tumor, whereby tumor-infiltrating lymphocytes (TILs) persisted in the recipient mice for several weeks. Successful tumor engraftment was achieved in 83% to 89% of TIL-PDX mice, and these were seen to harbor exhausted immuno-effector as well as functional immunoregulatory cells persisting for at least 6 months postengraftment. Combined treatment with interleukin-15 stimulation and immune checkpoint inhibition resulted in complete or partial tumor response in this model. Further, depletion of cytotoxic T lymphocytes and/or natural killer cells before combined immunotherapy revealed that both cell types were required for maximal tumor regression. Our TIL-PDX model provides a valuable resource for powerful mechanistic and therapeutic studies in solid tumors

Relevant Publications/Presentations:

Huynh T.R.*, Le D.T.*, Burt B., Van Buren G., Abeynaike S.A., Zalfa C., Nikzad R., Kheradmand F., Tyner J. J., Paust, S. (2021). Natural Killer Cells and Cytotoxic T-Lymphocytes are Required to Clear Solid Tumor in a Patient-Derived-Xenograft. JCI Insight.

Tridu Huynh, Le D.T.*, Burt B., Van Buren G., Abeynaike S.A., Zalfa C., Nikzad R., Kheradmand F., Tyner J. J., Paust, S. "*Natural Killer Cells and Cytotoxic T-Cells Modulation in a Patient-Derived-Xenograft Model of Human Lung Adenocarcinoma."* SITC Annual Conference. December 2021. Washigton, D.C.

Silke Paust and **Tridu Huynh.** Novel Syngeneic Immune Cell Solid Tumor PDX Mice for Superior Preclinical Studies. Workshop Leader. Predict: Tumor Models for Immuno-Oncology Summit. January 2021. San Francisco, CA.

Tridu Huynh. "*Natural Killer Cells and Cytotoxic T-Cells Modulation in a Patient-Derived-Xenograft Model of Human Lung Adenocarcinoma."* Scripps Clinic Grand Round. March 2021. La Jolla, CA.

2. Role of the Nuclear Receptor Nr4a1 (Nur77) in CD8 T Cell Development and Effector Function

The transcription factor IFN regulatory factor 4 (IRF4) was shown to play a crucial role in the protective CD8+ T cell response; however, regulation of IRF4 expression in CD8+ T cells remains unclear. Using a Nr4a1 knockout mouse model, we discovered a critical role for Nr4a1 in regulating the expansion, differentiation, and function of CD8+T cells through direct transcriptional repression of Irf4. Without Nr4a1, the regulation of IRF4 is lost, driving an increase in Irf4 expression and, in turn, resulting in a faster rate of CD8 T cell proliferation and expansion. Nr4a1-deficient mice show increases in CD8 T cell effector responses with improved clearance of Listeria monocytogenes. In addition, Nr4a1 is strongly induced in thymocytes undergoing selection, and has been shown to control the development of Treg cells; however the role of Nr4a1 in CD8+ T cells remained undefined. We also reported a novel role for Nr4a1 in regulating the development and frequency of CD8+ T cells through direct transcriptional control of Runx3. We discovered that Nr4a1 recruits the corepressor, CoREST to suppress Runx3 expression in CD8+ T cells. Loss of Nr4a1 results in increased Runx3 expression in thymocytes which consequently causes a 2-fold increase in the frequency and total number of intrathymic and peripheral CD8+ T cells. Our findings established Nr4a1 as a novel and critical player in the regulation of CD8 T cell development through the direct suppression of Runx3 as well as effector function through IRF4 regulation.

Relevant Publications:

Nowyhed H.N., **Huynh T.R.**, Thomas G.D., Blatchley A., Hedrick C.C. (2015). "Cutting Edge: The Orphan Nuclear Receptor Nr4a1 Regulates CD8+ T Cell Expansion and Effector Function Through Direct Repression of Irf4." *J Immunol*. http://www.jimmunol.org/content/195/8/3515.long

Nowyhed H.N., **Huynh T.R.**, Blatchley A., Wu R., Thomas G.D., Hedrick C.C. (2015). "The Nuclear Receptor Nr4a1 Controls CD8 T Cell Development Through Transcriptional Suppression of Runx3." *Sci Rep*. https://www.nature.com/articles/srep09059

3. Clinical Trial of Topical Bortezomib in Kaposi Sarcoma

Despite highly active anti-retroviral therapy (HAART) prolonging the lives of persons with HIV and HIV-Kaposi Sarcoma (HIV-KS), there is still no cure, and treatment is thus palliative. In the context of improved immune function, most persons in the United States with HIV-KS, as well as many of those with classic KS, have limited cutaneous disease. For limited cutaneous disease, such palliative treatments include radiation, cryotherapy, intralesional or topical therapies. While topical therapies are the least invasive, response rates to date are limited, with less than 50% responding to imiquimod. KS-associated herpesvirus (KSHV, also known as human herpesvirus-8, HHV-8) is the primary etiologic factor resulting in KS. HHV-8 infects endothelial cells, leading to their transformation into spindle cells characteristic of KS. The exact tumorigenic mechanism is unknown, however, several lines of evidence have implicated viral genes such as the latency associated nuclear antigen (LANA), the viral cyclin (vCYC), and vFLIP, which inhibits apoptosis and autophagy as well as activates nuclear factor kappa B (NF-kB). Bortezomib is a proteasome inhibitor which was initially approved for treatment of multiple myeloma and has activity in other malignancies attributed at least in part to inhibition of NF-kB. A previous phase I clinical trial of intravenous bortezomib demonstrated its activity in HIV-KS patients (AMC-063) with a median time to response of 2.1 months, an overall response rate of 60% across all dose levels and 83% response rate at the highest dose level tested. Recently, a 26-S proteasome inhibitor formulated for topical administration, ACU-D1, was shown to have activity in rosacea and was also well-tolerated without systemic side effects expected of bortezomib or other systemic proteasome inhibition. Based

on AMC-063 demonstrating efficacy of intravenous bortezomib in KS and this study demonstrating tolerability and efficacy of ACU-D1 in rosacea, we developed a phase I/II trial to assess ACU-D1's efficacy and tolerability in limited cutaneous KS.

Role: Co-Principal Investigator

4. Examination of interaction of ADAM proteins with oxidized phospholipids and their role in endothelial inflammation

Atherosclerosis is a chronic inflammatory disease characterized by lipid accumulation and subsequent inflammation of the artery walls that ultimately predispose to heart attacks and strokes. PAPC is one of the major phospholipids in low-density lipoprotein (LDL), and products of its oxidation (Ox-PAPC) interact and activate endothelial cells, which leads to the induction of chemokines, such as IL-8. IL-8 results in the migration and retention of monocytes into the subendothelial space, an initial step in atherogenesis. IL-8 induction is regulated by several pathways, one of which is the ADAM-mediated HBEGF-EGFR pathway. It has previously been shown that Ox-PAPC binds to several endothelial cell proteins, among which are some ADAMTS proteins. Using Ox-PAPE-N-biotin, a biotinylated analog of Ox-PAPC, we present evidence that Ox-PAPC activates ADAM proteins, specifically ADAMTS1 and ADAMTS4, both of which have been implicated in IL-8 regulation, by covalently binding to them.

Relevant Presentations:

Tridu Huynh, James R. Springstead, Sangderk Lee, Judith A. Berliner. "Examination of the interaction of ADAM proteins with oxidized phospholipids and their role in endothelial inflammation."

- Molecular, Cell, and Developmental Biology Research Poster Session; June 2013; UCLA
- Biomedical Research Minor Poster Symposium; May 2013; UCLA
- UCLA Science Poster Day; May 2013
- UCLA Science Poster Day; May 2012

5. Validation of Putative GPR120 Agonists for the Development of a Therapeutic Anti-Inflammatory and Insulin-Sensitizing Drug

The chronic activation of inflammatory pathways in the macrophage/adipocyte vicious cycle nexus plays a key role in the pathogenesis of insulin resistance in obesity. G protein-coupled receptors, an extensive family of seven-transmembrane domains molecules, play a crucial role in signaling for diverse cellular functions. It was reported that 5 orphan GPCRs could bind to free fatty acids (FFAs). One of them, GPR120, is highly expressed in adipose tissue and pro-inflammatory macrophages. Long-chain FAs, such as Omega-3 FAs (ω-3 FAs), activate GPR120. It is historically well known that ω-3 FAs possess anti-inflammatory properties, and it has previously been shown that stimulation of GPR120 with ω-3 FAs, such as docosahexaenoic acid (DHA), or a synthetic agonist, such as Compound A (cpdA), produces anti-inflammatory effects in macrophages as well as increased glucose uptake in adipocytes, resulting in improved insulin sensitivity in a diabetic mouse model. This has led to widespread interest in using cpdA as a novel antidiabetic drug. However, although cpdA has great activity and specificity, it has only been experimented with in a mouse model. Further drug development for clinical purposes require some criteria to be met, such as low concentration, good solubility, and good stability. CpdA is not optimal in these respects. In collaboration with the Drug Development Division of the NIH (NCAT), we screened 16 putative GPR120 agonist compounds that were structurally fundamentally different from cpdA in an effort to develop a more suitable compound for further therapeutic drug development. A luciferase-based assay in Human Embryonic Kidney (HEK) 293A transfected with GPR120 and SRE-Luciferase in order to test the putative compounds for biological activity. NIH compound 108's log of the half-maximum effective concentration (EC50) is -6.17 ± 0.07 M. In comparison, cpdA's EC50 is -6.84 ± 0.19. These data suggest that NIH compound 108 should be further pursued in a diabetic mouse model as a potential novel anti-inflammatory and insulin-sensitizing compound.

Relevant Presentations:

Tridu Huynh, Evelyn Walenta, Da Young Oh, Jerrold Olefsky. "Validation of Putative GPR120 Agonists for the Development of a Therapeutic Anti-Inflammatory and Insulin-Sensitizing Drug." NIDDK Medical Scholars Research Symposium (August 2015). Vanderbilt University, Nashville, TN.
https://www.diacomp.org/shared/document.aspx?id=2296&docType=SSApplication&app=1049

D. Additional Information: Research Support and/or Scholastic Performance

Completed Research Support

NIH NCI Loan Repayment Program Grant Recipient Huynh, Tridu (PI) 06/2021 – 06/2023
$100,000 Grant awarded based on patient-derived-xenograft immunotherapy project proposal to be used toward loan repayment.
Role: Principal Investigator

KL2 TR001112-02 Topol, Eric (PI) 06/2020 – 06/2022
The Scripps Translational Institute (STSI) was awarded a Clinical and Translational Science Award (CTSA) by the NIH to support translational research in San Diego. The grant permits young investigators funding to complete clinical & translational trials as well as graduate work at 80% effort with continued 20% clinical effort maintained.
Role: KL2 Scholar

3T32DK007044-35S1 Olefsky, Jerrold (PI) 06/2015 - 08/2015
$7000 stipend to support a summer research project and travel costs to Vanderbilt to present at a national NIH-sponsored research symposium.
Role: Medical Student Scholar

Scripps Clinic Medical Group Schaffer, Randy (PI) 07/2019-07/2021
$15,000 pilot grant awarded for single cell RNA sequencing of human pancreatic ductal adenocarcinoma with a focus on myeloid-derived suppressors cells and regulatory T-cells.
Role: Sub-Principal Investigator

Bibliography

1. Chousal J.N., Sargolzaeiaval F., Huynh T.R., Zhao M., Rodberg K., Kopko P.M., Gopal S., Allen E.S. (2024). Hemolysis due to anti-IH in a patient with beta-thalassemia and mycoplasma pneumoniae infection. Immunohematology.

2. Patel S.P., Othus M., Kwang Chae Y., Huynh T.R., Tan B., Kuzel T.M., McLeod C.M., Lopez G., Chen H.X., Sharon E., Streicher H., Ryan C.W., Blanke C.D., Kurzrock R. (2024). Phase II Basket Trial of Dual Anti-CTLA-4 and Anti-PD-1 Blockade in Rare Tumors (DART) SWOG S1609: Adrenocortical Carcinoma Cohort. JITC.

3. Abeynaike S.A., Huynh T.R., Mehmood A., Kim T., Frank K., Gao K., Zalfa C., Gandarilla A., Shultz L., Paust S. (2023). Human Hematopoietic Stem Cell Engrafted IL-15 Transgenic NSG Mice Support Robust NK Cell Responses and Sustained HIV-1 Infection. Viruses.

4. Huynh T.R.*, Botta G.*, Spierling-Bagsic S.R., Schaffer R., Lin R., Sigal D. (2023). Neoadjuvant Chemotherapy and Radiotherapy in Borderline-Resectable and Locally-Advanced Pancreatic Cancer Patients. Cancer Med.

5. Cham J., Pandey A.C., New J., Huynh T.R., Hong L., Orendain N., Topol E.J., Nicholson L.J. (2022). 6 month serologic response to the Pfizer-BioNTech COVID-19 vaccine among healthcare workers. PLOS One.

6. Huynh T.R.*, Le D.T.*, Burt B., Van Buren G., Abeynaike S.A., Zalfa C., Nikzad R., Kheradmand F., Tyner J. J., Paust, S. (2021). Natural Killer Cells and Cytotoxic T-Lymphocytes are Required to Clear Solid Tumor in a Patient-Derived-Xenograft. JCI Insight.

7. Huynh T.R., Decker B., Fries T., Tunguturi A. (2018). Lateral Medullary Infarction with Cardiovascular Autonomic Dysfunction: An Unusual Presentation with Review of the Literature. Clin Auton Res.

8. Huynh T.R., Lekovic G., Lu C., Drazin D. (2018). Myxopapillary Ependymoma with Anaplastic Features: A Case Report with Review of the Literature. Surg Neuro Intl.

9. Nowyhed H.N., Huynh T.R., Thomas G.D., Blatchley A., Hedrick C.C. (2015). Cutting Edge: The Orphan Nuclear Receptor Nr4a1 Regulates CD8+ T Cell Expansion and Effector Function Through Direct Repression of Irf4. J. Immunol.

10. Nowyhed H.N., Huynh T.R., Blatchley A., Wu R., Thomas G.D., Hedrick C.C. (2015). The Nuclear Receptor Nr4a1 Controls CD8 T Cell Development Through Transcriptional Suppression of Runx3. Sci Rep.

11. Frank K., Kim T., Abeynaike S., Huynh T.R., Jones C.A., Johnson S.K., Tompkins S.M., Paust S. (under review). PD-L1 Modulation of TRAIL Expression Suppresses Natural Killer Cell Response to Acute Respiratory Virus Infection. Cell Host Microbe.