BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: DAVID D. TRAN

eRA COMMONS USER NAME: DAVID_TRAN

POSITION TITLE: VISITING PROFESSOR AND CHIEF, DIVISION OF NEURO-ONCOLOGY

EDUCATION / TRAINING

INSTITUTION AND LOCATION	DEGREE (*if applicable*)	Completion Date	FIELD OF STUDY
University of Washington, Seattle, WA	BS	1992-1996	Biochemistry
Mayo Clinic College of Medicine, Rochester, MN	MD, PhD	1997-2005	Medicine, Biomedical Sciences
Barnes-Jewish Hospital, St Louis, MO	Residency	2005-2007	Internal Medicine
Washington University School of Medicine	Fellowship	2007- 2011	Oncology/Neuro-Oncology

A. Personal Statement:

Creativity and innovativeness are two personal qualities that I have strived to achieve throughout my scientific career. Since graduate school, I have developed an inclination to take intellectual calculated risks in my scientific approach. For my PhD thesis work, I studied the functions of Calcium-modulating Cyclophilin Ligand (CAML). CAML knockout resulted in early embryonic lethality. However, I made a critical observation that CAML-null ES cells were viable and indistinguishable from wild-type cells, suggesting that CAML function is critical for cellular survival but only when ES cells differentiate. Instead of abandoning the project, I decided to tackle this head-on by taking the risky approach of differentiating CAML-null cells into epithelioid cells so that the elusive defects of CAML deletion might become apparent. Using these cells and a conditional CAML KO mouse I later created, I discovered that CAML regulates intracellular recycling of key tyrosine kinases (i.e. EGFR and Lck) to prolong activation of their signaling pathways. These findings resulted in two first-author publications in *Developmental Cell* and *Immunity*, and have important implications in tyrosine kinase-dependent malignancies.

During my postdoctoral years, I focused on the role of EMT in cancer metastasis. Several EMT factors with overlapping functions are co-expressed in the same tumor, making targeting cancer EMT a daunting task. I made an important observation that investigators often used continuous treatment with EMT-inducing cytokines (e.g., TGFβ) to induce EMT whereas in vivo the signals are transient due to the spatiotemporal separation between EMT initiation (primary tumors) and maintenance (metastatic sites). Again, typical of my tendency to challenge current practice, I mimicked the in vivo condition by treating cells with TGFβ transiently and uncovered 3 distinct EMT stages - Initiation, Maintenance, and MET - and a spatiotemporal hierarchy between Snail1 (initiation) and Twist1 (maintenance), which was later validated in breast cancer patients. Interestingly, the postulate that EMT is critical for cancer metastasis has been controversial since it has not been directly observed in tumors that develop *de novo*. To address this debate, I created a mouse model, in which I could detect, initiate and inhibit EMT at will - all engineered into the Snail1 locus. This was a risky move as any of these manipulations could render the locus inactive. To reduce risks, I created other recombination features allowing for removal of interfering components if necessary. With this novel EMT model, I demonstrated a critical role for Snail1-initiated EMT and its transient nature in breast cancer metastasis. Using AI, we recently discovered a critical Twist1/IL-6/R/p38 axis in DTC dormancy. Targeting this axis reactivates DTCs, rendering them sensitive to chemotherapy. This novel approach is the major focus of a patent, a FDOH Bankhead Coley grant, and the **NCI R01CA238387** grant supporting a **first-in-human trial** targeting dormant DTCs in high-risk triple negative breast cancer.

Continuing with the tradition of high risk, high reward science, my current research program has 4 main objectives: 1) To understand mechanism of cancer progression; 2) To identify pan-cancer master regulators of CSCs; 3) To translate research discoveries into novel cancer therapeutics; and 4) To develop innovative and powerful AI to functionalize Big Data to achieve the first 3 objectives. Moving to the University of Florida in 2015 was a strategic decision as I embarked on this new bold direction taking advantage of the vast supercomputing infrastructure the University has built and recently expanded to become the largest owned by a university in the US. We have invented several innovative computational platforms, collectively named NETZEN, to identify novel aberrant signals and master regulators unique to various cancers to better understand the mechanism of cancer development and to develop safer and more effective therapies. NETZEN has a robust ability to predict cell fate determinants and provides instructions on how to optimally combine them. These works have resulted in **15**

pending patents, a business STTR award **NCI R42CA228875** to develop a gene therapy targeting master regulators of GBM using custom-designed GBM-specific AAV2 variants, 1 license with 2 under negotiation, and 3 research service contracts to advance multiple discoveries by NETZEN.

Working with collaborators, I have advanced several new immunotherapy in Neuro-Oncology, my area of clinical interests. Using NETZEN, we developed a novel single immune cell analysis algorithm in patients with newly diagnosed GBM treated with the new anti-mitotic treatment Tumor Treating Fields (TTFields) and proved that TTFields double as a formidable in situ vaccination modality (*JCI 2022*), and in patients with recurrent GBM to establish synergistic immune effects of hyperthermia with anti-PD-1 inhibitors (manuscript in preparation).

Overall, these projects exemplify my scientific originality and my disposition for tackling difficult questions. I am poised to contribute to the continued success of the USC Norris Comprehensive Cancer Center.

1. Chen, D, Le, SB, Hutchinson, TE, Calinescu, A, Sebastian, M, Jin, D, Liu, T, Ghiaseddin, A, Rahman, M, and **Tran, DD*** (2022). *Tumor Treating Fields dually activate STING and AIM2 inflammasomes to induce adjuvant immunity in glioblastoma*. *J Clin Invest*. 132(8):e149258. *Senior/corresponding author. https://doi.org/10.1172/JCI159073.
2. **Tran D.D.** and Le, S., "GeneRep and nSCORE: Method and Apparatus for Improved Determination of Node Influence in a Network." Patent Pending, 2018, 62/408,045.
3. Le, S and **Tran, D.D.**, "Core Master Regulators of Glioblastoma Stem Cells." Patent Pending, 2018 and 2019, 62/802,554 and 62/586,655. A finalist in the 2019 Global Brain Race – 5 companies are currently competing to earn the right to license and commercialize this invention.
4. Zolotukhin, S and **Tran, D.D.**, "AAV capsid variants targeting human glioblastoma stem-like cells." Patent Pending, 2019, 62/884,716. Exclusive license agreement to Lacerta Therapeutics.

B. Positions, Scientific Appointments and Honors:

Positions

2022-present	Visiting Professor of Neurosurgery and Neurology, , University of Southern California Keck School of Medicine, Los Angeles, CA, USA
2022-present	Co-Director, USC Keck Brain Tumor Center, University of Southern California, Los Angeles, CA, USA
2022-present	Chief, Division of Neuro-Oncology, Department of Neurosurgery, University of Southern California Keck School of Medicine, Los Angeles, CA, USA
2019-2022	Associate Professor of Neurosurgery with tenure, University of Florida, Gainesville, FL.
2016-2022	Co-Chair, Neuro-Oncology Disease Specific Group, UFHealth Cancer Center.
2015-2022	Associate Director, Preston A. Wells, Jr. Center for Brain Tumor Research, University of Florida, Gainesville, FL.
2015-2022	Chief, Division of Neuro-Oncology, Department of Neurosurgery, University of Florida, Gainesville, FL.
2015-2022	Assistant Professor of Neurosurgery, Neurology and Medicine, Tenure Track, University of Florida, Gainesville, FL
2013-2015	Co-leader, Neuro-Oncology Research Focus Group, Siteman Cancer Center, Washington University, St Louis MO
2012-2015	Assistant Professor of Medicine, Tenure Track, Washington University, St Louis MO
2011-2015	Director, Adult Neuro-Oncology Program, Washington University, St Louis MO
2011-2012	Instructor of Medicine, Oncology, Washington University, St Louis, MO
2007-2011	Fellow, Oncology/Neuro-Oncology, Washington University, St. Louis MO
2005-2007	Medical Resident, Internal Medicine, Barnes Jewish Hospital

Honors and Awards

2022	Best Abstract Award, the 6th Quadrennial Meeting of the World Federation of Neuro-Oncology Societies, Cpex, Seoul, Korea.
2021	Basic Science Award, the 26th Annual Meeting & Education Day of the Society for Neuro-Oncology, Boston, MA.
2020	Innovations of the Year, UF Innovate/Technology Licensing
2019	Finalist, 25 globally selected inventions in the Brain Race - Center for Advancing Innovation, Bethesda MD.

2019	Visiting Professor, Cho Ray Hospital and National University of Medicine and Pharmacy, Ho Chi Minh City, Vietnam. “Novel Approaches in Brain Metastasis.”
2019	Visiting Professor, Mayo Clinic Jacksonville. “Targeting the GBM State.”
2019	Awarded tenure, University of Florida
2018	*21st Century Cures Act - Beau Biden Cancer Moonshot Award*
2018	Excellent Awards for Assistant Professors, Office of the Provost, University of Florida
2016	Bankhead Coley Research Award - Florida Department of Health
2015	Finalist, NIH Director’s New Innovators Awards Program
2015	Visiting Professor, Fu Jen Catholic University, Taiwan
2014	Visiting Professor, University of Florida
2013	NIH, K08 – Career Development Award
2013	Cancer Frontier Fund Award, BJH Foundation
2013	Pardee Foundation Scholar Award
2012	Concept Award, Department of Defense
2011	Young Investigator Award, Conquer Cancer Foundation, ASCO
2011	Finalist, Burroughs Wellcome Fund Career Awards for Medical Scientists
2010	NIH, Student loan repayment award
2008	Mallinckrodt Foundation Postdoctoral Fellow, Washington University, St Louis MO
2005	Physician Scientist Training Program Fellow – Washington University, St Louis MO
2001	Best poster award, Mayo Clinic Foundation Research Symposium
1997	Medical Scientist Training Program, Mayo Clinic College of Medicine, Rochester, MN
1996	Presidential award for the graduating senior with the highest academic achievement, University of Washington, Seattle, WA
1996	Phi Beta Kappa Honor Society, invited
1994	Honor Undergraduate Research Scholar, University of Washington, Seattle, WA
1996	University Dean’s Lists

Other Experiences and Professional Membership

2022-present	Associate Editor, Frontiers in Oncology.
2021-2022	Scientitifc reviewer, 2021-2022 AACR-Novocure TTFields Research Grants Program.
2021	Scientific reviewer, The Dutch Cancer Society (KWF) grant program.
2020-2021	Scientific reviewer, the FY2020 Peer Reviewed Cancer Research (PRCRP), DOD.
2020-2023	Standing member, NIH/NCI – Career Development Study Section.
2020	Member, NIH/NCI – Special Emphasis Panel ZCA1 RTRB-4 (M2)R.
2019	The UF Clinical and Translational Science Institute CTSI Pilot RFA, Gainesville FL.
2019-present	Member, American Society for Radiation
2018-2020	Temporary member, NIH/NCI – Career Development Study Section.
2015-present	Member, UFHealth Cancer Center
2014-present	Member, American Association for Cancer Research
2014	Cancer Frontier Award Study Section, BJH Foundation and Siteman Cancer Center
2013	Reviewer, Research Development Awards Program, Siteman Cancer Center
2012-2015	Member, NCCN, CNS Cancer National Guidelines Panel
2011-2015	Member, Siteman Cancer Center, Washington University/BJH
2010-present	Member, Society for Neuro-Oncology (SNO)
2009-present	Member, American Society of Medical Oncology

C. Contribution to Science:

I. **Cancer EMT and metastasis**: EMT factors appear to have overlapping functions, making the goal of inhibiting cancer EMT and metastasis daunting. We have established that EMT can be divded into 3 distinct stages: Initiation, Maintenance, and MET, which corresponded to metastatic stages of invasion, dormancy of disseminated tumor cells (DTCs), and reactivated growth of dormant DTCs to form macrometastases, respectively. We uncovered a temporospatial functional hierarchy among EMT factors with Snail1 being uniquely required for EMT initiation and Twist1, dispensable for initiation, uniquely required for maintenance. These predictions were validated in breast cancer patients. We also created a unique mouse model of cancer EMT and demonstrated a critical role for Snail1-initiated EMT and its transient nature in breast cancer metastasis. Ongoing projects are focused on the role of EMT factors in tumorigenesis and dormancy.

1. **Tran, D.D.** "Master Regulators of Breast Cancer Metastasis." March 2020, Serial No. 62/985,785.
2. **Tran, D.D.** Inventor. "Chemotherapeutic Resensitization of Disseminated Cancer Stem Cells through Reactivation by P38 Inhibition and IL-6 Inhibition - Chemotherapeutic Methods." PCT - February 2017: Patent Pending, **No. 62/301,210**.
3. Tran, H, Luitel. K, Kim, M, Zhang, K, Longmore, GD, and **Tran, DD*** (2014). Transient Snail1 Expression is Necessary for Metastatic Competence in Breast Cancer. *Cancer Res* 74(21): 6330-6340.
4. **Tran, DD***, Corsa, C, Biswas, H, Aft, RL, and Longmore, GD (2011). Temporal and Spatial cooperation of Snail1 and Twist1 during Epithelial-Mesenchymal Transition predicts for human breast cancer recurrence**.** *Mol. Can. Res.* 9(12):1644-1657**.** *Corresponding author**.**

II. **Computational Biology and Synthetic Biology**: We have recently invented ***NETZEN***, an integrated deep learning and gene network-based target discovery platform for precision medicine. NETZEN is a suite of 3 engines: 1) GeneRep applies the theory of mutual information to expression data to infer gene networks and streamlines reverse engineering tools on computer clusters, making it suitable for large-scale genomics; 2) TeraView is a novel 3D visualization platform for whole networks with unlimited complexity enhanced by automated pathway annotations, providing detailed network comprehension unparalleled in other existing algorithms; and 3) deep nSCORE is an automated node importance scoring framework incorporating the power of data processing of a neural network with the high accuracy of network-based ranking. Some of the best examples demonstrating the predictive robustness of NETZEN are its uncanny ability to predict cell fate determinants in normal and pathologic conditions. To study cancer cell evolution, we also create the Molecular Cell Diary System (MCDS), which enables (i) tracking of large numbers of cells individually in vivo, and (ii) mapping of lineage relationship to determine cell-cell interactions with high accuracy and confidence.

1. Le, S. and **Tran, D.D**., inventors; the University of Florida, assignee. A Molecular Cell Diary System. US/International patent pending **62/301,813**. February, 2017.
2. Le, S and **Tran, D.D.**, inventors; the University of Florida, assignee. GeneRep and nSCORE: Method And Apparatus For Improved Determination Of Node Influence In A Network. US/International patent pending **62/408,045**. October, 2017.
3. Le, S and **Tran, D.D.**, "Core Master Regulators of Glioblastoma Stem Cells." Patent Pending, 2018 and 2019, 62/802,554 and 62/586,655. A finalist in the 2019 Global Brain Race – 5 companies are currently competing to earn the right to license and commercialize this invention.
4. Le, S and **Tran, D.D.** "Immunotherapy For Direct Reprogramming of Cancer Cells Into Immune Cells/Antigen Presenting Cells/Dendritic Cells." PCT filed, December 2020, 62/952,725.

III. **Novel Mechanisms of Tumor Treatment Fields (TTFields):** The novel approved GBM mesothelioma treatment TTFields employs alternating, intermediate-frequency (200kHz) electric fields to disrupt mitotic macromolecules leading to chromosome mis-segregation and apoptosis. I have involved in the early clinical development of the technology in GBM. More recently, we have established a novel mechanism by which TTFields induce focal disruption of the nuclear envelope, leading to cytosolic release of large free DNA clusters that intensely activate DNA sensors and their cognate inflammasomes, thereby releasing pro-inflammatory cytokines and type-1 interferons leading to activation of DCs and T cells. TTFields thus represent a powerful in situ vaccination modality for solid tumors and create a potential therapeutic synergy with immune checkpoint inhibitors, which are currently in clinical trial testing. In addition, we have also recently discovered a potential mechanism of resistance to TTFields through the novel Prostaglandin E receptor 3 (PTGER3) and ZNF488 axis with significant clinical implication and applicability.

1. Chen, D, Le, SB, Hutchinson, TE, Calinescu, A, Sebastian, M, Jin, D, Liu, T, Ghiaseddin, A, Rahman, M, and **Tran, DD** (2022). *Tumor Treating Fields dually activate STING and AIM2 inflammasomes to induce adjuvant immunity in glioblastoma*. *J Clin Invest*. 132(8):e149258. https://doi.org/10.1172/JCI159073.
2. Stupp R, Taillibert S, Kanner A, Read W, Steinberg DM, Lhermitte B, Toms S, Idbaih A, Ahluwalia MS, Fink K, Di Meco F, Lieberman F, Zhu JJ, Stragliotto G, **Tran DD**, Brem S, Hottinger AF, Kirson ED, Lavy-Shahaf G, Weinberg U, Kim CY, Paek SH, Nicholas G, Burna J, Hirte H, Weller M, Palti Y, Hegi ME, Ram Z (2017). *Effect of Tumor-Treating Fields Plus Maintenance Temozolomide vs Maintenance Temozolomide Alone on*

Survival in Patients with Glioblastoma: A Randomized Clinical Trial. JAMA. 318(23):2306-2316. doi: 10.1001/jama.2017.18718.

3. **Tran, D.D.** and Chen, D. *"Methods for Reducing Viability of Cancer Cells by Activation of the STING Pathway with TTFields."* PCT filed April 2020: Serial No. 16/673,246.
4. **Tran, D.D.**, Chen, D, and Le, S. "*Inhibiting Prostaglandin E Receptor 3 Resensitizes Resistant Cells to TTFields and Prevents Cells from Developing Resistance to TTFields.*" PCT filed October 2019: Serial No. 62/849,535.

IV. **Clinical Neuro-Oncology:** I have developed and participated in seminal clinical trials in the field. Besides translating novel clinical applications of hyperthermia in CNS drug delivery and immunotherapy, my clinical research interests have focused on determining the molecular, radiographic criteria for distinguishing true from pseudoprogression, a common and poorly understood phenomenon in brain tumor treatment. We demonstrated that the presence of 1p/19 q codeletions, a recurrent mutation on oligogliomas predicted against pseudoprogression. Ongoing projects use genomic approaches to establish a global genetic, molecular and radiographic signature of pseudoprogression.

1. Butt, OH, Zhou, AY, Huang, J, Chheda, MG, Johanns, T, Ansstas, G, Liu, J, Talcott, G, Nakiwala, R, Shimony, JS, Kim, AH, Leuthardt, EC, **Tran, DD***, Campian, JL* (2021). A phase II study of laser interstitial thermal therapy combined with doxorubicin in patients with recurrent glioblastoma. *Neurooncol Adv 3(1):vdab164*. *Co-Senior/corresponding author
2. Leuthardt, EC, Duan, C, Kim, MJ, Campian, JL, Kim, AH, Miller-Thomas, MM, Shimony, JS, and **Tran, DD** (2016). Hyperthermic Laser Ablation of Recurrent Glioblastoma Leads to Temporary Disruption of the Peritumoral Blood Brain Barrier. *Plos One*. 11(2):e0148613.
3. Weller, M, Butowski, N, **Tran, DD**, Recht, LD, Lim, M, Hirte, H, Ashby, L, Mechtler, L, Goldlust, SA, Iwamoto, F, Drappatz, J, O'Rourke, DM, Wong, M, Hamilton, MG, Finocchiaro, G, Perry, J, Wick, W, Green, J, He, Y, Turner, CD, Yellin, MJ, Keler, T, Davis, TA, Stupp, R, and Sampson, JH (2017). Rindopepimut with temozolomide for patients with newly diagnosed, EGFRvIII-expressing glioblastoma (ACT IV): results of a randomized, double-blind, international phase 3 trial. *Lancet Oncol.* 18(10):1373-1385. doi: 10.1016/S1470-2045(17)30517-X.
4. Lin, A, Liu, J, Evans, J, Leuthardt, E, Rich, K, Dacey, R, Kim, A, Zipfel, G, Huang, J, Robinson, C, Simpson, J, Chicoine, M, **Tran, D**D (2014). Codeletions at 1p and 19q predict for a lower risk of pseudoprogression in oligodendrogliomas and mixed oligoastrocytomas. *Neuro Oncol* 16(1):123-130.

V. **Function of Calcium-modulating Cyclophilin Ligand (CAML) in growth signaling:** When I started my PhD work, little was known about CAML beside its role in T cell activation *in vitro*. CAML knockout causes early embryonic lethality. However, CAML-null ES cells were viable and indistinguishable from wild-type cells, suggesting that CAML function is critical for cellular survival only when ES cells differentiate. By differentiating CAML-null ES cells *in vitro* into epithelial cells and later creating a conditional CAML KO mouse, I discovered that CAML regulates recycling of important tyrosine kinases (e.g. EGFR & Lck) from their intracellular pools to the plasma membrane, allowing them to be activated more efficiently and for longer. These findings have important implications in tyrosine kinases-dependent cellular transformation.

1. Yu, L, Malureanu, L, Karthibabu, J, **Tran, DD**, Lindquist, L, Bram, RJ (2009). CAML loss causes anaphase failure and chromosome missegregation. *Cell Cycle* 8(6)940-949.
2. Yuan, X, Yao, J, Norris, D, **Tran, DD**, Bram, R, Chen, G and Luscher, B (2008). Calcium-modulating cyclophilin ligand regulates membrane trafficking of postsynaptic $GABA_A$ receptors. *Mol. Cell. Neurosci.* 38(2)277-289.
3. **Tran, DD**, Heckman, K, et al (2005). CAML interacts with $p56^{Lck}$ and is required for T cell development. *Immunity* 23(8)139-152.
4. **Tran, DD**, Russell, H, Sutor, SL, van Deursen, J and Bram, RJ (2003). CAML is required for efficient EGF receptor recycling. *Developmental Cell* 5(2):245-256.

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/myncbi/david.tran.1/bibliography/public/