# MEET KEVIN THARP, PHD

## Tumor Microenvironment (TME) Junior Investigator Profile

Dr. Kevin Tharp is an Assistant Professor at the Sanford Burnham Prebys Medical Discovery Institute (SBPMDI) in San Diego, California. Kevin is a full member of the NCI-designated Cancer Center: Cancer Metabolism and Microenvironment program at SBPMDI. He completed his graduate studies at University of California, Berkeley with Dr. Andreas Stahl (Thesis Advisor and Primary Mentor) and Dr. Kevin Healy (Secondary Mentor), where he explored the relationship between biomaterials, stem cell differentiation, and thermogenic adipose tissues. Kevin became interested in the role of intrinsic and extrinsic biomechanical properties of cells and tissues affecting mitochondrial metabolism and joined Dr. Valerie Weaver's Center for Bioengineering and Tissue Regeneration at University of California, San Francisco for postdoctoral studies.



**Kevin Tharp, PhD**

*Let's talk about tumor microenvironment. Could you please tell us:*

**1. What are you most excited about with respect to your research?**
Kevin Tharp (K.T.): The potential to improve anti-cancer therapeutics. My laboratory uses multidisciplinary approaches to test how adaptive metabolic programming facilitates the construction of structural elements that mediate tumor progression. Currently, we are focused on two structural elements observed in the tumor microenvironment that impede anti-tumor immunity: 1. The accumulation of excessive collagen (fibrosis) 2. The synthesis of an immune suppressive glycocalyx (pericellular matrix composed of glycoconjugates). I'm particularly excited to explore the basic mechanism that connect these two processes and identify therapeutically actionable nodes of metabolism that facilitate the synthesis of these macromolecules that negatively impact T and NK-cell mediated anti-tumor immunity.

**2. What are the main challenges that remain to be addressed in the area of your research? How will your research address them?**
K.T.: Fibrotic collagen networks contain many potential binding sites that immune cells interact with in ways that limit their movement and activity against tumor cells. Similarly, the immune suppressive glycocalyx has many potential interactions, compositions, and topologies that affect immune surveillance of tumor cells. It is a massive challenge to define the exact binding sites in these molecules that mediate poor outcomes for patients, but that is what is required to develop therapeutics that act to block these molecular interactions that suppress anti-tumor immunity. While my primary efforts are to therapeutically target the metabolic programming which underpins the synthesis of these molecules, I will also use a variety of biochemical strategies to identify the exact binding sites within the cancer-associated glycocalyx and fibrotic collagen networks that negatively impact anti-tumor immunity.

**3. What might be the next opportunities in the area of your research that your lab would explore?**
K.T.: I think that model improvements to better match human physiology will aid our ability to identify therapeutics that durably cure. In vitro cultures and mouse models are excellent, but they are incomplete substitutes for the human body. I think that model systems the match physical and biochemical properties of the tissue and tumor microenvironment will aid our ability to model the physiology we need to develop effective therapeutics for people suffering with cancer. However, due to the genomic and non-genomic heterogeneity of tumors, it is an incredibly large challenge to generate in vitro cultures that faithfully recapitulate the breadth of cell physiology observed in human tumors. I am currently working to develop large scale screening-compatible in vitro models that faithfully match the mean mitochondrial composition of certain human tumors. However, this is just one organelle – and tumor phenotypes affect every aspect of cell physiology. I see many opportunities to democratize and scale biomaterials, cell mixtures, and culture media to improve the model systems we use to more faithfully recapitulate human tumor biology.

**4. What are 3 papers on the area of your research that you would recommend AACR-TME scientists to read?**

a) Tello-Lafoz M, Srpan K, Sanchez EE, Hu J, Remsik J, Romin Y, Calò A, Hoen D, Bhanot U, Morris L, Boire A, Hsu KC, Massagué J, Huse M, Er EE. Cytotoxic lymphocytes target characteristic biophysical vulnerabilities in cancer. Immunity. 2021 May 11;54(5):1037-1054. e7. doi: 10.1016/j.immuni.2021.02.020. Epub 2021 Mar 22. PMID: 33756102; PMCID: PMC8119359.

b) Weems AD, Welf ES, Driscoll MK, Zhou FY, Mazloom-Farsibaf H, Chang BJ, Murali VS, Gihana GM, Weiss BG, Chi J, Rajendran D, Dean KM, Fiolka R, Danuser G. Blebs promote cell survival by assembling oncogenic signalling hubs. Nature. 2023 Mar;615(7952):517-525. doi: 10.1038/s41586-023-05758-6. Epub 2023 Mar 1. PMID: 36859545; PMCID: PMC10881276.

c) Park S, Colville MJ, Paek JH, Shurer CR, Singh A, Secor EJ, Sailer CJ, Huang LT, Kuo JC, Goudge MC, Su J, Kim M, DeLisa MP, Neelamegham S, Lammerding J, Zipfel WR, Fischbach C, Reesink HL, Paszek MJ. Immunoengineering can overcome the glycocalyx armour of cancer cells. Nat Mater. 2024 Mar;23(3):429-438. doi: 10.1038/s41563-024-01808-0. Epub 2024 Feb 15. PMID: 38361041.

**5. What are your favorite things to do when you are not in the lab?**
K.T.: Adventures with my family, going to the beach with friends, and eating chili relleno burritos while watching the sunset.