

Molecular Mechanisms and Translational Oncology

Do you have a background in molecular, biochemical or chemical mechanisms and are interested in translational medicine? Are you interested in taking your mechanistic findings rapidly to the bedside in a vibrant clinical research program? If so, a postdoctoral fellowship position supported by the National Institutes of Health and the Prostate Cancer Foundation is available in the laboratory of Dr. Nima Sharifi at the Cleveland Clinic.

Our laboratory focuses on mechanistic discovery to understand the metabolic and molecular mechanisms that lead to cancer progression and treatment resistance. Specific areas include:

- 1) Metabolic and genetic changes required for hormone therapy resistance in prostate cancer, breast cancer and tumor progression
- 2) Clinical validation in patients and clinical trials using innovative approaches
- 3) Animal models of advanced cancer for translational and therapeutic studies
- 4) Identifying targets for the development of new pharmacologic therapies

We discovered the first example of a gain-of-function in a steroid-synthesizing enzyme that enables prostate cancer resistance to hormonal therapy (Chang, et al. *Cell*. 2013;154:1074-84). We also discovered that abiraterone works by conversion to a more active steroidal metabolite (Li, et al. *Nature*. 2015;523:347-51), that metabolism is pharmacologically modifiable to optimize therapy (Li, et al. *Nature*. 2016;533:547-51) and that these events are a class effect of steroidal androgen synthesis inhibitors (Alyamani, et al. *Cell Chem Biol*. 2017;24:825-32) and genetic determination of metabolite generation (Alyamani, et al. *J Clin Invest*. 2018;128:3333-40). View a quick summary of these discoveries here:

<https://www.youtube.com/watch?v=22dFzT4RFno>

This position is ideal for an individual with a strong interest in rapid translation of basic mechanistic discoveries to the bedside as this is a principal goal of the Sharifi Laboratory. For example, we have shown that our discovery of a gain-of-function in a steroid-synthesizing enzyme is a predictive biomarker of poor outcomes after prostate cancer hormonal therapy (Hearn, et al. *Lancet Oncol*. 2016;17:1435-44; *JAMA Oncol*. 2018;4:558-62; *JAMA Oncol*. 2020;6(4):e196496) and may account for about 5% of estrogen-driven postmenopausal breast cancers (Kruse, et al. *JCI Insight*. 2021;6(20):e150403). We have also recently discovered new metabolic targets for hormone therapy resistance (Li, et al. *Science Translational Medicine*. 2021.26;13(595):eabe8226). We are currently evaluating our discoveries in active clinical trials and are pursuing similar mechanisms in the lab.

The position will provide a unique and multidisciplinary exposure to tumor metabolism, molecular oncology, drug development and clinical trials. Further details are available at:

<http://www.lerner.ccf.org/cancerbio/sharifi/> and <http://newsroom.clevelandclinic.org/?s=sharifi>

The ideal candidate has a Ph.D. degree in biochemistry, chemistry or molecular biology; has the appropriate expertise in discovery of molecular, biochemical or chemical mechanisms; and is highly driven. Outstanding verbal and communication skills are required. Interested candidates should send their CV and contact information for 3 references to:

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