**BIOGRAPHICAL SKETCH**

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NAME: Alexander Valvezan

eRA COMMONS USERNAME: valvezan

POSITION TITLE: Assistant Professor of Pharmacology

EDUCATION/TRAINING

| INSTITUTION AND LOCATION | DEGREE *(if applicable)* | START DATE MM/YYYY | END DATE MM/YYYY | FIELD OF STUDY |
|---|---|---|---|---|
| University of Delaware, Newark, DE | BA | 09/2003 | 05/2006 | Biological Sciences |
| University of Pennsylvania, Perelman School of Medicine, Philadelphia, PA | PhD | 09/2006 | 05/2013 | Cell and Molecular Biology |
| Harvard University, T.H. Chan School of Public Health, Boston, MA | Postdoctoral fellow | 08/2013 | 08/2020 | Cell growth and cancer |

**A. Personal Statement**

My area of expertise encompasses the signaling and metabolic pathways that promote cell growth, with emphasis on the mechanistic Target of Rapamycin Complex 1 (mTORC1) network. My research program is focused on understanding how oncogenic mutations alter cancer cell metabolism to support uncontrolled growth, and whether specific mutations confer metabolic vulnerabilities that can be exploited and translated into anti-cancer therapy. The proposed research project will leverage my experience in these areas to determine the effects of PTEN loss and resultant mTORC1 activation on nucleotide homeostasis and sensitivity to nucleotide synthesis inhibitors in T-ALL.

As a graduate student at the University of Pennsylvania in the laboratory of Dr. Peter Klein, I discovered a novel function of the tumor suppressor APC as an inhibitor of mTORC1 activity and demonstrated that this function is disrupted by *APC* mutations in colorectal cancer (1,2). As a postdoctoral fellow at Harvard University in the laboratory of Dr. Brendan Manning, a world leader in the mTOR field, I focused on the regulation and function of mTORC1 in cell growth and cancer. I discovered a critical role for mTORC1 in coupling *de novo* nucleotide synthesis pathways to ribosome biogenesis pathways to maintain nucleotide homeostasis. Uncoupling those pathways unveiled a metabolic vulnerability that allows selective killing of tumor cells with active mTORC1 using clinically approved compounds, which could potentially be repurposed as anti-cancer agents (3,4). These experiences have given me the requisite knowledge and technical abilities to carry out the proposed research project, including the ability to take full advantage of the mouse models mass spectrometry-based techniques to be used here.

I opened my independent laboratory at Rutgers University in Sept 2020. Working at Rutgers as a full member of both the Center for Advanced Biotechnology and Medicine (CABM), and the Rutgers Cancer Institute of New Jersey (CINJ), an NCI-designated Comprehensive Cancer Center (where I am a member of the Cancer Metabolism Research Program), gives me the opportunity to work with world leaders in many related fields while being supported by state-of-the-art facilities and resources. These productive scientific interactions are further facilitated by my primary tenure-track faculty appointment in the Department of Pharmacology and secondary appointment in the Department of Medicine at the Rutgers Robert Wood Johnson Medical School (RWJMS). Our collaborator Dr. Xiaoyang Su is the Director of the Metabolomics/Mass Spectrometry Core Facility at the Rutgers Cancer Institute of New Jersey, and will assist in performing the metabolomics

experiments, metabolic flux assays, and quantification of IMPDH inhibitor levels as described in the Research Proposal.


1. **Valvezan AJ**, Zhang FS, Diehl JA, Klein PS. Adenomatous Polyposis Coli (APC) regulates multiple signaling pathways by enhancing glycogen synthase kinase-3 (GSK-3) activity. *Journal of Biological Chemistry*, 287(6):3823-32, Feb 2012. PMC3281685

2. **Valvezan AJ**, Huang J, Lengner CJ, Pack M, Klein PS. Oncogenic mutations in adenomatous polyposis coli (Apc) activate mechanistic target of rapamycin complex 1 (mTORC1) in mice and zebrafish. *Disease Models and Mechanisms*, 7(1):63-71, Jan 2014. PMC3882049

3. **Valvezan AJ**, Turner M, Belaid A, Lam HC, Miller SK, McNamara MC, Baglini C, Housden BE, Perrimon N, Kwiatkowski DJ, Asara JM, Henske EP, Manning BD. mTORC1 couples nucleotide synthesis to nucleotide demand resulting in a targetable metabolic vulnerability. *Cancer Cell,* 32(5):624-638, Nov 2017. PMC5687294

4. **Valvezan AJ,** McNamara MC, Miller SK, Torrence ME, Asara JM, Henske EP, Manning BD. IMPDH inhibitors for anti-tumor therapy in tuberous sclerosis complex. *JCI Insight*, 5(7):e135071, Apr 2020. PMC7205253


Research Support:

Ongoing Projects
Ludwig-Princeton Branch Cancer Metabolism Award
Valvezan (PI)
1/1/23 – 12/31/23
Enhancing the selective tumor cell-killing effects of purine synthesis inhibitors in mTORC1-driven tumors

New Jersey Dept of Health/New Jersey Commission on Cancer Research Pediatric Cancer Grant
Valvezan (PI)
6/1/2022 – 5/31/2025
Defining and targeting metabolic reprogramming in Familial Adenomatous Polyposis

Breast Cancer Alliance Young Investigator Grant
Valvezan (PI)
3/1/2022 – 2/28/2024
Targeting triple-negative breast cancer by exploiting a metabolic vulnerability downstream of mTORC1

Rutgers Cancer Institute of New Jersey Pediatric Cancer Award
Valvezan (PI)
8/1/2022 – 5/31/2023
Targeting PTEN-deficient T-cell acute lymphoblastic leukemia by exploiting a metabolic vulnerability downstream of mTOR Complex 1

Recently Completed Projects
Dept of Defense Exploration-Hypothesis Development Award TS190025
Valvezan (PI)
10/1/2020 – 9/30/2022
Defining cellular stresses sensed through the TSC complex to identify vulnerabilities in TSC tumors

Leukemia Research Foundation Research Grant
Valvezan (PI)
7/1/2021 – 7/31/2022

Repurposing IMPDH inhibitors for selective targeting of PTEN-deficient T-ALL cells

Rutgers Cancer Institute of New Jersey New Investigator Award
Valvezan (PI)
10/22/2020 – 10/21/2021
Regulation and function of mTORC1 in cell growth and cancer

## Positions, Scientific Appointments, and Honors

### Positions and Scientific Appointments

| | |
|---|---|
| 2020 – present | Assistant Professor, Rutgers University, Robert Wood Johnson Medical School, Department of Pharmacology, Department of Medicine, Center for Advanced Biotechnology and Medicine (CABM), Cancer Institute of New Jersey (CINJ) |
| 2013 – 2020 | Postdoctoral fellow, Harvard University, T.H. Chan School of Public Health, Department of Molecular Metabolism, laboratory of Brendan Manning, PhD. |
| 2006 – 2013 | Graduate Student, University of Pennsylvania, Perelman School of Medicine, Cell and Molecular Biology program, laboratory of Peter Klein, MD, PhD. |

### Honors

| | |
|---|---|
| 2023 | Ludwig-Princeton Cancer Metabolism Award |
| 2022 – 2025 | New Jersey Dept of Health/New Jersey Commission on Cancer Research Pediatric Cancer Award |
| 2022 – 2024 | Breast Cancer Alliance Young Investigator Award |
| 2022 – 2023 | Rutgers Cancer Institute of New Jersey Pediatric Cancer Pilot Award |
| 2021 – 2022 | Leukemia Research Foundation New Investigator Award |
| 2020 – 2022 | Department of Defense Tuberous Sclerosis Complex Research Program Exploration-Hypothesis Development Award |
| Dec 2022 | Invited speaker at the University of Pennsylvania Abramson Cancer Center |
| Mar 2021 | Selected for poster presentation at the Keystone International Symposium “Metabolic Decisions in Development and Disease” |
| Mar 2021 | Rutgers Office of Research Core Facility Utilization Award |
| Feb 2021 | Invited presentation at the Binghamton University Biology Symposium |
| Jan 2021 | Selected for poster presentation at the Keystone International Symposium “Tumor Metabolism and the Microenvironment” |
| Nov 2020 | Invited presentation at the CINJ-Princeton Cancer Research Symposium |
| Oct 2020 | Rutgers Cancer Institute of New Jersey New Investigator Award |
| Sept 2018 | Selected for poster presentation at the AACR Special Conference “Metabolism and Cancer” |
| Jan 2018 | Selected for poster presentation at the Keystone “Tumor Metabolism” Symposium |
| Mar 2017 | “Best Abstract” Award, and invited presentation at the Dana Farber/Harvard Cancer Center Kidney Cancer Symposium. |
| Oct 2016 | Selected for poster presentation at the national American Cancer Society conference |
| Aug 2016 | Selected for oral presentation at Cold Spring Harbor conference on “The PI3K-mTOR-PTEN network in health and disease” |
| 2015 – 2018 | Tuberous Sclerosis Alliance Rothberg Courage Award with B. Manning |
| 2014 – 2017 | American Cancer Society Postdoctoral Fellowship Award (PF-14-254-01-TBE) |
| 2011 – 2013 | Hematopoiesis Training Grant (T32-DK007780) |
| 2008 – 2011 | Neuropharmacology Training Grant (T32-MH014654) |
| 2006 | B.A. awarded *magna cum laude* (degree earned in 3 years) |

**Contributions to Science**

***1. Discovered a targetable metabolic vulnerability that results from uncontrolled mTORC1 activation in tumors.*** Mechanistic Target of Rapamycin Complex 1 (mTORC1) is a master regulator of anabolic cell growth that is active in the majority of human cancers across nearly all lineages (1). I discovered that mTORC1 activation increases cellular dependence on ribonucleotide synthesis pathways, unveiling a metabolic vulnerability that can be exploited using clinically approved inhibitors of the rate-limiting enzyme in *de novo* guanylate nucleotide synthesis, inosine 5'-monophosphate dehydrogenase (IMPDH) (2,3). In tumor cells with uncontrolled mTORC1 activity, but not in control cells, IMPDH inhibition causes rapid nucleotide depletion, which leads to DNA replication stress, DNA damage, and apoptosis. Clinically approved IMPDH inhibitors demonstrate strong anti- tumor efficacy in genetic and xenograft mouse models of mTORC1-driven tumor growth, at therapeutically relevant plasma concentrations. The selective effects of IMPDH inhibition stem from an increased demand for nucleotides created by mTORC1-driven synthesis of ribosomal RNA (rRNA) to support ribosome biogenesis, a classical function of mTORC1. In this manner, mTORC1 creates dependence on nucleotide synthesis pathways, which are also stimulated by mTORC1 in parallel to meet this demand and sustain sufficient free NTP pools for conversion to dNTPs for DNA synthesis. This insight into the importance of metabolic coordination by mTORC1 reveals a vulnerability that could potentially be exploited to treat cancers and genetic tumor syndromes with active mTORC1.

a. **Valvezan AJ** and Manning BD. Molecular logic of mTORC1 signaling as a metabolic rheostat. *Nature Metabolism,* 1:321-333, Mar 2019. PMID:32694720

b. **Valvezan AJ**, Turner M, Belaid A, Lam HC, Miller SK, McNamara MC, Baglini C, Housden BE, Perrimon N, Kwiatkowski DJ, Asara JM, Henske EP, Manning BD. mTORC1 couples nucleotide synthesis to nucleotide demand resulting in a targetable metabolic vulnerability. *Cancer Cell,* 32(5): 624- 638, Nov 2017. PMC5687294

c. **Valvezan AJ,** McNamara MC, Miller SK, Torrence ME, Asara JM, Henske EP, Manning BD. IMPDH inhibitors for anti-tumor therapy in tuberous sclerosis complex. *JCI Insight*, 5(7):e135071, Apr 2020. PMC7205253

***2. Discovered novel roles for the tumor suppressor APC, including suppression of mTORC1 activity*.** The Wnt pathway plays essential roles in embryonic development, stem cell regulation, and cancer. Inhibition of Glycogen Synthase Kinase-3 (GSK-3) is an essential step during Wnt signal transduction, but how this occurs was a longstanding question (1). I discovered that the tumor suppressor Adenomatous Polyposis Coli (APC) directly and constitutively enhances the enzymatic activity of GSK-3, and that Wnt signaling dissociates APC from GSK-3, resulting in reduced GSK-3 activity. These results also led to the unexpected finding that APC suppresses mTORC1 activity, and that robust activation of mTORC1 is an important consequence of truncating mutations in *APC*, which give rise to ~80% of human colorectal cancers (2,3).

a. **Valvezan AJ** and Klein PS. GSK-3 and Wnt Signaling in Neurogenesis and Bipolar Disorder. *Front Mol Neurosci*, 5:1, Jan 2012.

b. **Valvezan AJ**, Zhang FS, Diehl JA, Klein PS. Adenomatous Polyposis Coli (APC) regulates multiple signaling pathways by enhancing glycogen synthase kinase-3 (GSK-3) activity. *Journal of Biological Chemistry*, 287(6):3823-32, Feb 2012. PMC3281685

c. **Valvezan AJ**, Huang J, Lengner CJ, Pack M, Klein PS. Oncogenic mutations in adenomatous polyposis coli (Apc) activate mechanistic target of rapamycin complex 1 (mTORC1) in mice and zebrafish. *Disease Models and Mechanisms*, 7(1):63-71, Jan 2014. PMC3882049

***3. Identified synthetic lethal interactions to inform potential targets for treating cancers with active mTORC1.*** To identify dependencies unique to cells with uncontrolled mTORC1 activation, I collaborated

with Benjamin Housden and Norbert Perrimon at Harvard Medical School, to perform RNAi and CRISPR-based synthetic lethal screens in drosophila S2 cells that either express or lack the essential negative regulators of mTORC1, Tsc1 and Tsc2. The results of these screens were validated in mouse embryonic fibroblasts and human patient tumor-derived, TSC2-deficient renal angiomyolipoma (AML) cells. This conservation of synthetic lethality across drosophila, mouse, and human cells was used as an "evolutionary filter" to identify new potential targets for the treatment of cancers with active mTORC1. Targets identified in these studies include enzymes involved in mRNA capping and splicing, RNA Polymerase II-mediated transcription, lysosomal transport, and mitochondrial fission/fusion (1,2).

a. Housden BE, **Valvezan AJ**, Kelley C, Sopko R, Hu Y, Roesel C, Lin S, Buckner M, Tao R, Yilmazel B, Mohr SE, Manning BD, Perrimon N. Identification of potential drug targets for tuberous sclerosis complex by synthetic screens combining CRISPR-based knockouts with RNAi. *Sci Signal*, 8(393), Sept 2015. PMC4642709

b. Housden BE, Li Z, Kelley C, Wang Y, Hu Y, **Valvezan AJ**, Manning BD, Perrimon N. Improved detection of synthetic lethal interactions in *Drosophila* cells using variable dose analysis (VDA). *Proc Natl Acad Sci USA*, 114(50):E10755-E10762, Nov 2017. PMC5740648

**For a complete list of publications please see: https://www.ncbi.nlm.nih.gov/pubmed/?term=valvezan**