BIOGRAPHICAL SKETCH

NAME: Douglas Edmund Feldman

eRA COMMONS USER NAME: FELDMAN.DOUGLAS

POSITION TITLE: Assistant Professor, Research.

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
Harvard College	A.B.	06/1994	Biochemistry
Stanford University	Ph.D.	06/2003	Molecular Cell Biology
Stanford University Medical Center	Postdoctoral	08/2007	Molecular Oncology
USC Keck Medical Center	Postdoctoral	09/2012	Molecular Oncology

A. Personal Statement

My laboratory utilizes a combination of synthetic biology, protein engineering and in vivo mouse genetic and disease models to understand the role of the immune system in cancer, with a particular interest in understanding how innate immune signaling is suppressed in tumors. We seek to take advantage of recent advances in synthetic biology and stem cell biology to design, engineer, and develop new and more effective therapeutic platforms to treat lethal and incurable cancers.
My background and deep expertise in protein engineering and immune cell engineering will provide a strong foundation for directing this project to a successful outcome. The project will require extensive interactions with oncologists, bioinformaticians and experts in cell manufacturing, requiring a multidisciplinary approach. My training and prior experience both at the bench and as a laboratory director will enable the successful completion of all experimental goals set forth in this proposal.

Ongoing and recently completed projects that I would like to highlight include:

R21 AA027535-01A1
Feldman (PI)
09/01/2019–02/28/2022
Engineering CAR-T for treatment of alcoholic liver disease

RA210134 US DOD/CDMRP
Feldman (PI)
08/15/2022-08/14/2023
STING-Activating CAR-NK Cell Therapy for the Treatment of Rare Gynecological Cancers

Citations

1. **Feldman DE,** Chen C, Punj V, Tsukamoto H, Machida K. Pluripotency factor-mediated expression of the leptin receptor (OB-R) links obesity to oncogenesis through tumor-initiating stem cells. *Proc. Natl. Acad. Sci. USA.* 2012 Jan 17; 109(3):829-34. PMCID: PMC3271911.

2. Kweon S-M., Chen Y, Moon E, Kvederaviciute K, Klimasauskas S, **Feldman DE**. An Adversarial N6-Methyladenine-Sensor Network Preserves Polycomb Silencing. *Molecular Cell.* 74(1):1-10, 2019. PMID: 30982744

3. Yeh D-W, Zhao X, Siddique H, Hernandez JC, Zheng M, Choi HY, Machida M, Narayanan P, Kou Y, Punj V, Tahara SM, **Feldman DE**, Chen L, Machida K. *Hepatology*, 74 (S1):362, 2021. https://doi.org/10.1002/hep.32188

4. Ho P, Chen Y, Biswas S, Canfield E, **Feldman DE**. Bacteriophage anti-defense genes that neutralize TIR and STING immune responses. *bioRxiv*, 2022. doi.org/10.1101/2022.06.09.495361

B. Positions, Scientific Appointments, and Honors

Positions and Employment

10/2015-present	Assistant Professor of Research, USC Keck School of Medicine Department of Pathology
10/2012-09/2015	Assistant Professor of Research, USC Keck School of Medicine Department of Pathology, USC Liver and Pancreas Disease Center
10/2010-09/2012	CIRM Postdoctoral Scholar, USC Keck School of Medicine
10/2009-09/2010	Postdoctoral Scientist, USC Keck School of Medicine
10/2007-08/2009	Scientist and Corporate Development Associate, LS9 Inc.
10/2003-09/2007	Postdoctoral Fellow, Stanford University Medical Center

Other Experience and Professional Memberships

2014-2015	American Association for Cancer Research
2013-present	American Association for the Study of Liver Disease

Honors

2017	Wright Foundation Trust Research Award
2017	James H. Zumberge Research Award
2017	USC Keck Dean's Research Award
2010	CIRM Postdoctoral Scholarship
2006	Multiple Myeloma Research Foundation, Research Fellowship
1995	Dean's Fellowship, Stanford University Medical Center
1994	AB *Magna cum laude*, Harvard University

C. Contributions to Science

1. My research has advanced our understanding of the molecular etiology of alcohol-induced liver tumor-initiating stem-like cells (TICs)-- rare, highly malignant cancer cells that share key characteristics with embryonic stem cells, including the expression of pluripotency-associated transcription factors. Analysis of tumor-initiating cells generated in the mouse liver provided some of the first in-depth characterization of the critical signaling networks underpinning their deregulated proliferation and immune cloaking.

a. **Feldman DE,** Chen C, Punj V, Tsukamoto H, Machida K. Pluripotency factor-mediated expression of the leptin receptor (OB-R) links obesity to oncogenesis through tumor-initiating stem cells. *Proc. Natl. Acad. Sci. USA.* 2012 Jan 17; 109(3):829-34. Epub 2011 Dec 29. PMCID: PMC3271911.

b. **Feldman DE,** Chen C, Punj V, Machida K. Feldman DE, Chen C, Punj V, Machida K. The TBC1D15 Oncoprotein Controls Stem Cell Self-Renewal through Destabilization of the Numb-p53 Complex. *PLoS ONE* 2013; 8(2): e57312. PMCID: PMC3584131

c. Siddique HR*, **Feldman DE***, Chen CL, Punj V Tokumitsu H, Machida K. NUMB phosphorylation destabilizes p53 and promotes self-renewal of tumor-initiating cells by NANOG-dependent mechanism in liver cancer. *Hepatology*. 2015 PMID: 26174965. (*co-author)

d. Yeh D-W, Zhao X, Siddique H, Hernandez JC, Zheng M, Choi HY, Machida M, Narayanan P, Kou Y, Punj V, Tahara SM, **Feldman DE**, Chen L, Machida K. *Hepatology*, 74 (S1):362, 2021. https://doi.org/10.1002/hep.32188

2. My laboratory has recently elucidated the molecular infrastructure of encoders, sensors, and erasers of DNA base modifications in embryonic stem cells, and how these components are in turn deregulated in alcohol-induced liver tumors. We have also investigated the function of these modified bases, as well as cyclic nucleotide immune signals, in the context of liver pathobiology and liver immunobiology. Our long- term vision seeks to translate insights gained from these studies towards applications in immune engineering for the treatment of ALD and fibrotic disease.

a. Kweon S.M., Zhu B, Chen Y, Xu S.Y., Aravind L, **Feldman DE**. Erasure of Tet-oxidized 5-methylcytosine by a SRAP nuclease. *Cell Reports.* 21(2):482-494, 2017. PMID: 29020633.

b**.** Kweon S.M., Chen Y, Moon E, Kvederaviciute K, Klimasauskas S, **Feldman DE**. An Adversarial N6-Methyladenine-Sensor Network Preserves Polycomb Silencing. *Molecular Cell.* 74(1):1-10, 2019. PMID: 30982744*.*

c. Shukla V, Halabelian L, Balagere S, Samaniego-Castruita, **Feldman DE**, Arrowsmith CH, Rao A, Aravind L. HMCES Functions in the Alternative End-Joining Pathway of the DNA DSB Repair during Class Switch Recombination in B Cells. *Molecular Cell,* 77(2):384-394*,* 2020*.* PMID: 31806351.

d. Ho P, Chen Y, Biswas S, Canfield E, **Feldman DE**. Bacteriophage anti-defense genes that neutralize TIR and STING immune responses. *bioRxiv*, 2022. https://doi.org/10.1101/2022.06.09.495361

3. Work from my postdoctoral fellowship at Stanford revealed that sustained tumor hypoxia, a condition prevalent in liver cancers and many other types of solid tumors, drives activation the unfolded protein response (UPR), a conserved, adaptive stress response triggered by the accumulation of misfolded proteins in the endoplasmic reticulum. We demonstrated that the central UPR components IRE1 and XBP1 are centrally activated in tumors and went on to identify small molecule inhibitors of IRE1 as candidate anti-tumor agents. This resulted in two patent filings in addition to the two publications listed below.

a. **DE Feldman**, V Chauhan, AC Koong. The Unfolded Protein Response: A Novel Component of the Hypoxic Stress Response in Tumors. *Mol. Cancer Res.* 2005; 3: 597-605. PMID: 16317085

b. C Coumenis, M Bi, J Ye, **D Feldman,** AC Koong**.** Hypoxia and the unfolded protein response. *Methods Enzymol.* 2007; 435: 275-293. PMID: 17998059

4. My graduate studies analyzed the biochemistry, mechanism of action and folding substrates of the chaperonin CCT/TRiC, a barrel-shaped, oligomeric folding chamber present in all eukaryotes. We identified the VHL tumor suppressor protein as a substrate of TRiC, and further demonstrated that naturally-occurring point mutations in VHL that give rise to renal carcinoma result in destabilization of the VHL-TRiC complex. These studies were the first to link specific mutations in a tumor suppressor protein to aberrant chaperonin-mediated folding.

a. **DE Feldman**, V Thulasiraman, R Ferreyra, J Frydman. Chaperonin-mediated folding of the VHL tumor suppressor protein. *Molecular Cell* 1999; 4:1051-1061. PMID: 10635329

b. **DE Feldman**, J Frydman. Protein folding in vivo: the importance of molecular chaperones. *Curr. Op. Struct. Biol.* 2000; 10: 26-33. PMID: 10679467

c. **DE Feldman**, C Spiess, D Howard, J Frydman. Tumorigenic mutations in VHL disrupt folding in vivo by interfering with chaperonin binding. *Molecular Cell* 2003*;* 12: 1213-1224. PMID: 14636579

Complete List of Published Work in My Bibliography:
https://www.ncbi.nlm.nih.gov/myncbi/1toM-N-kSoe5d/bibliography/public/