Modeling Human SDH-Deficient GIST

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Division of Surgical Oncology
Moores UCSD Cancer Center

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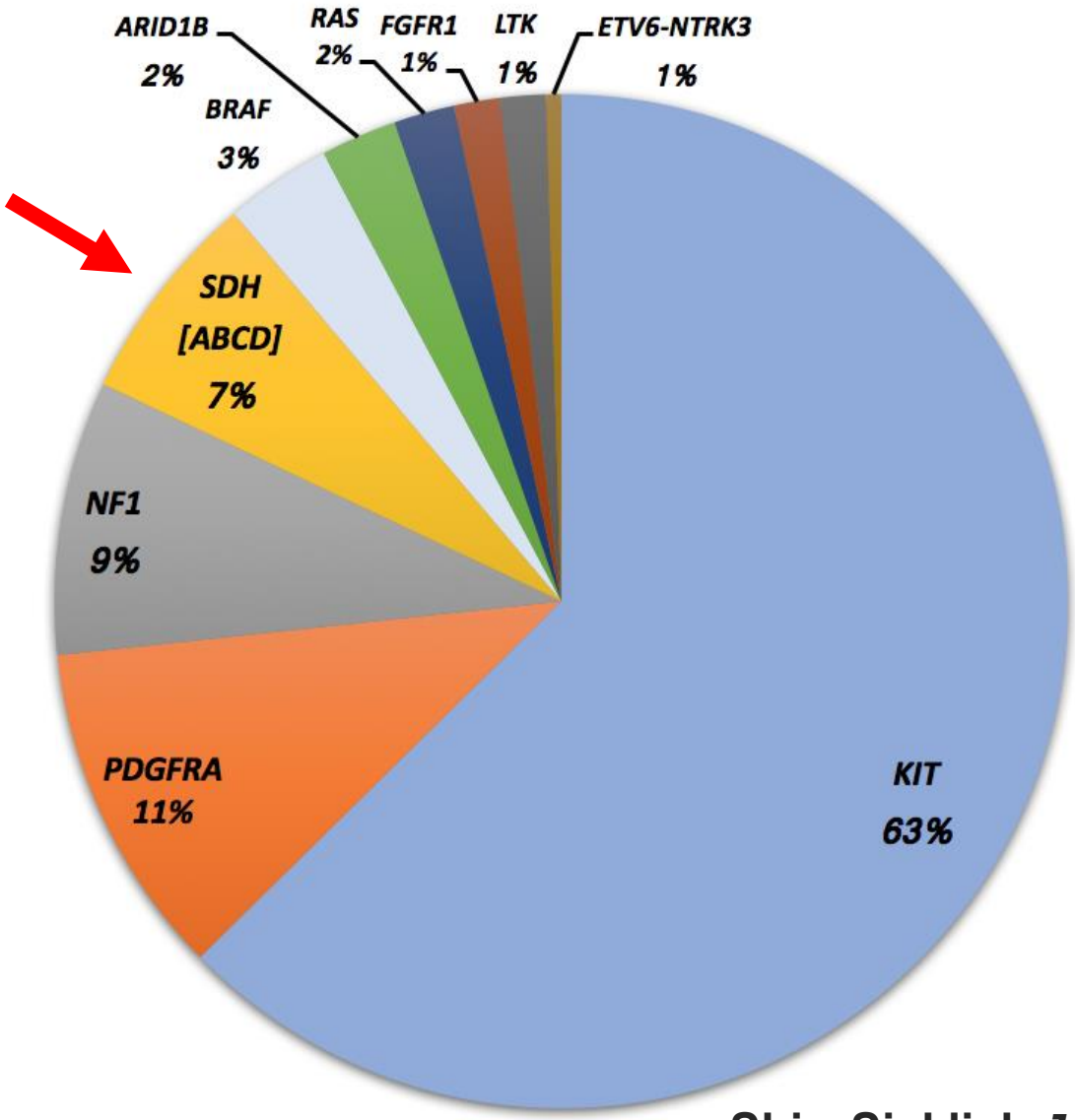
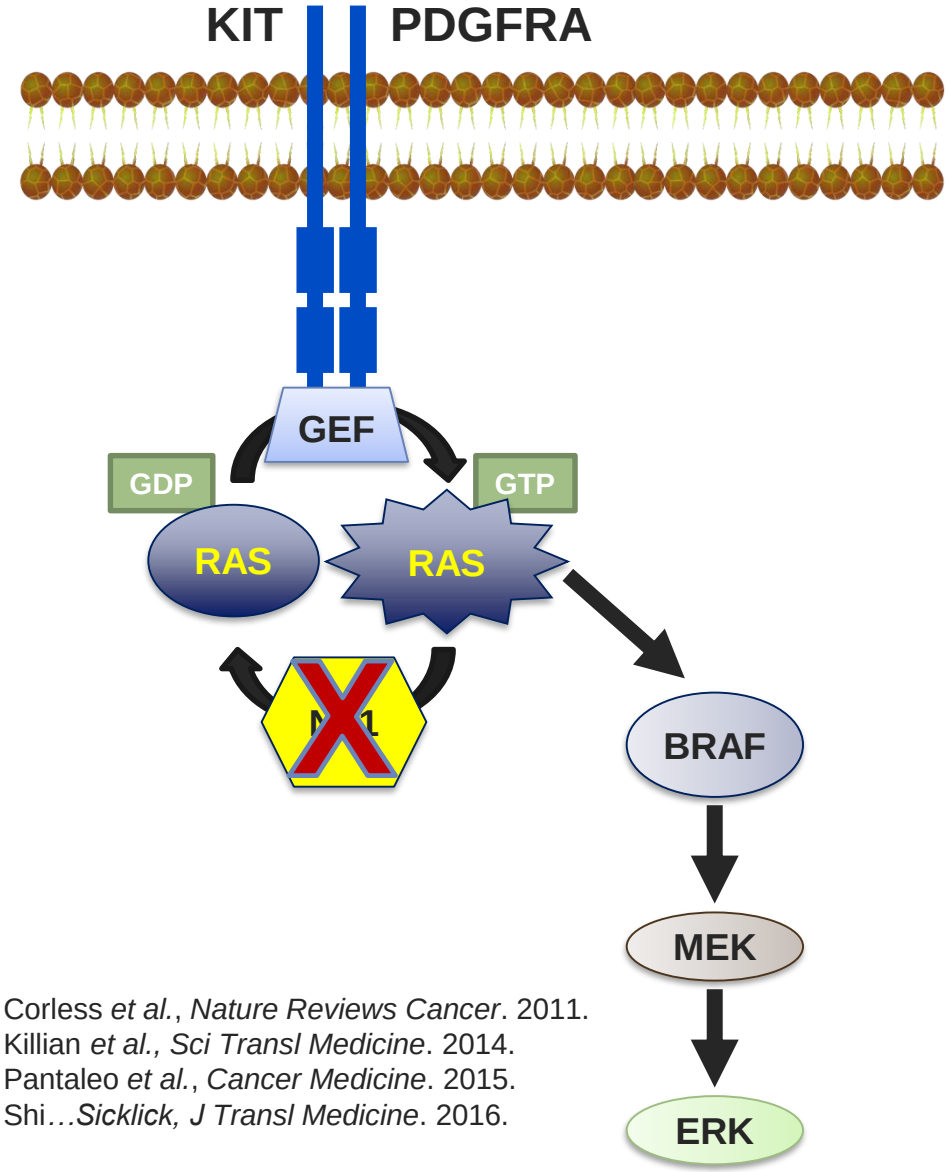
HEALTH SYSTEM

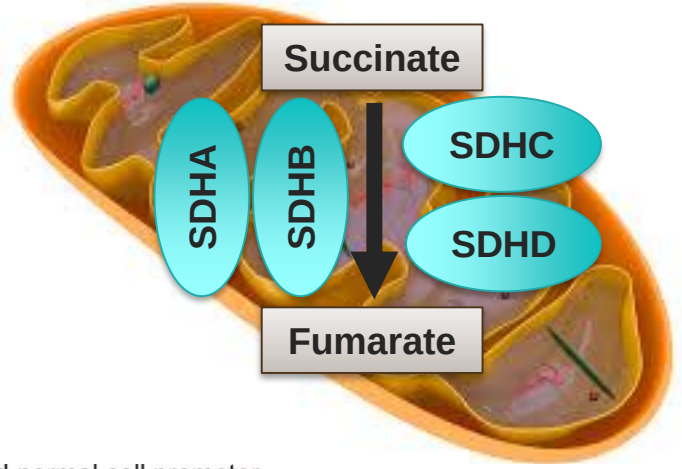
GIST is Becoming Increasingly Diverse

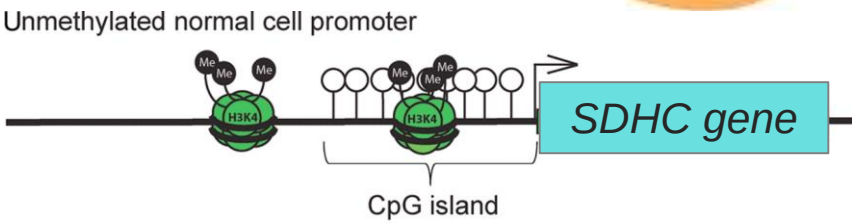


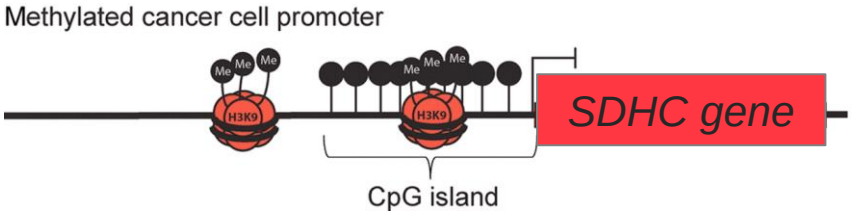
Shi…Sicklick *J Transl Med*. 2016.

GIST is Becoming Increasingly Diverse

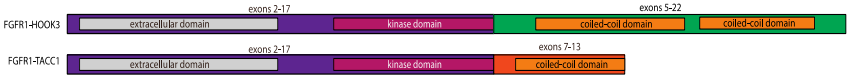








***FGFR1-HOOK3 or –TACC1* fusions**

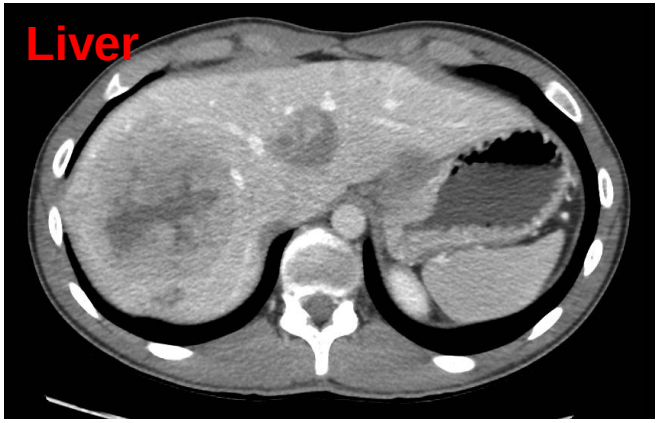


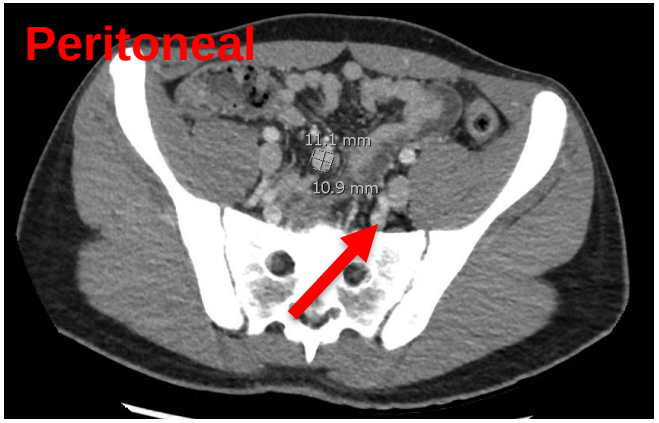
***ETV6-NTRK3* fusion**

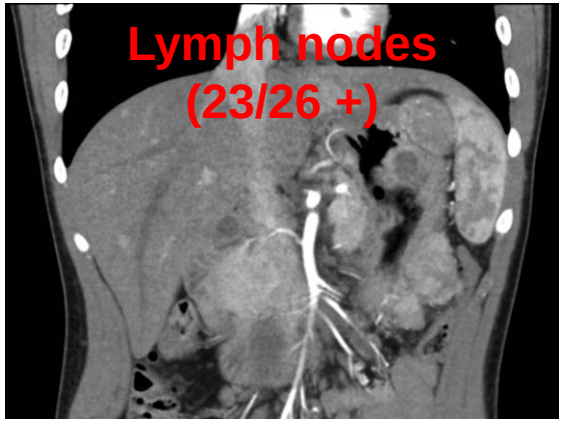
Corless *et al.*, *Nature Reviews Cancer*. 2011.
Killian *et al., Sci Transl Medicine*. 2014.
Pantaleo *et al.*, *Cancer Medicine*. 2015.
Shi…*Sicklick, J Transl Medicine*. 2016.

The Problem

1. SDH-deficient GIST and PGL often occur in adolescents and young adults
2. Since these *SDH* mutations are germline, multiple generations of family members are affected
3. Metastasis via blood, peritoneal spread, and lymphatics







4. Lack of TKI Clinical Efficacy

Author	Journal	Year	Study	Imatinib	Sunitinib	Regorafenib	Nilotinib	Sorafenib
Boikos	*JAMA Oncology*	2016	Retrospective cohort study	1/49 (**2.0%**)	4/38 (**10.5%**)			
Ben Ami	*Annals of Oncology*	2016	GRID Study			2/6 (**33.3%**)		
Janeway	*Pediatric Blood Cancer*	2009	Treatment use protocol		1/7 (**14.3%**)			
Heinrich	*JAMA Oncology*	2017	SWOG Intergroup Trial S0033	1/12 (**8.3%**)				
Call	*CTOS 2018*	2017	Retrospective patient reported cohort study	6/41 (**14.6%**)	10/28 (**35.7%**)	1/9 (**11.1%**)	1/7 (**14.3%**)	2/5 (**40%**)
Janeway	*Life Fest Talk*	2018	NIH	7/38 (**18.4%**)				

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Completed Clinical Trials

- **Phase II Trial of Vandetanib in Children and Adults With Wild-Type Gastrointestinal Stromal Tumors**

  Targets: VEGFR/EGFR/RET

  - Vandetanib was not tolerated by adults at the 300 mg daily dose
  - 2 of 9 (22.2%) patients had prolonged SD
  - No PR or CR were observed (Glod, ASCO 2016)

- **SARC 022, a phase II multicenter study of linsitinib in pediatric and adult wild-type gastrointestinal stromal tumors**

  Target: IGF-1R

  - Linsitinib was well tolerated in patients with WT GIST
  - Clinical benefit rate was 45%
  - No PR or CR were observed (von Mehren, ASCO 2014)

Currently Enrolling Clinical Trials

- **Study of the Glutaminase Inhibitor CB-839 in Solid Tumors**

  Target: Glutamine Addiction

  - Efficacy to be determined

- **Phase II Trial of the DNA Methyl Transferase Inhibitor, Guadecitabine (SGI-110), in Children and Adults With Wild Type GIST, Pheochromocytoma and Paraganglioma Associated With Succinate Dehydrogenase Deficiency and HLRCC-associated Kidney Cancer**

  Target: Promoter Hypermethylation

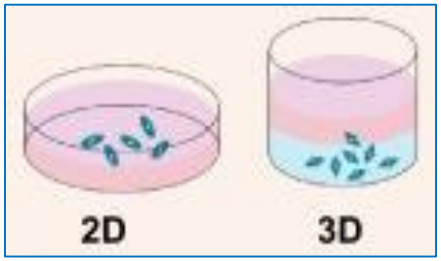
  - Efficacy to be determined

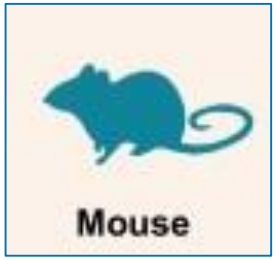
Central Question

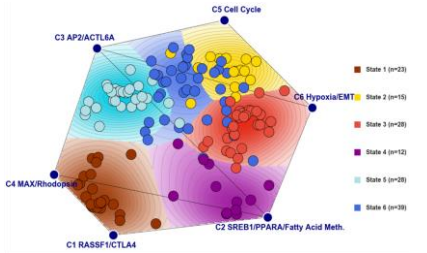
Can we better predict drug efficacy in the preclinical setting?

Typical Preclinical Models

- Cell lines
  - Murine
  - Hamster
  - Human
- Animal models
  - Murine
- Human tumor tissue
  - Fresh
  - FFPE
  - Viably frozen
  - Patient-Derived Xenografts (PDX)
- *In Silico* Bioinformatics







What Exists for SDH-deficient Tumors?

- Cell lines
  - Murine
  - Hamster
  - Human
- Animal models
  - Murine
- Human tumor tissue
  - Fresh
  - FFPE
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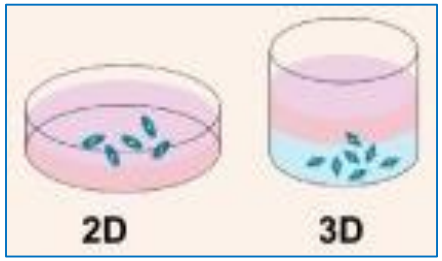

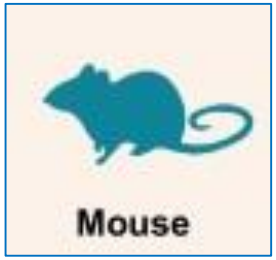

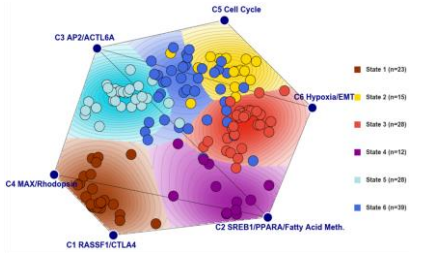

In Vitro Model

Nat Cell Biol. 2015 October ; 17(10): 1317–1326. doi:10.1038/ncb3233.

Pyruvate carboxylation enables growth of SDH-deficient cells by supporting aspartate biosynthesis

Simone Cardaci[1], **Liang Zheng**[1], **Gillian MacKay**[1], **Niels J.F. van den Broek**[1], **Elaine D. MacKenzie**[1], **Colin Nixon**[1], **David Stevenson**[1], **Sergey Tumanov**[1,2], **Vinay Bulusu**[1,2], **Jurre J. Kamphorst**[1,2], **Alexei Vazquez**[1], **Stewart Fleming**[3], **Francesca Schiavi**[4], **Gabriela Kalna**[1], **Karen Blyth**[1], **Douglas Strathdee**[1], and **Eyal Gottlieb**[1,*]

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Abstract

Succinate dehydrogenase (SDH) is a hetero-tetrameric nuclear-encoded complex responsible for the oxidation of succinate to fumarate in the tricarboxylic acid (TCA) cycle. Loss-of-function mutations in any of the SDH genes are associated with cancer formation. However, the impact of SDH loss on cell metabolism and the mechanisms enabling growth of SDH-defective cells are largely unknown. Here, w ***Sdhb-ablated kidney mouse cells*** ative

In Vitro Model

nature COMMUNICATIONS

ARTICLE

Received 28 Jul 2015 | Accepted 2 Oct 2015 | Published 2 Nov 2015

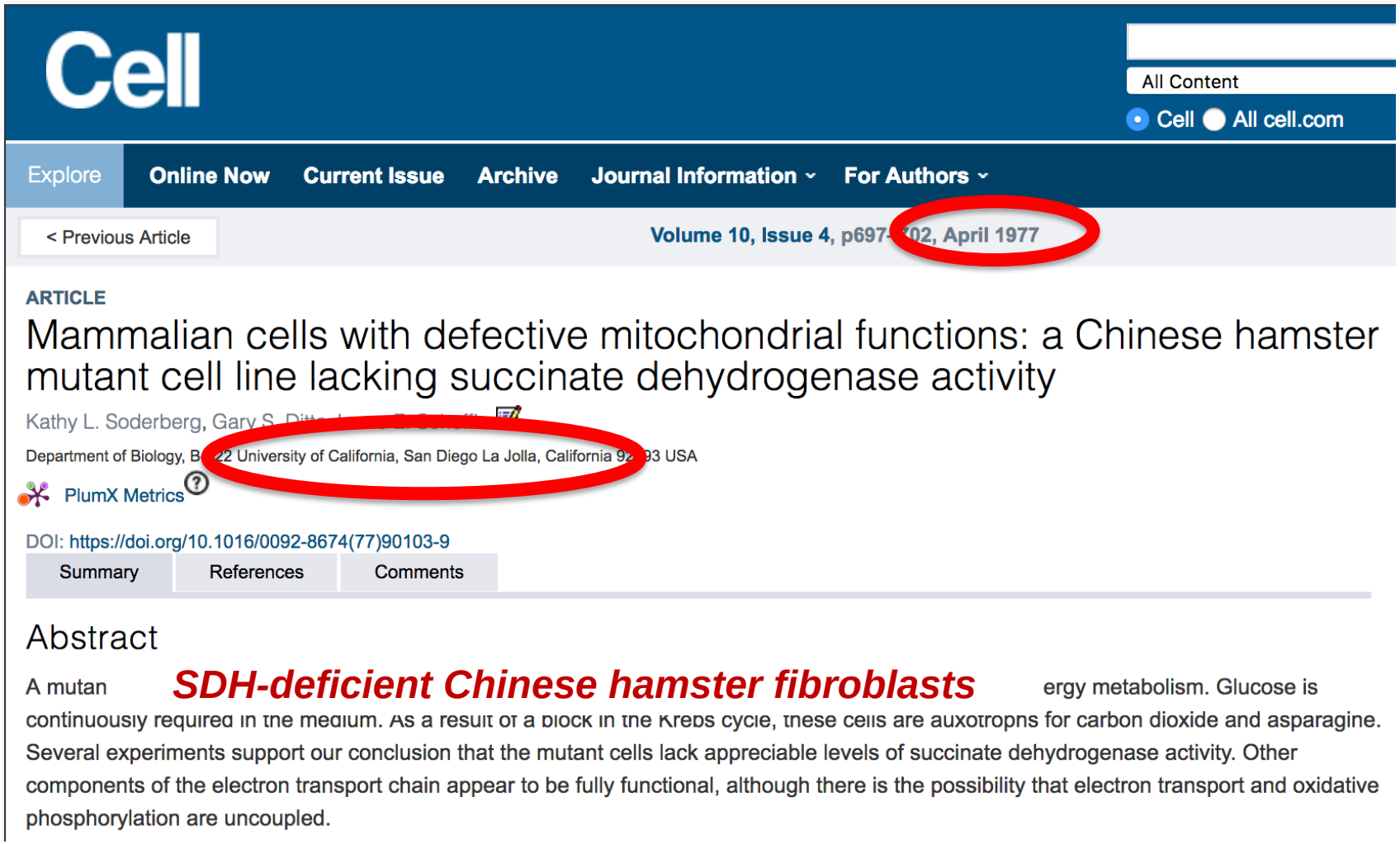
DOI: 10.1038/ncomms9784 OPEN

Loss of succinate dehydrogenase activity results in dependency on pyruvate carboxylation for cellular anabolism

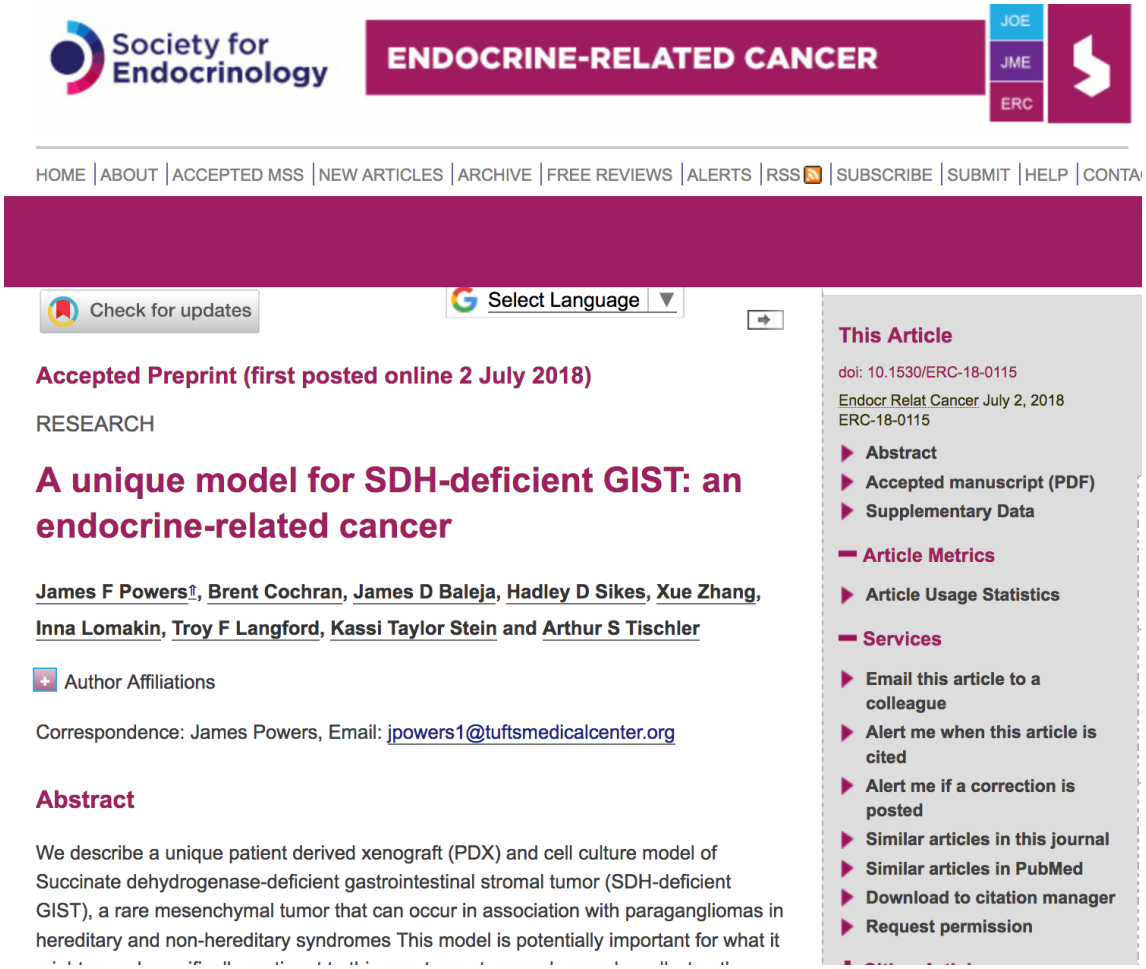
Charlotte Lussey-Lepoutre[1,2,3,*], Kate E.R. Hollinshead[4,*], Christian Ludwig[4,*], Mélanie Menara[1,2,*], Aurélie Morin[1,2], Luis-Jaime Castro-Vega[1,2], Seth J. Parker[5], Maxime Janin[2,6,7], Cosimo Martinelli[1,2], Chris Ottolenghi[2,6,7], Christian Metallo[5], Anne-Paule Gimenez-Roqueplo[1,2,3], Judith Favier[1,2,**] & Daniel A. Tennant[4,**]

immortalized Sdhb$^{-/-}$mouse chromaffin cell (imCC) line

In Vitro Model



In Vitro Model



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Accepted Preprint (first posted online 2 July 2018)

RESEARCH

A unique model for SDH-deficient GIST: an endocrine-related cancer

James F Powers, Brent Cochran, James D Baleja, Hadley D Sikes, Xue Zhang, Inna Lomakin, Troy F Langford, Kassi Taylor Stein and Arthur S Tischler

Author Affiliations

Correspondence: James Powers, Email: jpowers1@tuftsmedicalcenter.org

Abstract

We describe a unique patient derived xenograft (PDX) and cell culture model of Succinate dehydrogenase-deficient gastrointestinal stromal tumor (SDH-deficient GIST), a rare mesenchymal tumor that can occur in association with paragangliomas in hereditary and non-hereditary syndromes This model is potentially important for what it

This Article

doi: 10.1530/ERC-18-0115

Endocr Relat Cancer July 2, 2018 ERC-18-0115

- Abstract
- Accepted manuscript (PDF)
- Supplementary Data

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SDHB-mutant, KRAS G12D human GIST line (For Ian Project)

In Vivo Models

Endocr Relat Cancer. 2015 June ; 22(3): 345–352. doi:10.1530/ERC-15-0069.

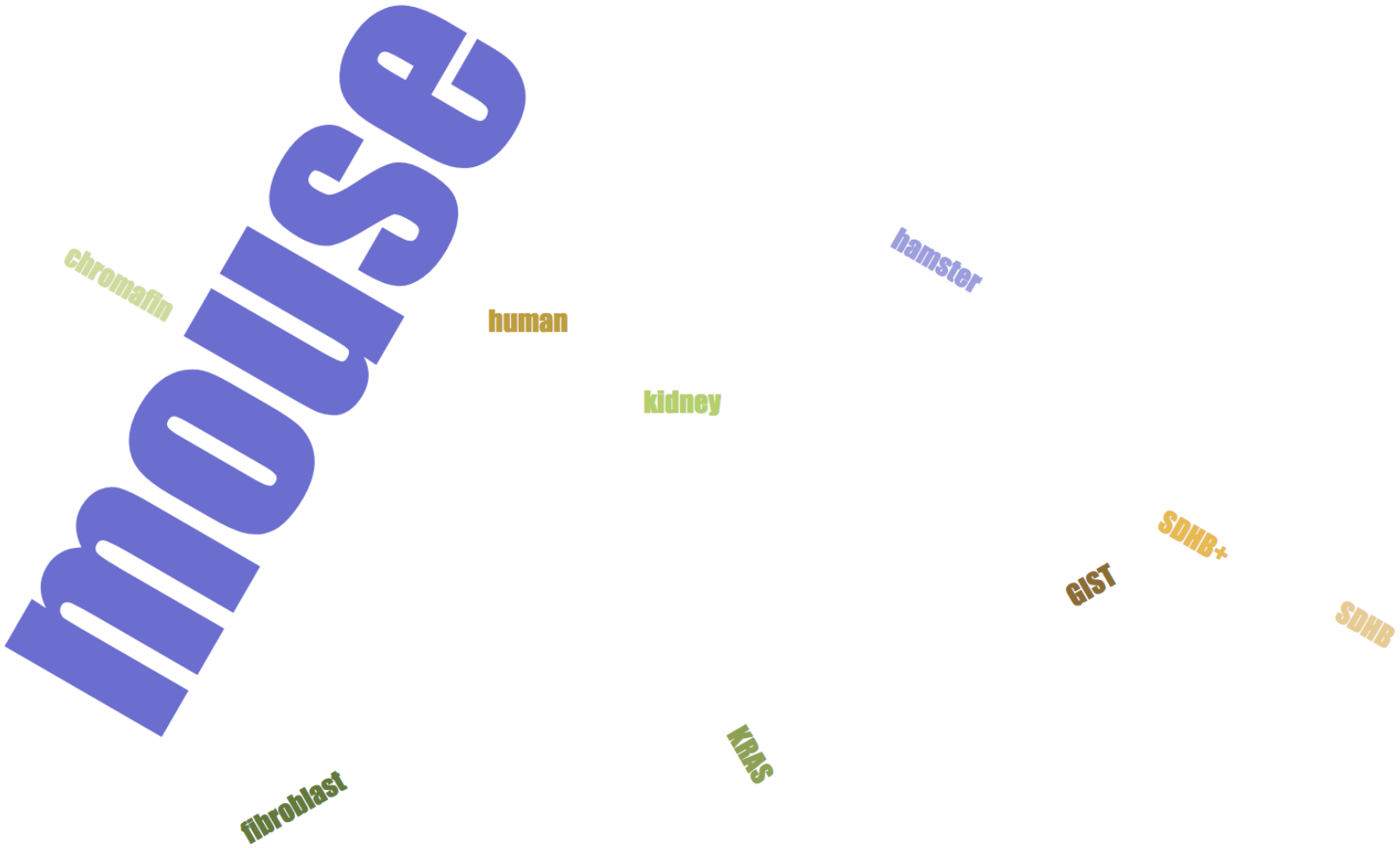
Carney Triad, SDH-deficient tumors, and *Sdhb*$^{+/-}$ mice share abnormal mitochondria

Eva Szarek[1], **Evan R. Ball**[1], **Alessio Imperiale**[2,3], **Maria Tsokos**[4], **Fabio R. Faucz**[1], **Alessio Giubellino**[5], **François-Marie Moussallieh**[2,3], **Izzie-Jacques Namer**[2,3], **Mones S. Abu-Asab**[6], **Karel Pacak**[5], **David Taïeb**[7,8], **J. Aidan Carney**[9], and **Constantine A. Stratakis**[1]

***Sdhb+/-* mice**

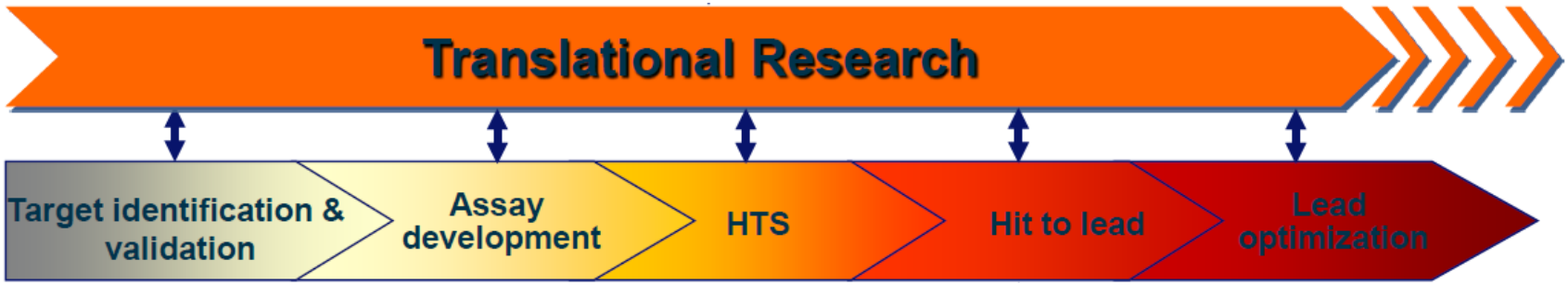
Summary of Current Models

Limited *in vitro* & *in vivo* models of SDH-deficient GIST

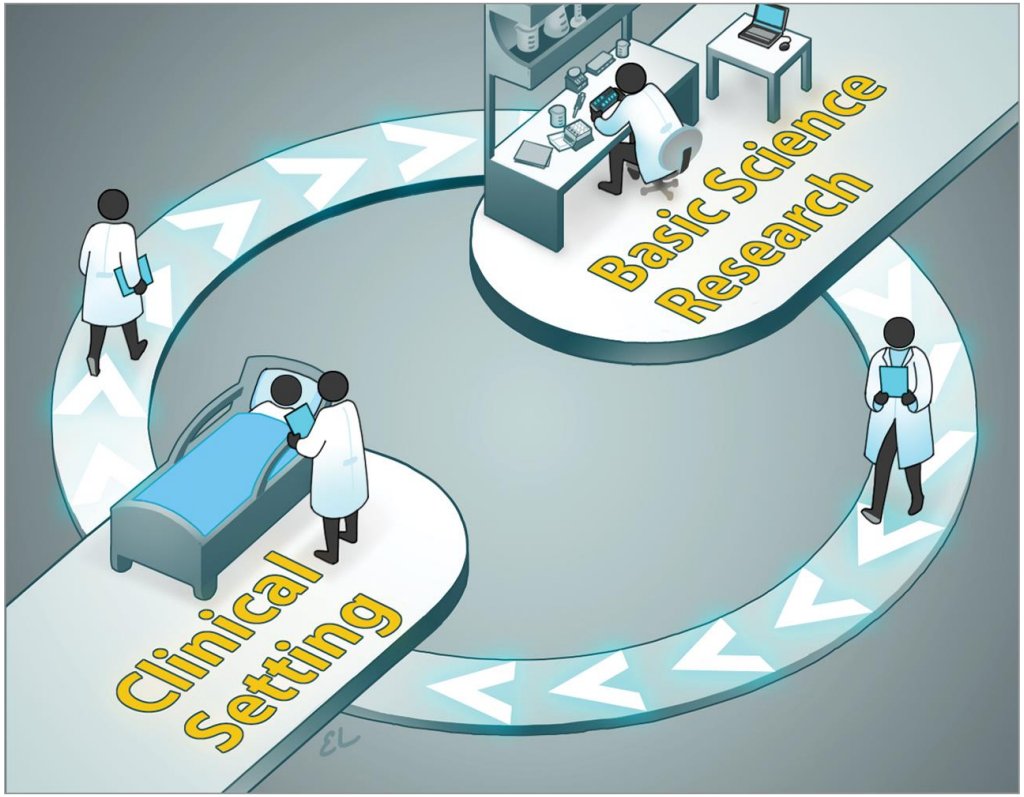


Central Question

Can we develop better SDH-deficient models to predict drug efficacy in the preclinical setting?



Full Circle



Clinical Trial

Phase II Study of Temozolomide (TMZ) In Advanced Succinate Dehydrogenase (SDH)-Mutant/Deficient Gastrointestinal Stromal Tumor

(ClinicalTrials.gov Identifier: NCT03556384)

- IND approval - February 2018
- Open to acrual - August 2018
- Enrolled 1st patient - September 2018
- FDA/NIH R01 funding is pending

UCSD PI:
Adam Burgoyne, MD, PhD
Medical Oncology

Thank You

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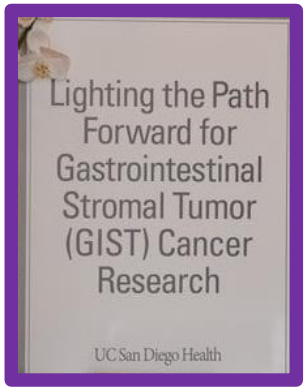
NIH

The David Foundation
Project PDGFRA D842V
Defeating the GIST Goliath

PEDAL THeCAUSE
A WORLD WITHOUT CANCER.

The Society for Surgery of the Alimentary Tract
SSAT



SDH-RA
SDH-Deficient GIST Research Advocates

Hope for a Cure Foundation
Support and Hope in the Quest for a Cure

PRICE PHILANTHROPIES

gsi GIST Support International

Anonymous Patient-Advocate Donors (*UCSD Foundation Fund #3661 & #2570*)

The Life Raft GROUP

AMGEN

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Acknowledgements

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Robert Mallory, PA-C
Stacey Silverman

Our Patients and their Families

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