Modeling Human SDH-Deficient GIST

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GIST is Becoming Increasingly Diverse

Shi...Sicklick *J Transl Med.* 2016.
GIST is Becoming Increasingly Diverse


FGFR1-HOOK3 or –TACC1 fusions

ETV6-NTRK3 fusion
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

<table>
<thead>
<tr>
<th>Author</th>
<th>Journal</th>
<th>Year</th>
<th>Study</th>
<th>Imatinib</th>
<th>Sunitinib</th>
<th>Regorafenib</th>
<th>Nilotinib</th>
<th>Sorafenib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boikos</td>
<td><em>JAMA Oncology</em></td>
<td>2016</td>
<td>Retrospective cohort study</td>
<td>1/49 (2.0%)</td>
<td>4/38 (10.5%)</td>
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<tr>
<td>Ben Ami</td>
<td><em>Annals of Oncology</em></td>
<td>2016</td>
<td>GRID Study</td>
<td></td>
<td></td>
<td></td>
<td>2/6 (33.3%)</td>
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<tr>
<td>Janeway</td>
<td><em>Pediatric Blood Cancer</em></td>
<td>2009</td>
<td>Treatment use protocol</td>
<td></td>
<td></td>
<td>1/7 (14.3%)</td>
<td></td>
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<tr>
<td>Heinrich</td>
<td><em>JAMA Oncology</em></td>
<td>2017</td>
<td>SWOG Intergroup Trial S0033</td>
<td>1/12 (8.3%)</td>
<td></td>
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<tr>
<td>Call</td>
<td><em>CTOS 2018</em></td>
<td>2017</td>
<td>Retrospective patient reported cohort study</td>
<td>6/41 (14.6%)</td>
<td>10/28 (35.7%)</td>
<td>1/9 (11.1%)</td>
<td>1/7 (14.3%)</td>
<td>2/5 (40%)</td>
</tr>
<tr>
<td>Janeway</td>
<td><em>Life Fest Talk</em></td>
<td>2018</td>
<td>NIH</td>
<td>7/38 (18.4%)</td>
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</table>
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
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
  - Viably frozen
  - Patient-Derived Xenografts (PDX)
- *In Silico* Bioinformatics
In Vitro Model


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

Simone Cardaci¹, Liang Zheng¹, Gillian MacKay¹, Niels J.F. van den Broek¹, Elaine D. MacKenzie¹, Colin Nixon¹, David Stevenson¹, Sergey Tumanov¹,², Vinay Bulusu¹,², Jurre J. Kamphorst¹,², Alexei Vazquez¹, Stewart Fleming³, Francesca Schiavi⁴, Gabriela Kalna¹, Karen Blyth¹, Douglas Strathdee¹, and Eyal Gottlieb¹.

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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, with Sdhh ablabeled kidney mouse cells
In Vitro Model

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

Charlotte Lussey-Lepoutre¹,²,³,⁎, Kate E.R. Hollinshead⁴,⁎, Christian Ludwig⁴,⁎, Mélanie Menara¹,²,⁎, Aurélie Morin¹,², Luis-Jaime Castro-Vega¹,², Seth J. Parker⁵, Maxime Janin²,⁶,⁷, Cosimo Martinelli¹,², Chris Ottolenghi²,⁶,⁷, Christian Metallo⁵, Anne-Paule Gimenez-Roqueplo¹,²,³, Judith Favier¹,²,⁎⁎ & Daniel A. Tennant⁴,⁎⁎

*immortalized Sdhb⁻/⁻ mouse chromaffin cell (imCC) line*
**In Vitro Model**

Mammalian cells with defective mitochondrial functions: a Chinese hamster mutant cell line lacking succinate dehydrogenase activity

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DOI: https://doi.org/10.1016/0092-8674(77)90103-9

Abstract

**SDH-deficient Chinese hamster fibroblasts**

A mutation in the succinate dehydrogenase (SDH) gene is known to be required for normal cell growth and survival. As a result of this mutation, the cell line lacks the ability to produce energy through oxidative phosphorylation. Glucose is continuously required in the medium. As a result of a block in the Krebs cycle, these cells are auxotrophs for carbon dioxide and asparagine. Several experiments support our conclusion that the mutant cells lack appreciable levels of succinate dehydrogenase activity. Other components of the electron transport chain appear to be fully functional, although there is the possibility that electron transport and oxidative phosphorylation are uncoupled.
In Vitro Model

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


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

Eva Szarek¹, Evan R. Ball¹, Alessio Imperiale²,³, Maria Tsokos⁴, Fabio R. Fauz¹, Alessio Giubellino⁵, François-Marie Moussallieh²,³, Izzie-Jacques Namer²,³, Mones S. Abu-Asab⁶, Karel Pacak⁵, David Taïeb⁷,⁸, J. Aidan Carney⁹, and Constantine A. Stratakis¹

*Sdhb*+/- mice
Summary of Current Models

Limited *in vitro* & *in vivo* models of SDH-deficient GIST
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 accrual - August 2018
- Enrolled 1st patient - September 2018
- FDA/NIH R01 funding is pending

UCSD PI: Adam Burgoyne, MD, PhD
Medical Oncology
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Stacey Silverman

Collaborators
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Chris Corless, MD, PhD
Ian Pass, PhD

Our Patients and their Families

UC San Diego
Moores Cancer Center