Rare and very rare subtypes in GIST: Where are we currently with "Non KIT/PDGFRA Wild Type Paediatric-GIST"?

Ramesh Bulusu

Consultant Oncologist

Clinical Lead for PAWS GIST Clinic UK

Please shout from the top of every building

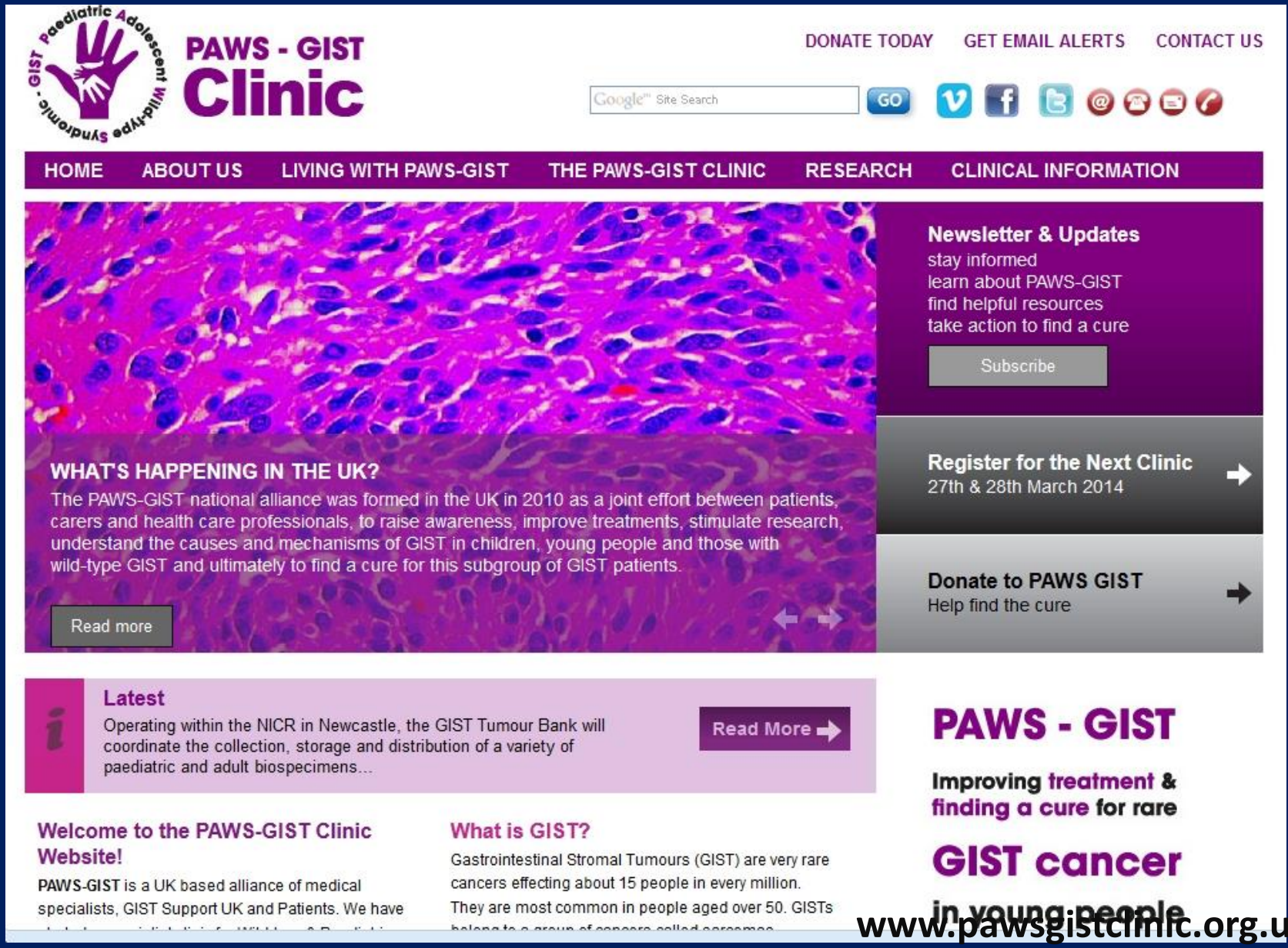
I am not 'WILD'
I have a SDH Deficient Cancer

Give me a name
Find an oncogenic driver druggable target

I have NF1 related GIST

NIH Clinic 2011

www.pawsgistclinic.org.uk



www.pawsgistclinic.org.uk

The PAWS-GIST Clinic - Addenbrooke's Hospital, Cambridge UK

PAWS-GIST Clinic

We plan to hold three clinics each year, using each one to bring together up to 12 patients who will meet with GIST specialists from a variety of disciplines.

We will review:

- your medical history
- previous treatment and response to treatment
- scans
- tumour histopathology results (where it exists)
- genetic/molecular analyses
- undertake further tests, where appropriate and understand your unique situation
- make recommendations specifically tailored to your individual needs.

Attending the clinic will allow you to meet others living with this rare cancer which in itself is an invaluable experience and collectively you will generate a wealth of information that assist the PAWS-GIST muliti-disciplinary team to discover the underlying mechanisms behind paediatric, adolescent, wild-type and syndromic GIST.

Aim

Our goals are:

- to examine the results that we accumulate from these clinics in order to design an innovative national treatment protocol.
- to stimulate research to try to identify some of the genetic changes that underlie PAWS-GIST.
- to populate the PAWS-GIST database. As part of the National GIST database.

We will not be taking over the medical care of the patients that attend our clinics but hope to be in a position to make recommendations, based on information that we gather. In addition, we may be able to offer services or tests and access to specialists that may not be available to you locally.

Our plan is to work in collaboration with the Consortium for Pediatric and Wildtype GIST Research (CPGR) at the NIH Clinic in Washington DC, USA, researchers in Dublin and Europe to advance research that will improve treatment and ultimately find a cure for PAWS-GIST patients.

The PAWS-GIST Clinic - FAQs

Am I eligible?

To be eligible for the PAWS-GIST clinic you will be someone who has been diagnosed with GIST in childhood/adolescence or who has been diagnosed with wild-type or a syndromic form of GIST as an adult.

If you do not know what type of GIST you have please request mutational testing. There are six specialist centre who will be able to help with this. They are based at:

- The Royal Marsden Hospital, London
- The Christie Hospital, Manchester
- Queen Elizabeth Hospital, Birmingham
- University College London Hospitals (UCLH), London
- Bristol Royal Infirmary, Bristol
- Newcastle

How will I benefit by participating?

Your individual case will be examined by the most specialist team of experts in the UK. Having reviewed your individual circumstances you and your local oncologist will receive a report containing recommendations and a treatment plan tailored to your specific needs.

Will the clinic benefit others?

Collectively each individual patient who attends the clinic will assist in building our specialist team's knowledge of PAWS-GIST. Through time the data that we collect will be used to undertake research to understand this disease in greater detail and will lead us to answers about what causes PAWS-GIST and eventually what can be done to cure it.

What is the goal of the clinic?

Our aim is to optimize treatment regimes for PAWS-GIST patients, provide treatment plans tailored to individual circumstances. We aim to be a catalyst for reaerch which will improve treatments and eventually find a cure.

When is the clinic?

We plan to hold up to three clinics each year, using each one to bring together up to 8 patients who will meet with GIST specialists from a variety of disciplines.

You will be with us for a day and will ideally join us the evening before for a welcome meal. There will be assistance with your travel and accommodation will be booked for you.

Please see the dates for the next clinic.

How do I register?

- Please complete the online registration form.

Who will pay for my visit to the clinic?

- **Transportation –** Support is available to for travel to and from the clinic
- **Lodging & meals –** Hotel accommodation for the night prior to the clinic and a Welcome meal involving all of the patients attending the clinic are organised and paid for by GIST Support UK's PAWS-GIST Fund..

Who are the PAWS-GIST Team?

- See our Specialist Team page.

Where is the Addenbrooke's Clinic?

- See our Clinic Location page.

Register for the Next Clinic

Title: First Name: Surname:

Address: City: Postcode:

Telephone: Mobile:

Email:

NHS No: DOB:

Age at Diagnosis: Year diagnosed:

Primary Tumour location: GIST tumour type: Wildtype Unknown

Hospital:

Oncologist Name: Email address: Tel No:

Can we contact oncologist?: Yes No

Surgeon Name: Email address: Tel No:

Can we contact surgeon?: Yes No

I am happy for my details to be shared with the Patient Director of the PAWS-GIST Initiative: Yes No

Submit details

UK PAWS GIST Consortium














PAWS GIST-Clinical data

- 13 Clinics so far
- Around 6-8 pts per clinic
- Male:Female ratio 1:2
- Median age 38 yrs Range 9-74 yrs (age at diagnosis)
- Heterogeneity is the hallmark
  - SDH Deficient
  - Quadruple Negative
  - NF1 GISTs
  - KIT/PDGFRA mutations ! (KIT EXON 8 & 11, PDGFRA EXON 14)

Social side of PAWS GIST Clinic

NIH Clinic

Original Investigation

Molecular Subtypes of *KIT/PDGFRA* Wild-Type Gastrointestinal Stromal Tumors

A Report From the National Institutes of Health Gastrointestinal Stromal Tumor Clinic

Sosipatros A. Boikos, MD; Alberto S. Pappo, MD; J. Keith Killian, MD, PhD; Michael P. LaQuaglia, MD; Chris B. Weldon, MD; Suzanne George, MD; Jonathan C. Trent, MD, PhD; Margaret von Mehren, MD; Jennifer A. Wright, MD; Josh D. Schiffman, MD; Margarita Raygada, PhD; Karel Pacak, MD, PhD; Paul S. Meltzer, MD, PhD; Markku M. Miettinen, MD; Constantine Stratakis, MD, DSci; Katherine A. Janeway, MD; Lee J. Helman, MD

JAMA ONCOLOGY 2016

NIH Clinic Report

Table. Patient Demographics and Tumor Characteristics

Characteristic	Group 1: SDH-Competent GIST (n = 11)	Group 2: *SDHX*-Mutant GIST (n = 63)	Group 3: *SDHC*-Epimutant GIST (n = 21)	All Patients (n = 95)
Age, median (range), y[a]	46 (30-78)	23 (7-58)	15 (8-50)	23 (7-78)
Female sex, No. (%)[b]	7 (64)	39 (62)	20 (95)	66 (70)
Tumor size at resection, median (range), cm	8.9 (4.7-13.5)	5.6 (1.5-21)	4.7 (2-16)	5.6 (1.5-21)
Focality, proportion (%)[c,d]				
Unifocal	9/10 (90)	33/55 (60)	5/18 (28)	47/83 (57)
Multifocal	1/10 (10)	22/55 (40)	13/18 (72)	36/83 (43)
Primary location, No. (%)[e]				
Gastric	1 (9)	63 (100)	21 (100)	85 (89)
Small bowel	9 (82)	0	0	9 (9)
Abdominal	1 (9)	0	0	1 (1)
Histologic subtype, proportion (%)[d,f]				
Epithelioid	1/11 (9)	22/59 (37)	9/20 (45)	32/90 (36)
Spindle	9/11 (82)	9/59 (15)	2/20 (10)	20/90 (22)
Mixed	1/11 (9)	28/59 (47)	9/20 (45)	38/90 (42)

JAMA ONCOLOGY 2016

Research Focus in PAWS GIST

- Collaboration
- GIST Tumour bank established for researchers
- GIST Registry
- Cell line development
- Better understanding of biology, targets
- Active engagement with pharma
- **Regional, National, International cooperation**

Where are we currently with NON KIT NON PDGFRA WILD type GISTS

Current Clinical Status

- Still treated with Imatinib 1st line
- 2nd line Sunitinib
- 3rd line Regorafenib
- Imatinib does not have any impact
  - Anecdotal responses
  - Natural history of disease
- Sunitinib and Regorafenib—Non KIT effects through VEGF inhibition
- Often stable disease with minor responses
- Mindful of toxicities—often on these multi kinase inhibitors for much longer than mutated gist pts

Where do we go from here ?
Clinical trials and Research

Completed early phase studies so far

Results of SARC 022, a phase II multicenter study of linsitinib in pediatric and adult wild-type (WT) gastrointestinal stromal tumors (GIST).

ClinicalTrials.gov Identifier: NCT01560260

Margaret von Mehren, Suzanne George, Michael C. Heinrich, Scott Schuetze, Martin G. Belinsky, Katherine A. Janeway, Lori Rink, Kristen N. Ganjoo, Jian Qin Yu, Jeffrey T. Yap, John Joseph Wright, Annick D. Van Den Abbeele

- IGF1R is often highly expressed in WT GISTs
- Linsitinib is an oral IGF1R inhibitor
- 20 pts (12 female and 8 male)
- Qualitative, minor and FDG PET metabolic responses were seen in 35% of pts
- At 9 m 45% had some clinical benefit

ASCO 2014

A phase II trial of vandetanib (ZD6474) in children and adults with wild-type gastrointestinal stromal tumors.

ClinicalTrials.gov Identifier: NCT02015065

John Glod, Fernanda Arnaldez, Lori Wiener, Melissa Amaya, Joanne Derdak, Ramaprasad Srinivasan,

- Vandetanib is an oral multi kinase inhibitor
- Inhibits VEGFR2, EGFR, RET dependent signals
- 300 mg not tolerated, 200 mg –Median 4 cycles
- NO objective responses
- NOT considered active in wild type GIST

ASCO 2016

All comers studies
i.e all types of GISTs included

DCC-2618 vs placebo: Phase III randomised study in Metastatic GISTs

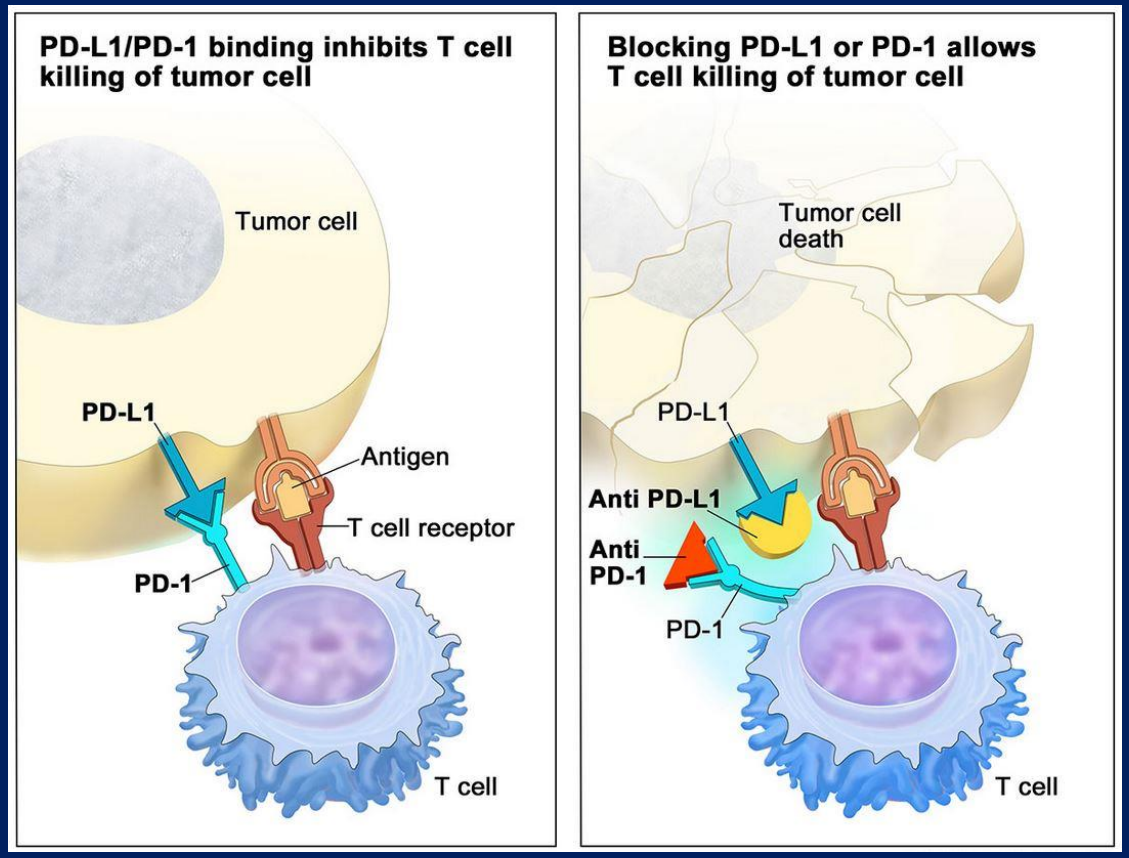
- ClinicalTrials.gov Identifier: NCT03353753
- Multi centre, multinational
- DCC 2618 is switch pocket kinase inhibitor
- 3 prior lines of Rx
- 2:1 randomisation
- Cross over at progression on placebo
- Ongoing

Famitinib in GISTs:Chinese Ph II study

- ClinicalTrials.gov Identifier: NCT02336724
- Imatinib resistant/intolerant GIST pts
- All types of GISTs
- Famitinib is a c-Kit, VEGFR2, PDGFR, VEGFR3, Flt1 and Flt3 multi kinase inhibitor
- 25 mg once daily
- NO results yet

Immunotherapy in GISTs

- ClinicalTrials.gov Identifier: NCT02880020
- UCLA Jonsson Comprehensive cancer centre
- Nivolumab with or without Ipilumab
- Wild type GIST pts are not excluded
- Post imatinib 2nd line
- PD-L1 and other immuno biomarkers
- Ongoing



Immunotherapy in GISTS

- ClinicalTrials.gov Identifier: NCT03291054
- Columbia university USA
- PD-1 Inhibitor Pembrolizumab with IDO inhibitor Epacadostat
- Unresectable or metastatic GIST
- NO mention of mutational status
- Up to 4 prior treatments allowed
- Ongoing

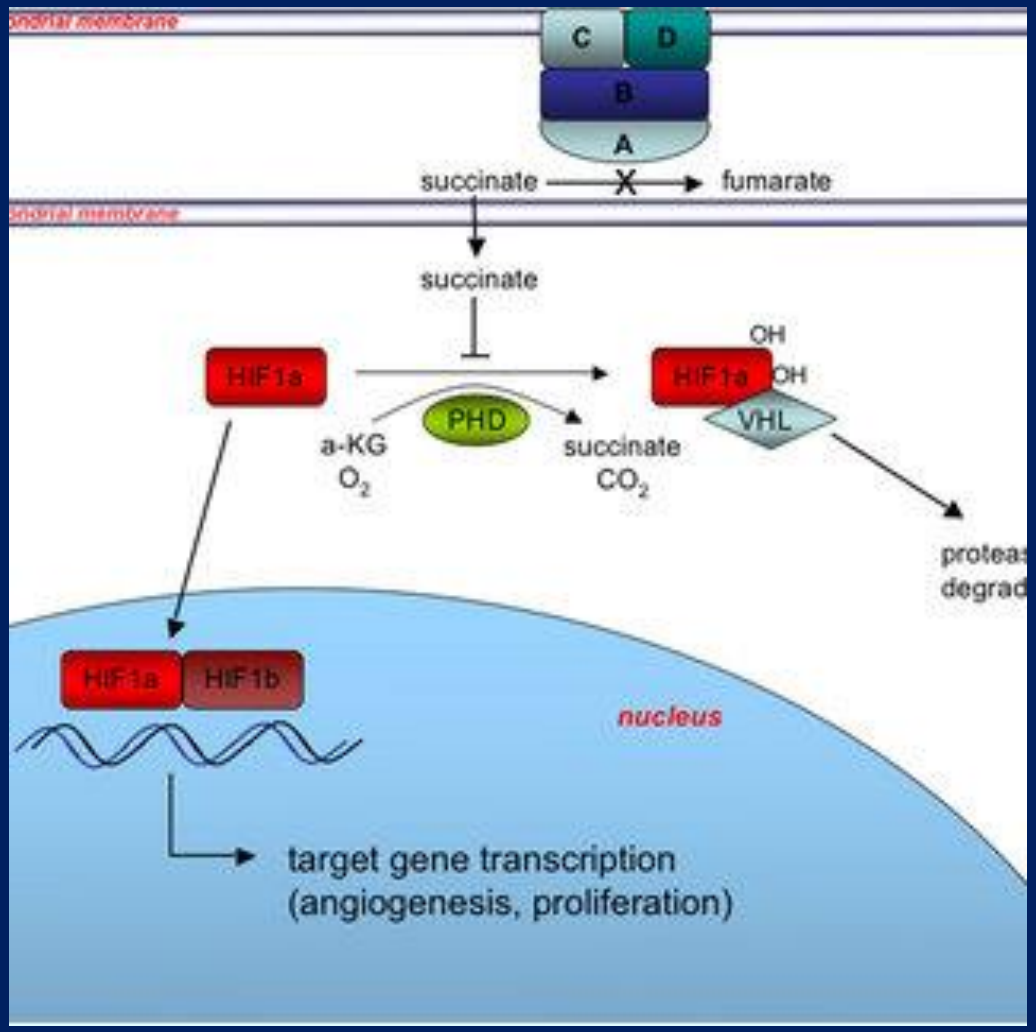
Trials in Specific subtypes

SDH Deficient GIST Consortium
LifeFest Miami July 2018

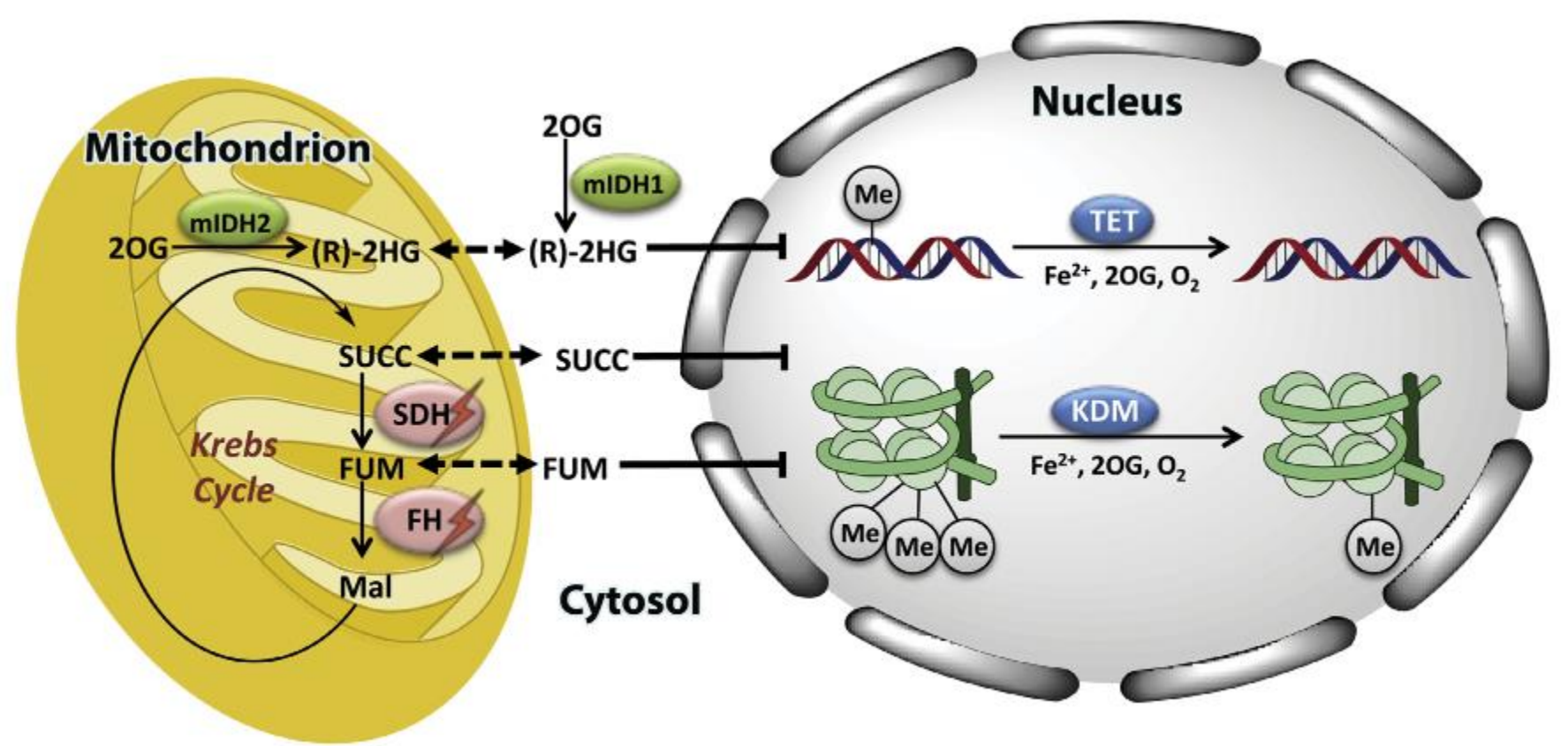
SDH Deficient GISTS

- Predominantly female
- Gastric
- Epithelioid
- Multifocal
- Germline SDH subunit mutation or
- SDHC promoter hypermethylation
- Hypermethylation of DNA

SDH Deficiency
Pseudohypoxia & Tumour causation



Epigenetic reprogramming by Oncometabolite 2HG, Succinate, Fumarate



Phase II Study of Guadecitabine in SDH deficient GISTS, Pheo, Paragangliomas

- ClinicalTrials.gov Identifier: NCT03165721
- John Glod NIH Bethesda
- Guadecitabine (SGI-110)
  - DNA methyl transferase inhibitor (demethylation)
  - Subcut inj 45 mg/m2 daily for 5 days q 28 days
  - Pro drug activated in the liver
- Strong rationale
- Trial opened in 2017 3 pts recruited so far !!
- Ongoing

Temozolomide in SDH Def GISTs

- ClinicalTrials.gov Identifier: NCT03556384
- Jason Sicklick UCLA San Diego
- Temozolomide is a DNA Alkylating agent (Chemo)
- Used to treated Brain tumours (GBM)
- Temozolomide 85mg/m2 oral 21/28 days
- Up to 6 months
- Overall Survival, PFS, Response rates, Toxicity
- Just opened

Glutaminase Inhibitor CB 839

- ClinicalTrials.gov Identifier: NCT02071862
- Cancer cells are dependent upon glutamine
- The enzyme glutaminase, which converts glutamine to glutamate, has been identified as a critical choke point in the utilization of glutamine by cancer cells.
- CB-839 is a potent, selective, reversible and orally bioavailable inhibitor of human glutaminase
- Oral compound
- USA multi centre
- Safety and tolerability primary outcomes
- Concerns regarding toxicities

Tropomyosin Related Kinase (TRK) Fusion GISTs

- Rare around 1%
- Genes involved Neurotrophic Tropomyosin Related Kinase NTRK1, 2 & 3
- Translocation leads to a fusion protein with TRK and a partner (remember CML)
- 20 different tumours so far have been shown to have TRK fusion protein
- Ongoing trials including GISTs

NTRK Fusion protein +ve Solid tumour trial

- ClinicalTrials.gov Identifier: NCT02576431
- Larotrectinib (LOXO 101)
- Oral 100 mg twice daily continuous dosing

Drug name	Targets	Development stage	Clinical trial identifier	Company
LOXO-101 (larotrectinib)	NTRK1/2/3	Phase II	NCT02122913 NCT02637687 NCT02576431 NCT03213704	Loxo Oncology
LOXO-195	NTRK1/2/3 (resistant)	Phase I/II	NCT03215511	Loxo Oncology
RXDX-101 (entrectinib)	NTRK1/2/3, ALK, ROS1	Phase I/II, Phase II, Phase I/Ib	NCT02097810 NCT02568267 NCT02650401	Ignyta
TPX-0005 (ropotrectinib)	NTRK1/2/3, ALK, ROS1 (resistant), JAK2, SRC, DDR1, FAK	Phase I/II	NCT03093116	TP Therapeutics
LY2801653 (merestinib)	NTRK1/2/3, MET, MST1R, FLT3, AXL, MERTK, TEK, ROS1, DDR1/2, MKNK1/2	Phase II	NCT02920996	Eli Lilly and Company
DS-6051b	NTRK1/2/3, ROS1	Phase I	NCT02675491 NCT02279433	Daiichi Sankyo
PLX7486	NTRK1/2/3, CSF1R	Phase I	NCT01804530	Plexxikon/Daiichi Sankyo
MGCD516 (sitravatinib)	NTRK1/2/3, MET, KIT, PDGFRA, KDR, DDR2, RET, CBL	Phase I/Ib	NCT02219711	Mirati Therapeutics

Any other bright ideas ??

www.impactjournals.com/oncotarget/ Oncotarget, 2017, Vol. 8, (No. 17), pp: 28922-28938

Research Paper

Succinate dehydrogenase B-deficient cancer cells are highly sensitive to bromodomain and extra-terminal inhibitors

Satoshi Kitazawa[1], Shunsuke Ebara[1], Ayumi Ando[2], Yuji Baba[1], Yoshinori Satomi[2], Tomoyoshi Soga[3], Takahito Hara[1]

we established SDHB knockout cancer cell lines from human colon cancer HCT116 cells using the clustered regularly interspaced short palindromic repeat (CRISPR)/ Cas9 knockout system, and clarified its metabolic characteristics.

screening revealed that a bromodomain and extra-terminal (BET) inhibitor, which downregulated c-Myc, suppressed the growth of the SDHB knockout cells more potently than that of control cells. These findings provide an understanding of the metabolic characteristics of SDHB-deficient cancer and its vulnerabilities, which may lead to new therapeutic options.

LETTERS
https://doi.org/10.1038/s41588-018-0170-4
nature genetics

Krebs-cycle-deficient hereditary cancer syndromes are defined by defects in homologous-recombination DNA repair

Parker L. Sulkowski[1,2], Ranjini K. Sundaram[1], Sebastian Oeck[1,3], Christopher D. Corso[1,4], Yanfeng Liu[1], Seth Noorbakhsh[1], Monica Niger[1,5], Marta Boeke[6], Daiki Ueno[6], Aravind Nambiar Kalathil[1], Xun Bao[7], Jing Li[7], Brian Shuch[6,9*], Ranjit S. Bindra[1,8,9*] and Peter M. Glazer[1,2,9*]

- Succinate and Fumarate both suppress homologous recombinant DNA repair pathway required for DNA double strand breaks repair
- Poly (ADP)-ribose polymerase (PARP) inhibitors can take advantage of this vulnerability
- Potential therapeutic target

Phase I study of HIF-2 alpha inhibitor all solid tumours

Drug: PT2977

PT2977 is a highly selective small molecule that inhibits the function of the HIF-2α transcription factor. As a result, hypoxic signaling in cancer cells is impaired, blocking the transcription of several genes involved in oncogenesis

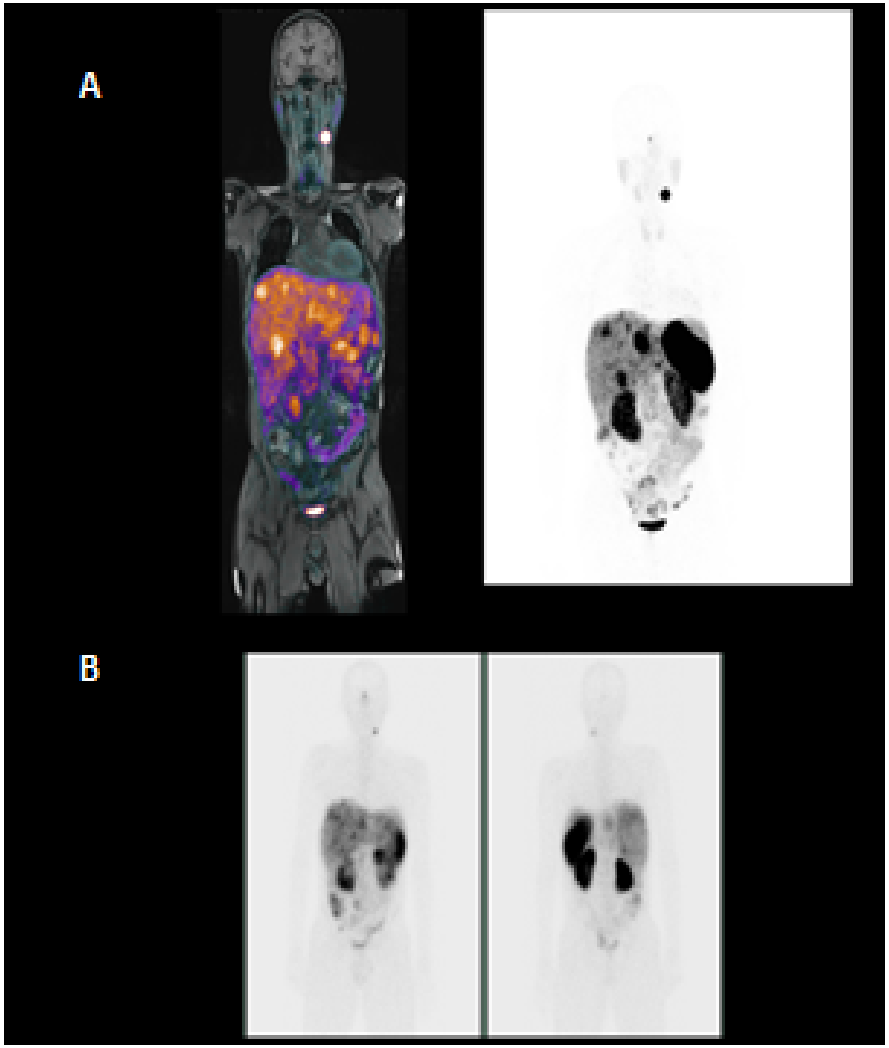
- ClinicalTrials.gov Identifier: NCT02974738
- First in humans, define the MTD
- Recommended dose for phase II
- Peloton Therapeutics
- Multi centre USA

MEK 1 &2 inhibitor Selumetinib in NF-1 GISTS

- ClinicalTrials.gov Identifier: NCT03109301
- NIH NCI Dr Brigitte Widemann
- Selumetinib 50 mg od continuous dosing
- Trial opened in 2017
- No pts recruited as of AUG 2018
- Ongoing

PAWS GIST Clinic UK-Study CI Dr Ruth Casey

Future studies:



Prospective study
Investigating the potential of Gallium-68 (^{68}Ga) DOTA-conjugated peptide PET/CT to develop theranostic applications in wild-type gastrointestinal stromal tumours (GISTs)

Slide courtesy of Ruth Casey
Cambridge

Conclusions

- Ongoing early phase studies in rarer subtypes of GISTs
- Challenging recruitment timelines—too slow
- Personalised medicine
  - Ideally tailor the drug to the pt
  - Difficult in rare cancers
- Patient advocacy groups + Oncologists + Researchers + Pharma need to drive this together

IF you are a patient with a subtype of GIST, what should you do ?

- Seek a specialist multi disciplinary opinion
  - Regional, national or
  - even international (I say cautiously)
- Make sure it is a rare subtype of GIST
- Engage with your patient advocacy group
- Explore what can be done and what needs to be done
- Clinical trials if available

Thank you