the NIH Pediatric & Wildtype GIST Clinic

Clinical and Research Advances In Pediatric and wildtype GIST

Su Young Kim MD PhD
Pediatric Oncology Branch National Cancer Institute

NATIONAL CANCER INSTITUTE
Pediatric ONCOLOGY BRANCH

Eunice Kennedy Shriver NICHD
National Institute of Child Health & Human Development

the NIH pediatric GIST clinic

Goal

To define new targets for potential treatment

To design innovative national treatment protocols





the NIH pediatric GIST clinic

Objectives

To assess every child and young adult with GIST

Obtain clinical parameters and samples for research testing

Continue long-term follow-up

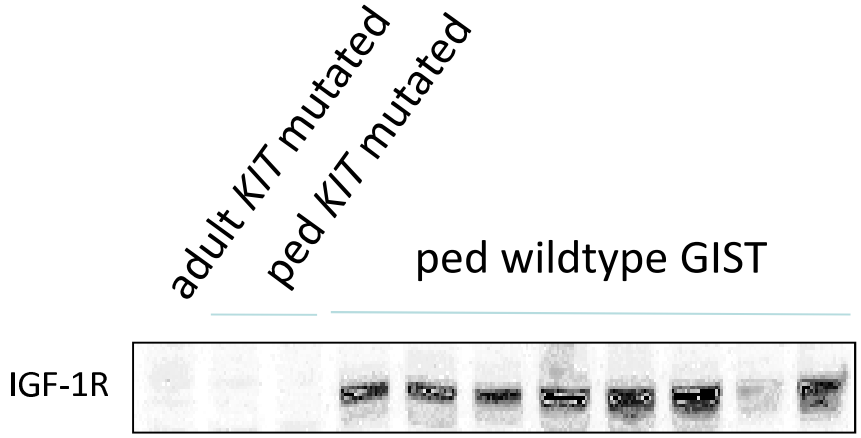
NATIONAL CANCER INSTITUTE

national pediatric GIST team

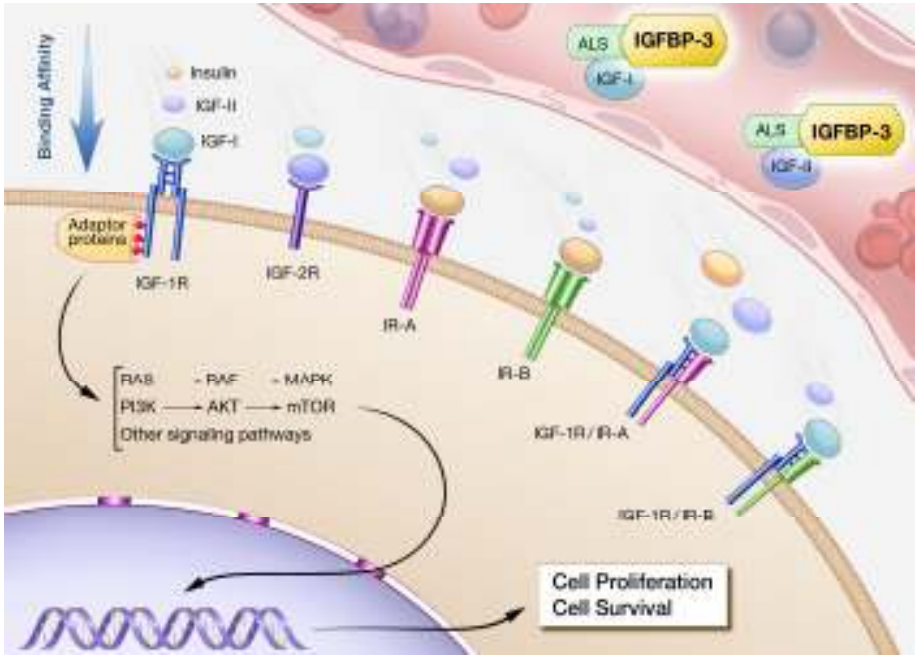
Alberto Pappo	Pediatric Oncologist	St Jude's Children Hospital
Katherine Janeway	Pediatric Oncologist	Dana Farber Cancer Center
Michael LaQuaglia	Pediatric Surgeon	Memorial Sloan Kettering
George Demetri	Medical Oncologist	Dana Farber Cancer Center
Cristina Antonescu	Pathologist	Memorial Sloan Kettering
Constantine Stratakis	Endocrinologist	NICHD
Lee Helman	Pediatric Oncologist	NCI
Su Young Kim	Pediatric Oncologist	NCI
Phyllis Gay	GSI	
Tricia McAleer	Life Raft Group	

1st Clinic

A Phase II Trial of an IGF-1R Antibody for wildtype GIST



Courtesy of Katherine Janeway, Boston Children's



Several pharmaceutical companies have terminated their IGF-1R antibody projects
We are currently pursuing other options, including small molecule inhibitors

Many centers offer Phase I/II IGF-1R antibody trials for those with advanced cancer

What is the Role of Surgery for Recurrence?

12 patients remain in first remission (26%)
19 - 67 months
34 patients have recurred (74%)
3 mo - 32 years

18 have undergone a second surgery
14 have recurred (78%)

4 underwent complete gastrectomy
3 have recurred (75%)

What is the Role of Surgery for Recurrence?

Conclusion

Surgery in itself is not curative in the vast majority of cases of recurrence in the setting of wildtype GIST

Avoid radical surgery

- **resection the entire stomach**
- **resection of small bowl leading to short-gut syndrome**

Undergo limited surgery only if the lesion results in symptoms

- **pain**
- **obstruction**
- **ulceration and hemorrhage**
- **impingement upon vital organs**
- **if only one lesion is getting bigger, while others remain stable**

2nd Clinic

DANA-FARBER CANCER INSTITUTE

FOX CHASE CANCER CENTER

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Making Cancer History®

What is the Role of Tyrosine Kinase Inhibitors?

	CR	PR	SD	PD	side effects	TOTAL
Imatinib	0	(2)	5	25	4	34
HD Imatinib	0	0	6	7	1	14
Sunitinib	1	0	5	11	3	20
Nilotinib	0	0	5	3	0	8
Sorafenib	0	0	1	0	3	4
Dasatinib	0	0	0	0	1	1
TOTALS	1	0	22	46	12	81
	(1%)	(0%)	(27%)	(57%)	(15%)	

What is the Role of Tyrosine Kinase Inhibitors?

Conclusion

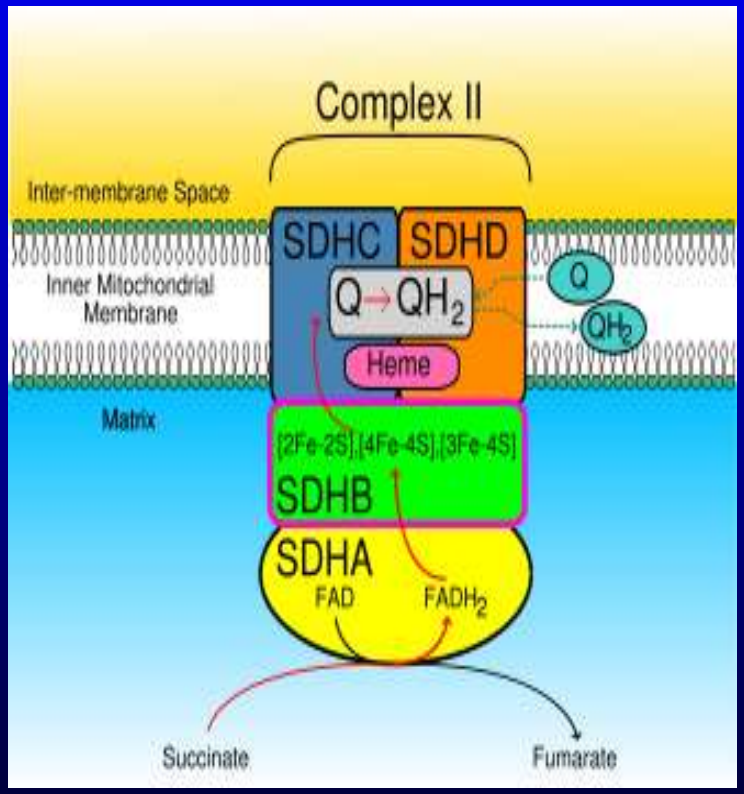
The response rate to TKI therapy is much lower than for adults with KIT/PDGFRA mutated GIST

Take TKIs in the neo-adjuvant setting

- **if there is recurrence, do not have surgery**
- **rather, begin TKI and assess for response**

DESPITE THESE FININGS
THE VAST MAJORITY OF OUR PATIENTS ARE DOING VERY WELL

3rd Clinic



Succinate Dehydrogenase (SDH)

- a component of the Kreb's cycle

Involved in cellular energy

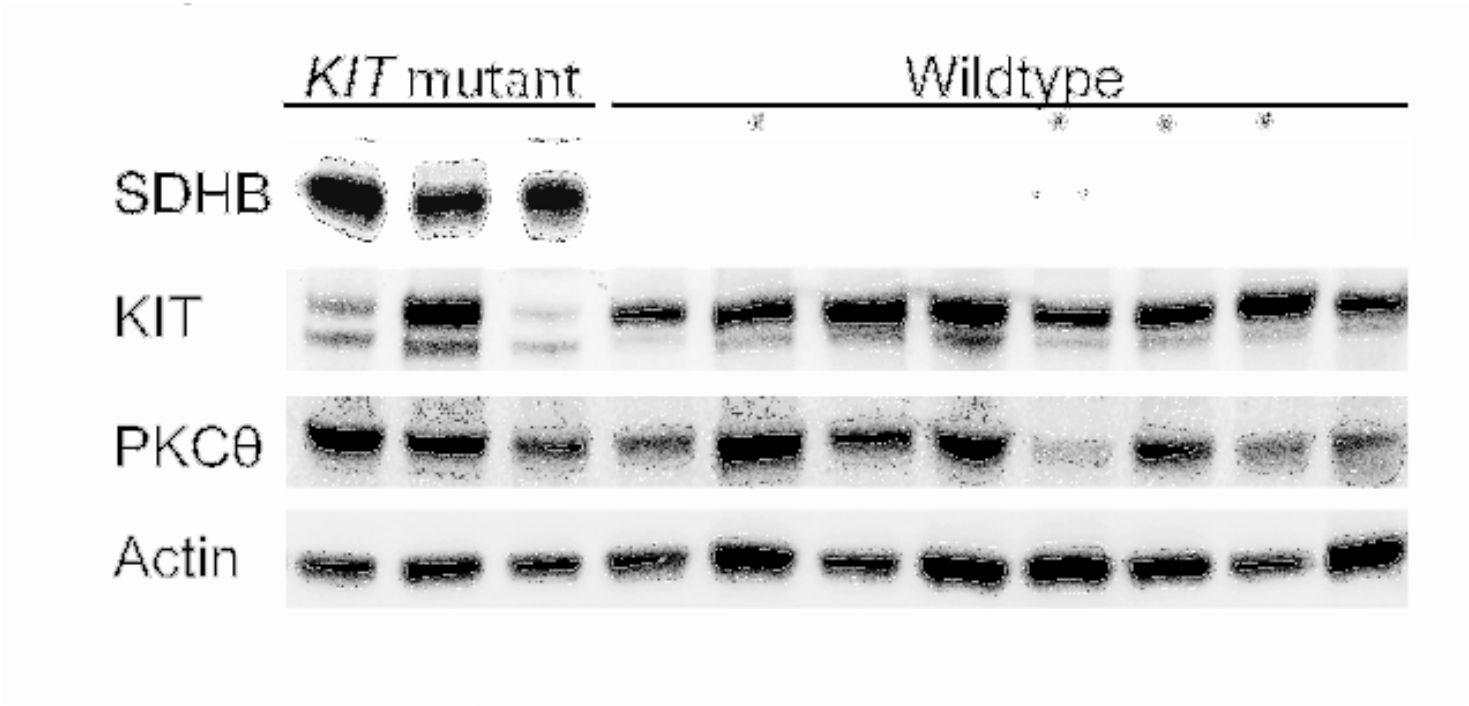
Carney-Stratakis Syndrome

- GIST
- Paragangliomas
- SDH germline mutations

Germline *SDH* mutations in wildtype GIST

Gene	Mutation	Type	Age		Clinical Status
SDH B	c.274 T>A/T	missense	18	M	NED – 1st remission
	c.380 T>G/T	missense	33	F	never NED – stable
	c.600 G>G/T	missense	22	M	1st recurrence – stable
	c.725 G>A/G	missense	21	F	deceased
	c.17_42 dup26	duplication	49	F	1st recurrence
SDH C	c.397 C>T	missense	19	M	never NED - CSS
	c.405+1 G>A	splice site	16	F	NED – 2nd remission
SDH D	c.34 G>A	polymorphism	7	F	NED – 1st remission
	c.34 G>A	polymorphism	58	F	1st recurrence

Germline *SDH* mutations in wildtype GIST



Katherine Janeway, et al (Boston Children's Hospital)

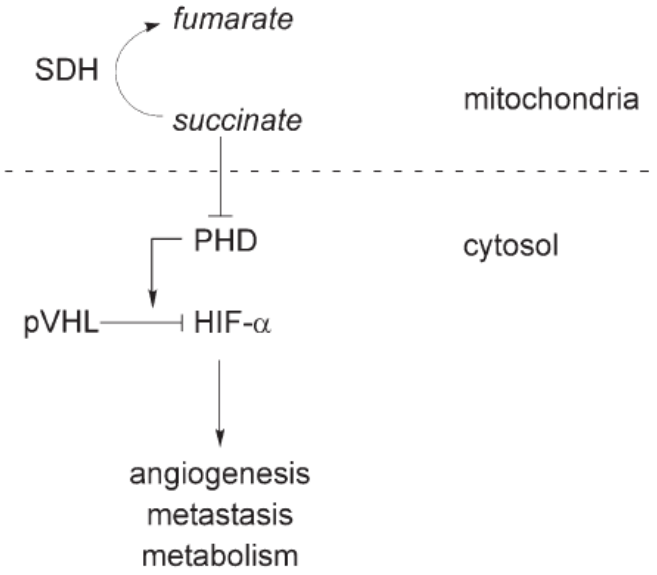
Germline *SDH* mutations in wildtype GIST

Treatment Implications

Currently therapy that targets SDH mutations is not available

Patients are undergoing
HIF 1α expression analysis

Indirect HIF 1α inhibitors
. Bevacizumab
. Topotecan



Germline *SDH* mutations in wildtype GIST

Conclusions

SDH mutations are associated with

- **GIST**
- **GIST and paragangliomas (Carney-Stratakis)**
- **GIST and pulmonary hamartomas**

Patients have increased risk of paragangliomas

- **MRI of the neck (in addition to chest/abd/pelvis)**
- **yearly monitoring of catecholamine/metanephrines**
- **extensive genetic counseling**

All pediatric and wildtype patients should undergo testing

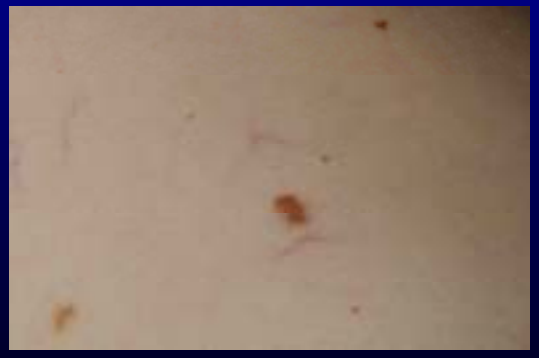
4th Clinic

Dr. Heidi Kong
Department of Dermatology
NCI / NIH

Expertise in dermatological manifestations of tyrosine kinase inhibitors

Benign melanocytic nevi

BRAF mutations



BRAF Mutations

Gender	Age	Location	Size	Mitoses
M	38	Small Intestine	2	5
M	41	Small Intestine	2	3
F	49	Small Intestine	9	50
F	50	Peritoneum	3	50
F	51	Small Intestine	2	10
F	52	Small Intestine	10	90
M	53	Small Intestine	20	6
F	55	Small Intestine	10	5
M	58	Small Intestine	2	1
M	58	Small Intestine	2	6
M	63	Stomach		
M	78	Stomach	3	1

Agaram et al. 2008 *Genes, Chromosomes & Cancer* 47:853. Hostein et al. 2010 *American Journal of Clinical Pathology* 133:141.

BRAF Mutation

3 of 33 (9%) samples tested were positive for BRAF V600E

Age	<40	1 / 21	5 %
	>40	2 / 12	17 %
Gender	female	0 / 24	0 %
	male	3 / 9	33 %
Location	stomach	0 / 26	0 %
	other	3 / 7	43 %

Clinical Course

- second remission — over ten years since original diagnosis
- third recurrence — now three years since diagnosis
- never resectable — recently diagnosed

BRAF Mutation

Treatment Implications

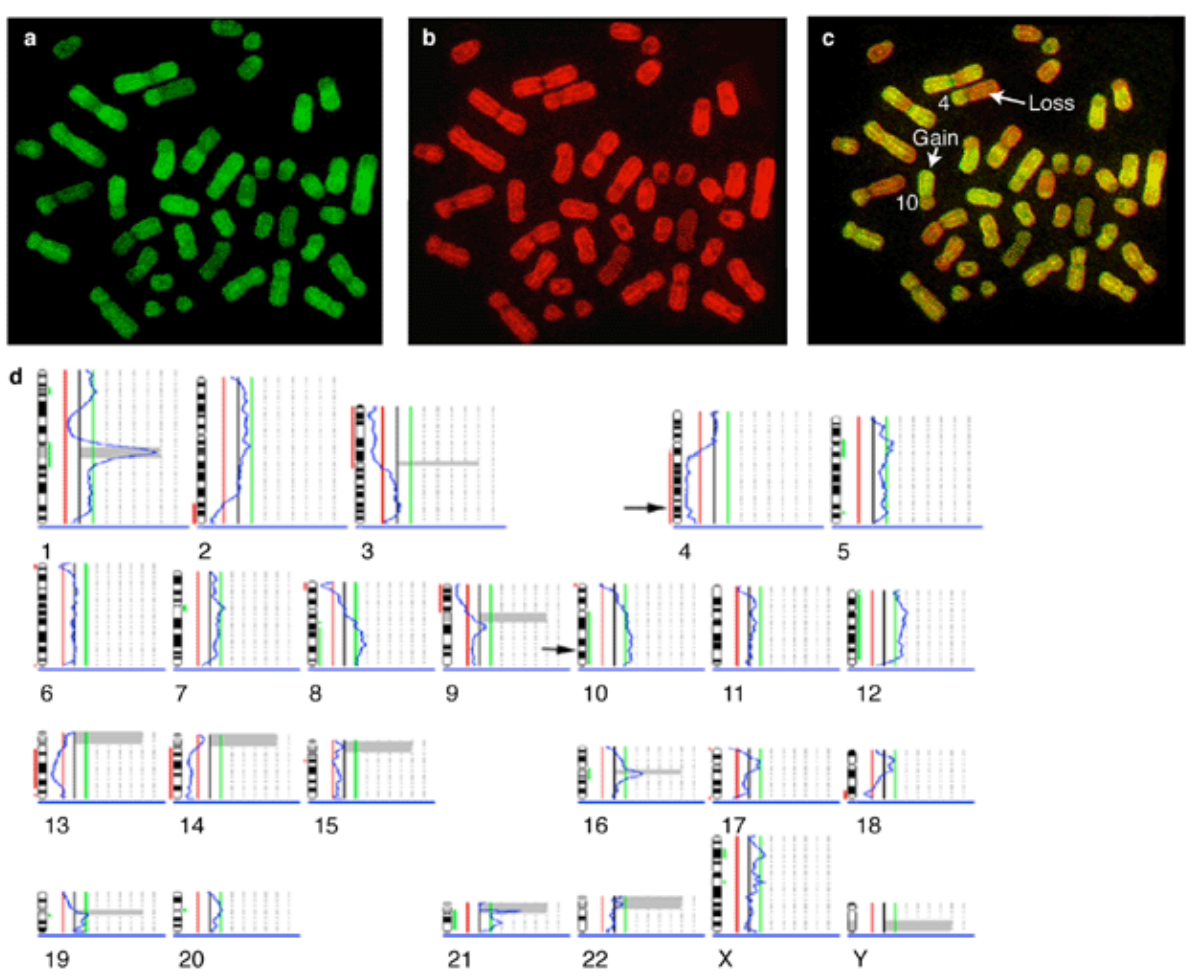
BRAF inhibitors	PLX4708	for melanoma only
	regoRAFenib	multi TKI
	AZD 6044	MEK inhibitor

Conclusion

BRAF testing should be part of mutational analysis
Patients who have V600E should be evaluated for trials

5th Clinic

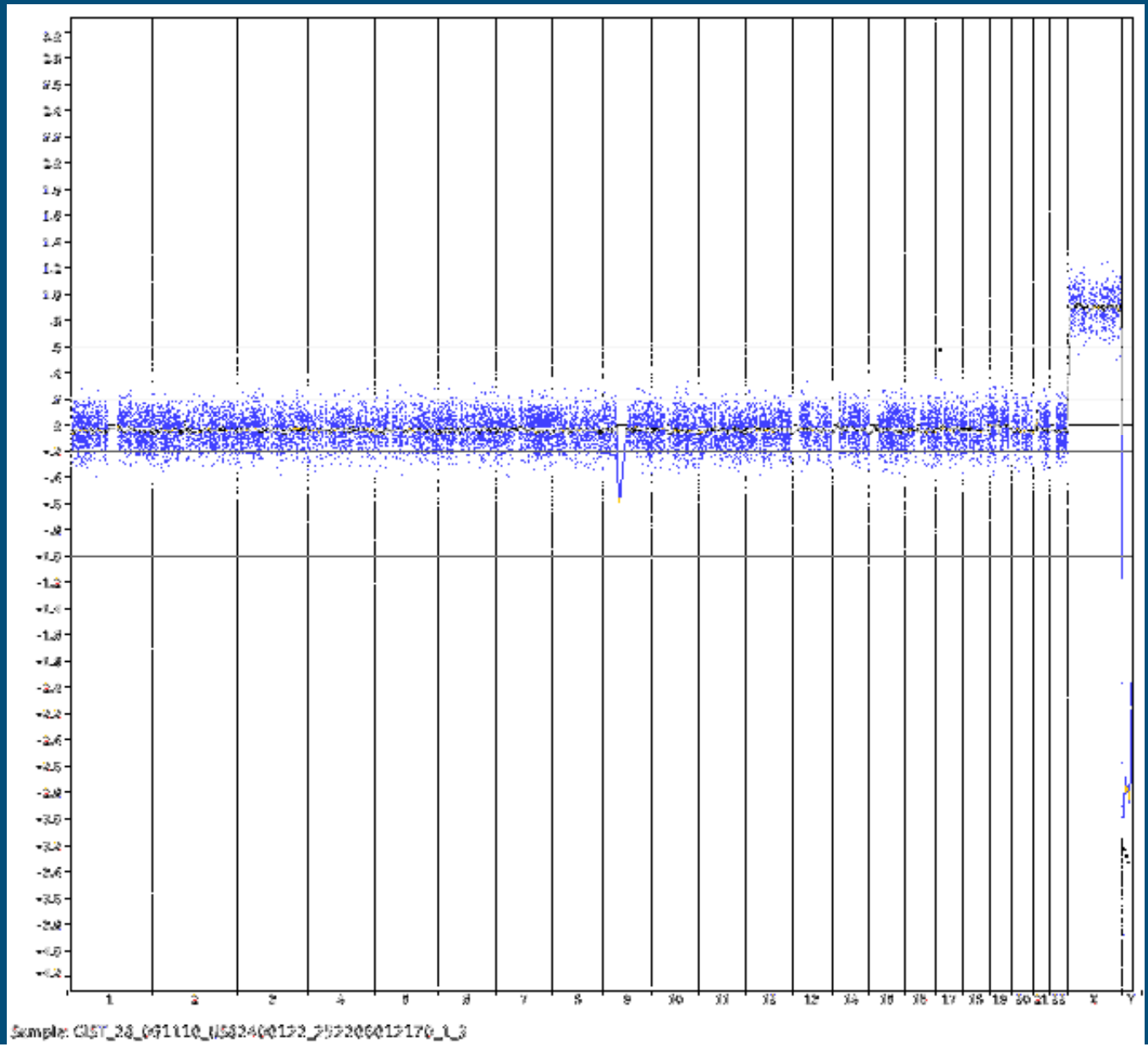
COMPARATIVE GENOMIC HYBRIDIZATION



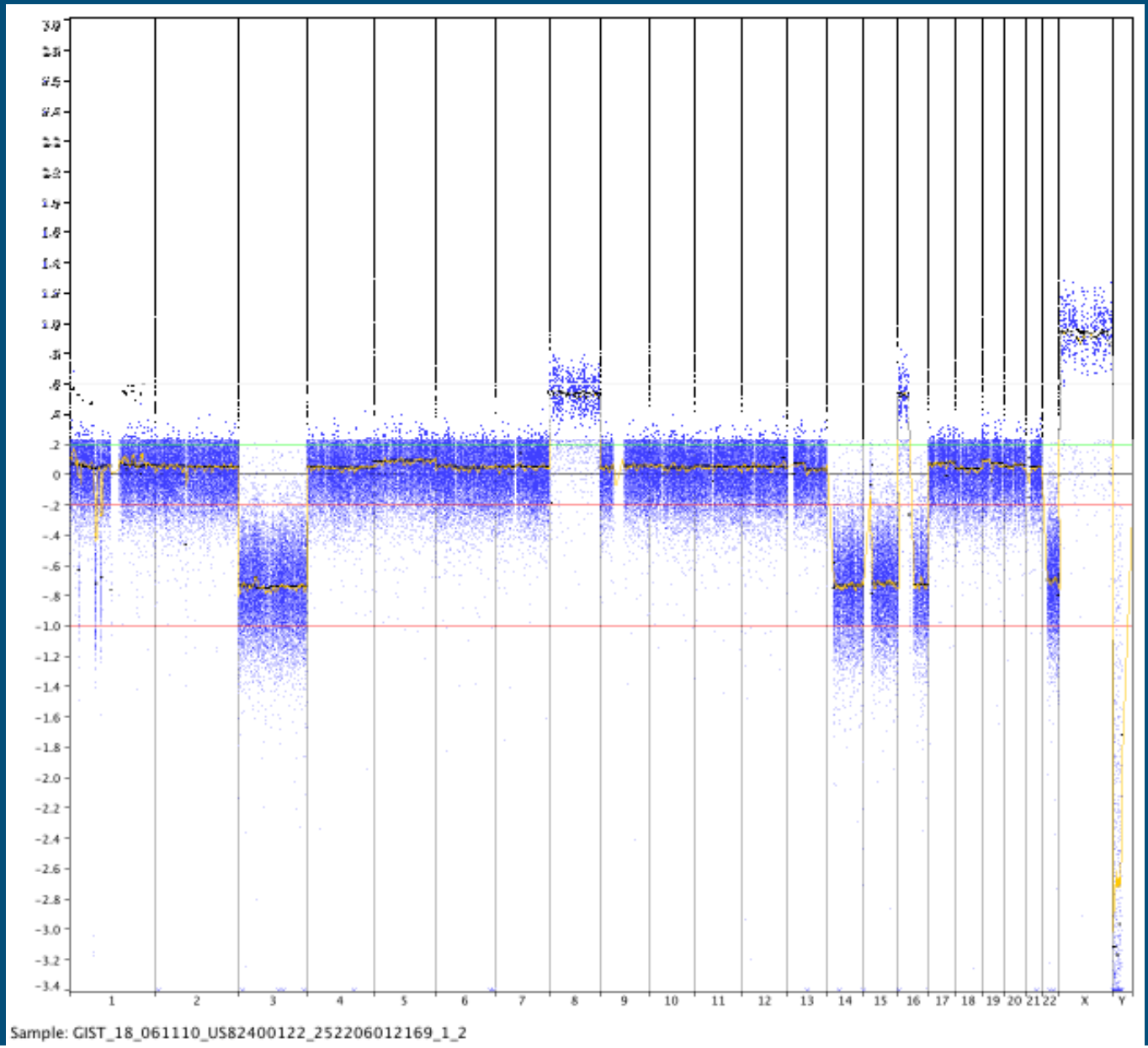
Comparative genomic hybridisation (CGH) analysis of a lymph node metastasis from a renal cell carcinoma

Expert Reviews in Molecular Medicine © 2000 Cambridge University Press

CASE WITHOUT ABERRATIONS



MULTIPLE ABERRARATIONS WITH COMPLEX CHANGES



FREQUENT ABERRATIONS

LOSSES	GAINS
1p	1q
9p	5
13	7
14	8q
15	19p
22	

OUTCOME

- 22 PATIENTS STUDIED
- 20 GENERATED USEFUL DATA
- 6/20 (**30%**) NO ABERRATIONS
- 14/20 (**70%**) ABNORMAL CGH
- SPECTRUM OF ABNORMALITIES OBSERVED

Paul Meltzer, Keith Killian, Miia Suuriniemi, Dan Edelman (NCI)

COMPARATIVE GENOMIC HYBRIDIZATION

CONCLUSIONS

WE NEED TO DETERMINE IF A COPY-NEUTRAL (NORMAL) CGH PATTERN CORRELATES WITH ANY CLINICAL PARAMETER

WE ARE COLLECTING MATCHED NORMAL BLOOD FROM PATIENTS WITH COPY-NEUTRAL SAMPLES TO BEGIN TRANSCRIPTOME SEQUENCING

6th Clinic January 19-21 2011

8 of 12 appointments scheduled Waitlist for adult wildtype patients

Anette Duensing
University of Pittsburgh

Maureen O'Sullivan
Trinity College Dublin
Colaiste na Trionoide, Baile Atha Cliath

Joshua Schiffman
Huntsman Cancer Institute

the NIH pediatric GIST clinic

Goal

To define new targets for potential treatment

To design innovative national treatment protocols

What is the Vision for the Future

Sequencing based detection of mutations that drive the formation of pediatric GIST

What is the Vision for the Future

1. **Whole genome sequencing of 4 fresh frozen samples**

2. **Transcriptome sequencing of 8 copy-neutral CGH samples**

3. **Genome wide amplification followed by sequencing of archived samples**

4. **Multiple collaborative efforts**

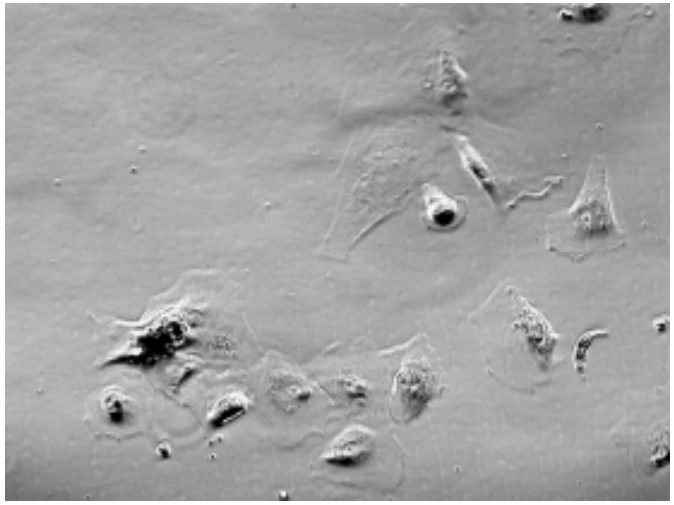
Research Samples

Fresh frozen tumor
-Immediately after surgery, freeze the tumor

Archived paraffin blocks

Consecutive unstained slides

At the time of surgery,
initiate a cell line



Please contact the NIH for details
ncipediatricgist@mail.nih.gov

the NIH pediatric GIST team

Art Therapist	Megan Robb
Clinical Nurses	Joan Sheeren, Patty McGinley
Complementary Medicine	Scott Miller
Coordinator	Sherri DePollar
Dermatologist	Heidi Kong
Geneticists	Constantine Stratakis, Margarita Raygada, Maya Lodish
Medical Oncologist	Shivanni Kumar
Nutritionist	Jennifer Graf
Pediatric Oncologists	Lee Helman, Su Young Kim
Radiologists	Baris Turkbey, Peter Choyke
Research Nurses	Christine Graham, Donna Bernstein, Lauren Long, Robyn Bent
Pain Specialists	Ann Berger, Dan Handel
Pathologist	Maria Tsokos
Psychosocial Specialist	Lori Wiener
Rehabilitation Medicine	Donna Gregory
Social Worker	Barbara Santangini
Videography	Demetrio Domingo

Pediatric
ONCOLOGY BRANCH

the NIH Pediatric & Wildtype GIST Clinic

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FOX CHASE
CANCER CENTER

St. Jude Children's
Research Hospital

National Human
Genome Research
Institute

HUNTSMAN
CANCER INSTITUTE
UNIVERSITY OF UTAH

Peter Mac
EXCELLENCE INNOVATION COMPASSION

National Institute of Dental
and Craniofacial Research

Our Thanks

To the physicians and researchers

To GIST Support International

To the patients and families