Biology of GIST
Translating Cancer Research into Targeted Therapeutics

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Spindle-cell GIST
Epithelioid GIST
GIST Biologic Progression

Micro-GIST

Proliferating GIST

Invasive, metastatic GIST

VERY COMMON!

KIT, PDGFRA, NF1, SDH

-14q, -22q, -1p (tumor suppressors?), ...

Cell cycle (CDKN2A, TP53, RB1, ...)

Dystrophin

benign

malignant
GIST Biologic Progression

**Micro-GIST**

**Proliferating GIST**

**Invasive, metastatic GIST**

KIT, PDGFRA, NF1, SDH

-14q, -22q, -1p (tumor suppressors?), ...

Cell cycle (CDKN2A, TP53, RB1,...)

**New Therapeutic Targets**

benign

malignant

Dystrophin
GIST Biologic Progression

Micro-GIST

Proliferating GIST

Invasive, metastatic GIST

KIT, PDGFRA, NF1, SDH

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Cell cycle (CDKN2A, TP53, RB1,...)

Dystrophin

benign

malignant

New Therapeutic Target
KIT and PDGFRA Mutations in >2000 GISTs (Heinrich-Corless)

Overall Mutation Frequency: 86%

KIT (78.5%)
- Exon 9 (9%)
- Exon 11 (67%)
- Exon 13 (1%)
- Exon 17 (1%)

PDGFRA (7.5% total)
- Exon 12 (2%)
- Exon 14 (rare)
- Exon 18 (5.5%)
Metastatic GIST
Major response after 6 months of Imatinib

KIT exon 11 mutation
Secondary imatinib-resistance 

**KIT** mutations in GIST

- **Dimerization domain**
  - ATP-binding: 9
  - Juxtamembrane domain: 11
- **Juxtamembrane domain**
  - Activation Loop: 13
    - V654A
  - 17: D816, D820, N822, Y823
Secondary resistance in GIST

SECONDARY MUTATIONS

- Exon 13: V654
- Exon 14: T670
- Exon 17: D816, D820, N822, Y823

FREQUENCY

- V654: 40%
- D816, D820, N822, Y823: 30%

SUNITINIB (SUTENT)

- ATP-binding pocket
- Activation Loop

References:
Debiec-Rychter M, 2005
Antonescu CR, 2005
Wardelmann E, 2006
Heinrich MC, 2008
Lieglo B, 2008
Secondary resistance in GIST

SECONDARY MUTATIONS

Exon 9
Exon 11
Exon 13
Exon 14
Exon 17

V654
T670
D816
D820
N822
Y823

40%
30%

ATP-binding pocket

REGORAFENIB (STIVARGA)

Activation Loop
Rapid alternation regimen might minimize toxic effects.

Alternation of complementary drugs increases the spectrum of effective inhibition of IM-resistant clones.

SuRe Trial – (Drs. Serrano, George and colleagues)
Regorafenib correlative studies in GIST: Clinical response with KIT partial inhibition

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**Regorafenib**

**KIT Resistance mut**

- D820Y
- N822K

**pKIT Y703**

- 44%
- 33%
- 19%
- 60%

**KIT**

- 44%
- 33%
- 19%
- 60%

**PI3-K**

- 44%
- 33%
- 19%
- 60%
Mutations **activate** KIT/PDGFRA, causing GIST cells to grow and survive.
Imatinib and other kinase inhibitors down-regulate KIT/PDGFRA activation to levels that no longer support cell growth.
KIT and PDGFRA imatinib-resistance mutations are life-savers for GIST but at same time they STRESS the cells.

Optimal energy-level for GIST

2nd Mutation Imatinib-resistance

Destroy GIST by selectively STRESSING the most Gleevec-resistant cells
Darwin: fittest/fitness → "just-right" theory of signal transduction

- KIT/PDGFRA
- RAS-GDP
- RAF
- SHC
- SOS
- GRB2
- DOK
- RAS-GAP
- PI3K
- AKT
- mTOR
- BCLX_L
- BAD
- 14-3-3
- BAD
- 14-3-3

- Adhesion, motility
- PAK1
- FAK
- JAK
- STATs
- SAPK
- MAPK
- ETV1
- MEK1/2
- MERTK
- MEGF8
- PAK1
- PAK2

Nucleus
Mitochondria
Survival
Proliferation
Adhesion, motility

14-3-3
HSP90: Key KIT oncoprotein chaperone in GIST

Chaperone family:
- protein folding
- translocation
- stabilization

Paul Workman
Screen **11,000 genes** to determine which the GIST cells need most

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Adrian Marino-Enriquez – Oncogene, 2014
CDC37 targeting 10-fold more selective than HSP90 targeting

Chaperone family:
- protein folding
- translocation
- stabilization
shRNA pooled library screen in GIST

- KIT
- CDC37
- Hsp90
shRNA pooled library screen in GIST
Can we Target KIT/PDGFRA by Immunotx???

Overall Mutation Frequency: 86%

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3 TKI-resistant GIST metastases (same patient): Varied cytoplasmic **NOT MEMBRANE** oncoprotein target expression

**SPINDLE CELL**
KIT: **DIFFUSE-STRONG**

**EPITHELIOID**
KIT: **WEAK**

**SHORT SPINDLE CELLS**
KIT: **GOLGI PATTERN**

*Strong Cytoplasmic*
*Variable Cytoplasmic*
*Golgi Pattern*
Models: Defining GIST Biology

► Cell Lines
  - Cell cultures created from GIST surgical specimens
  - Studies are quick & inexpensive
  - Cells can lose dependence on key targets

► Xenografts
  - GIST surgical specimens implanted into mice
  - Nuanced evaluation of complex biology

► Genetically-engineered models
  - GIST developing in a mouse, eg due to a KIT mutation in the mouse
  - Potentially most nuanced, although might not represent the true biology of human GIST
  - Most expensive