



Brigham and Women's Hospital, Harvard Medical School



# **Biology of GIST**

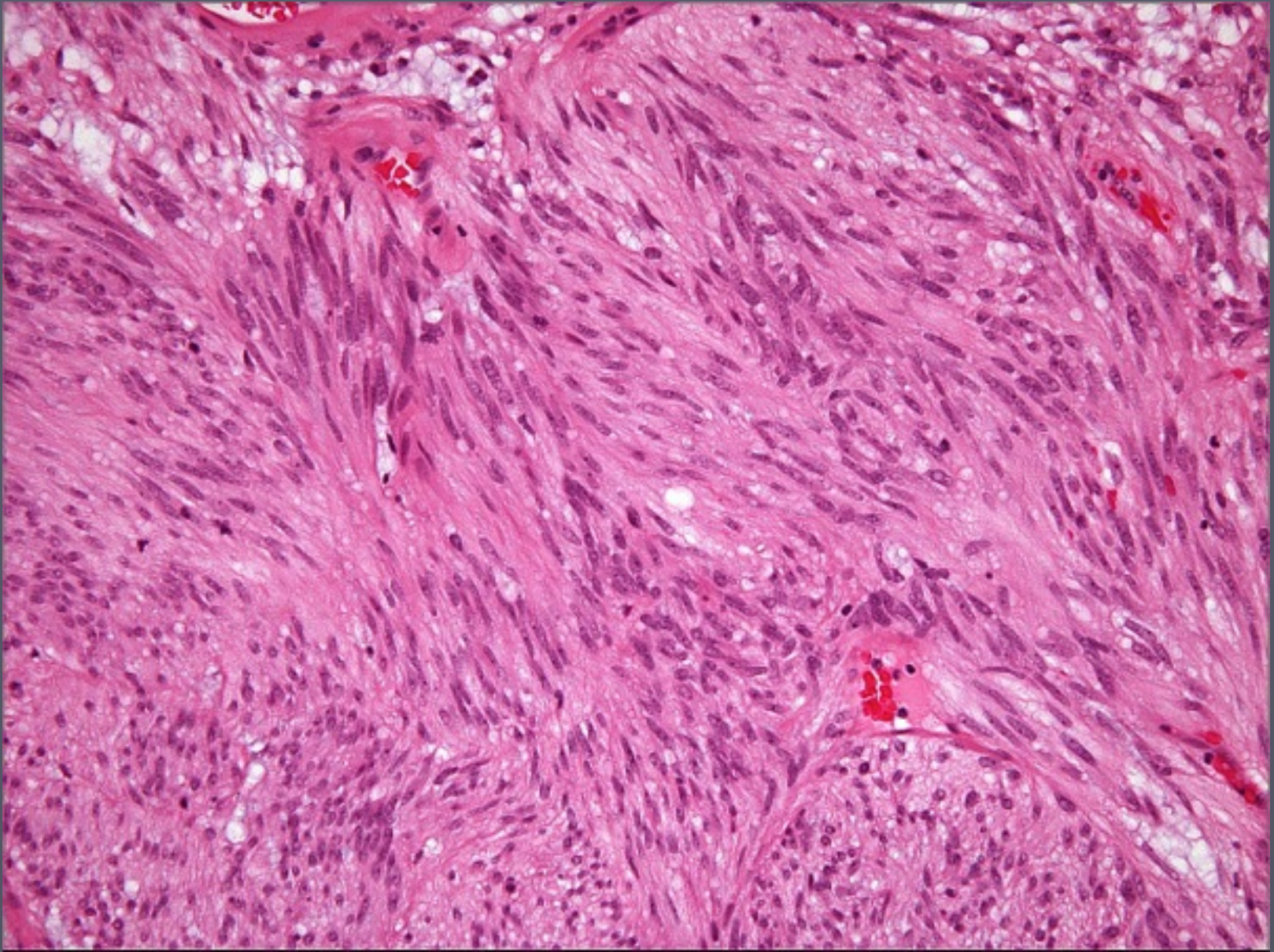
## **Translating Cancer Research into Targeted Therapeutics**

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Brigham and Women's Hospital  
Dana-Farber Cancer Institute  
Harvard Medical School

Dana-Farber/Harvard Cancer Center

# Spindle-cell GIST

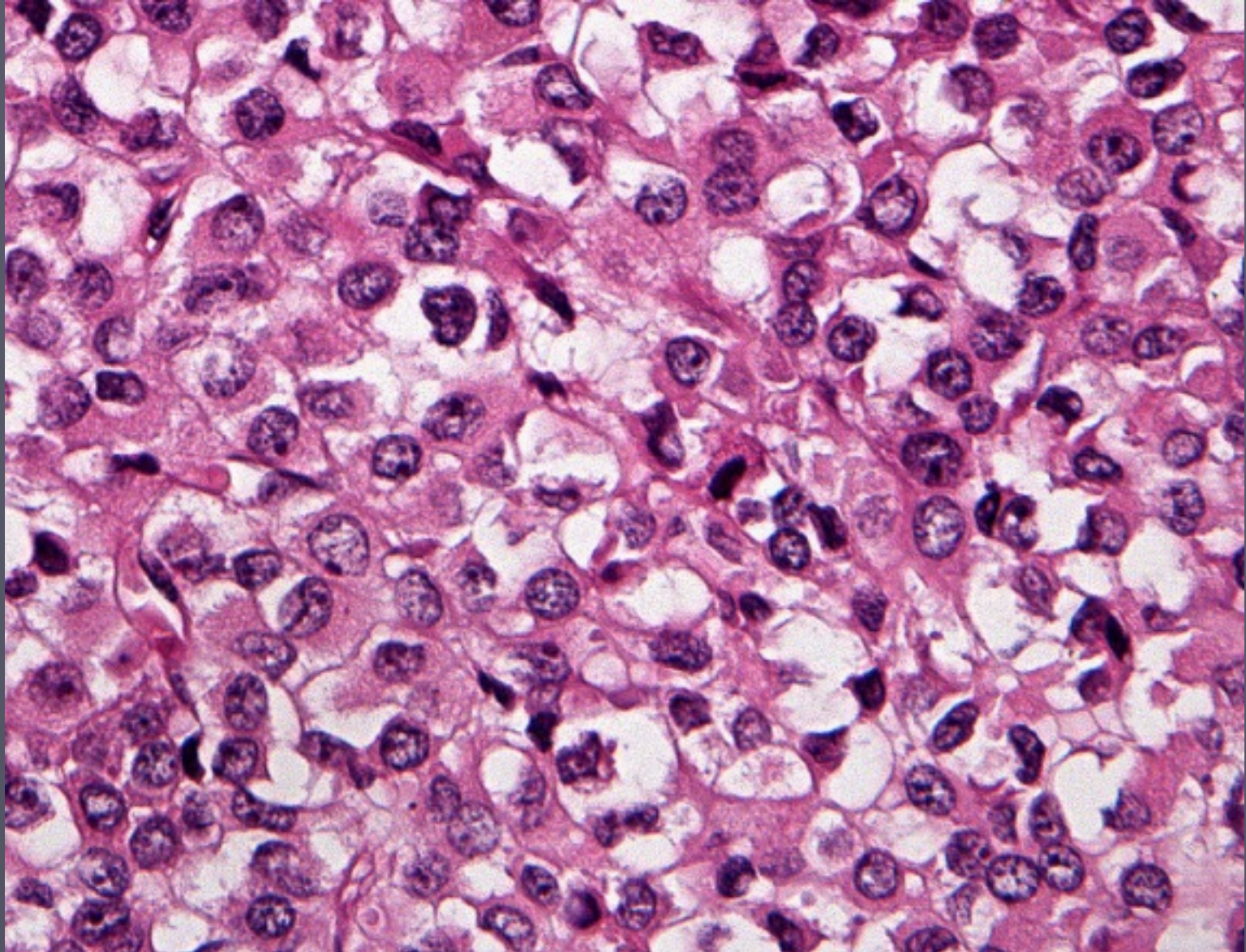
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# Epithelioid GIST

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# GIST Biologic Progression

Micro-GIST

**VERY COMMON!**

Proliferating GIST

Invasive, metastatic GIST

**KIT, PDGFRA, NF1, SDH**

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

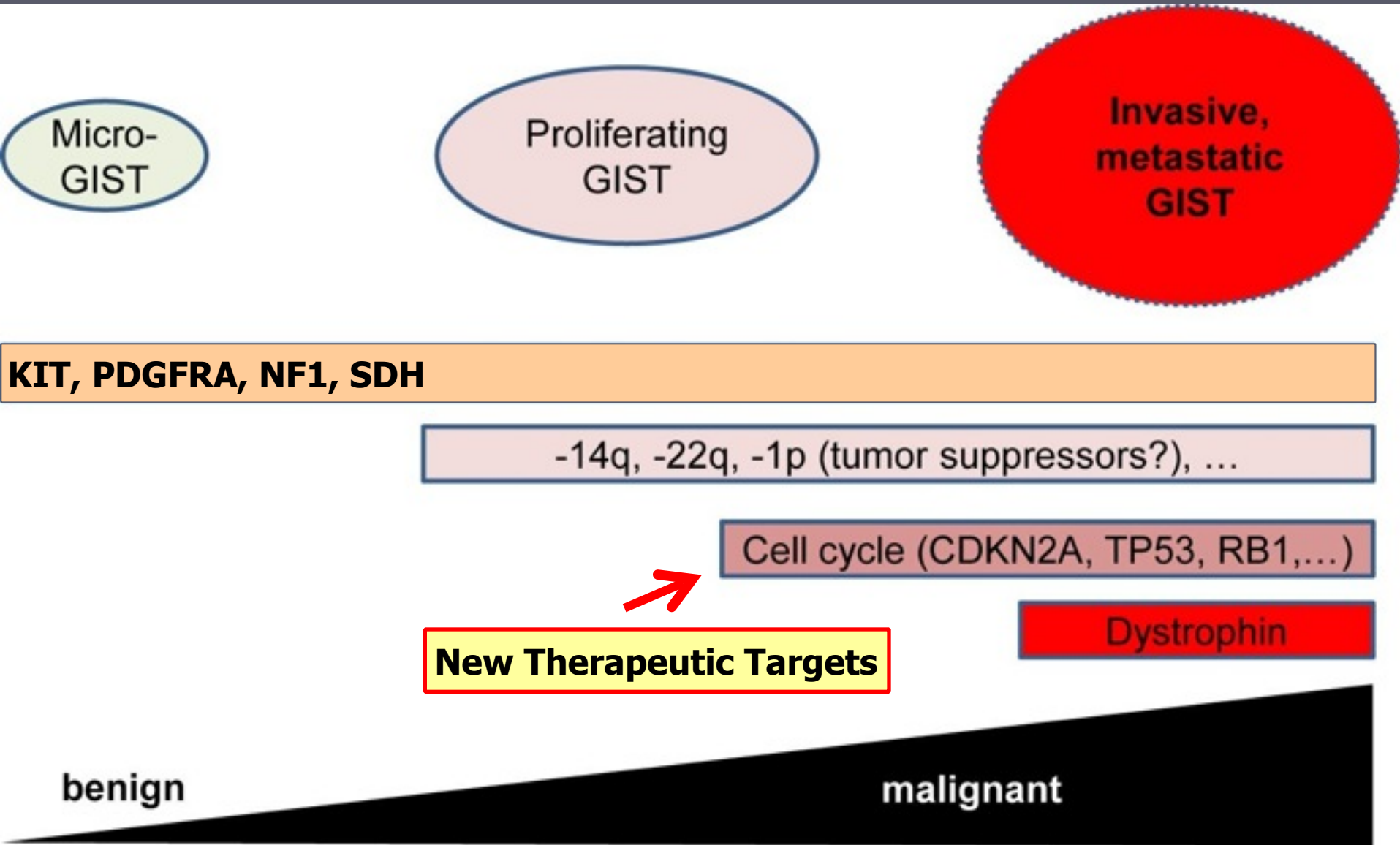
Cell cycle (CDKN2A, TP53, RB1,...)

Dystrophin

benign

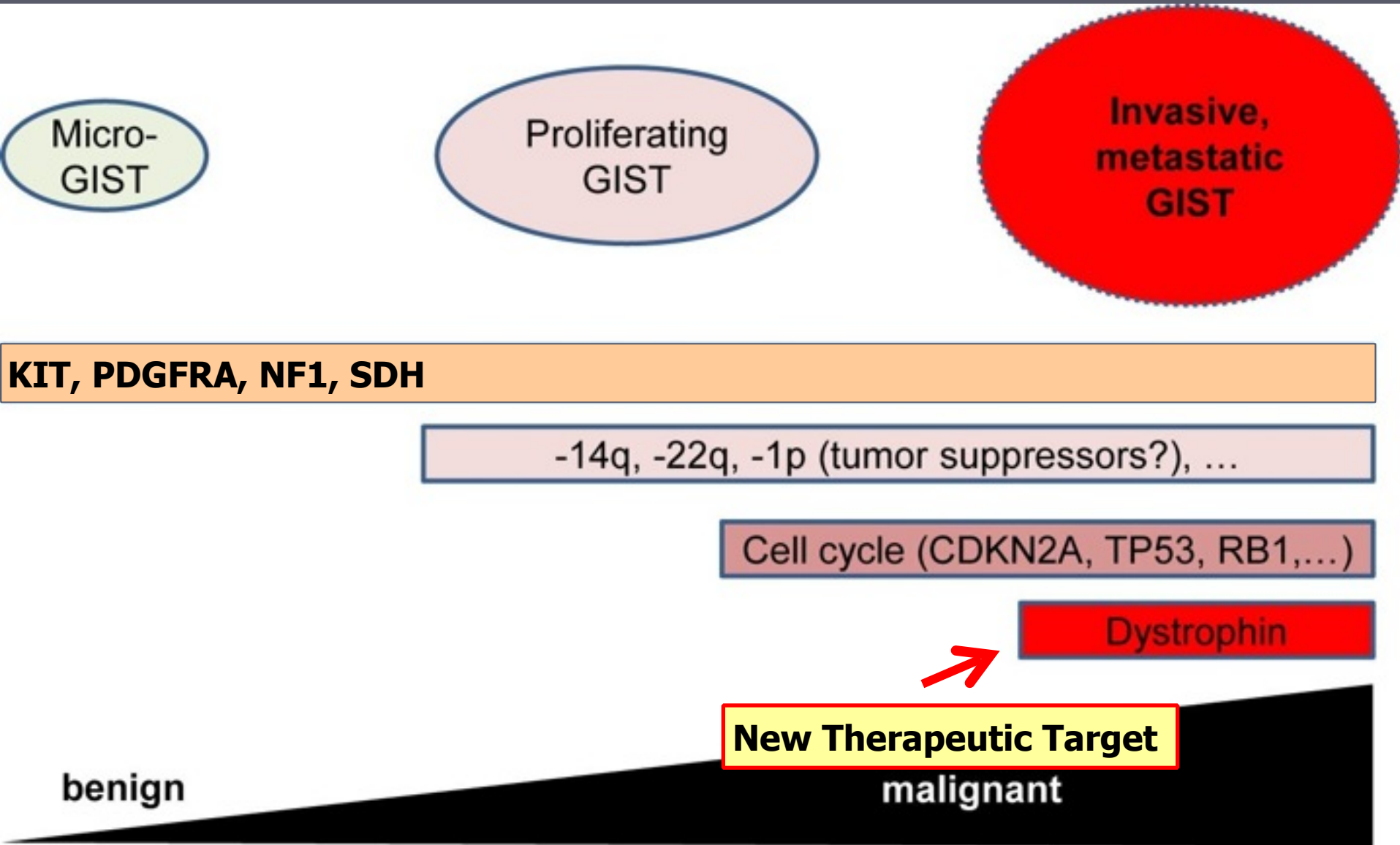
malignant

# GIST Biologic Progression





# GIST Biologic Progression

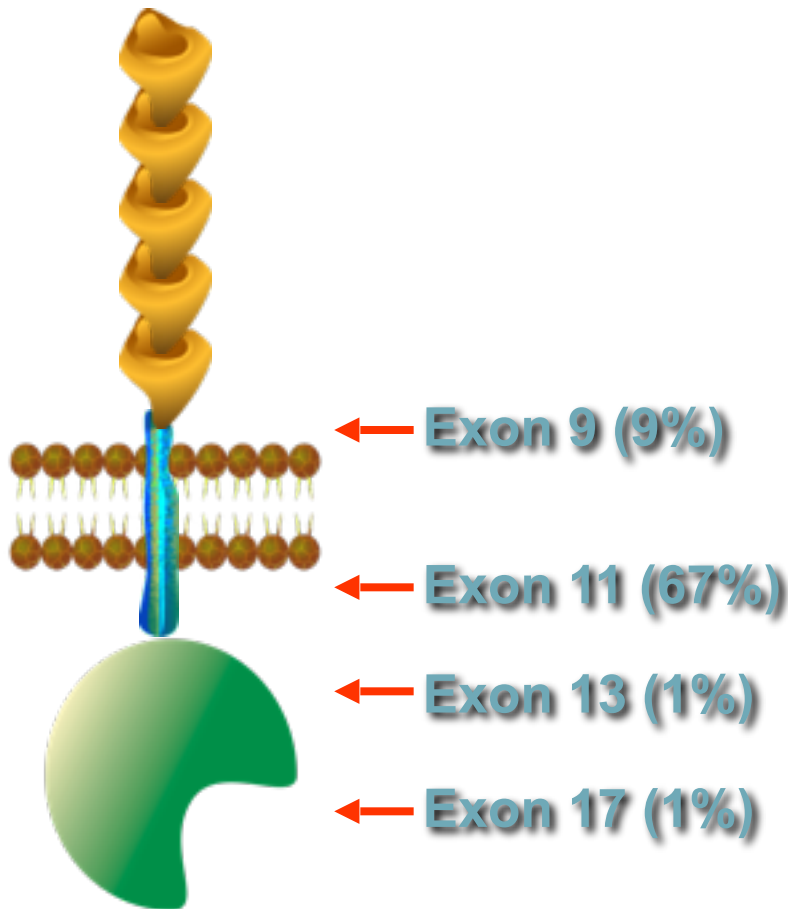




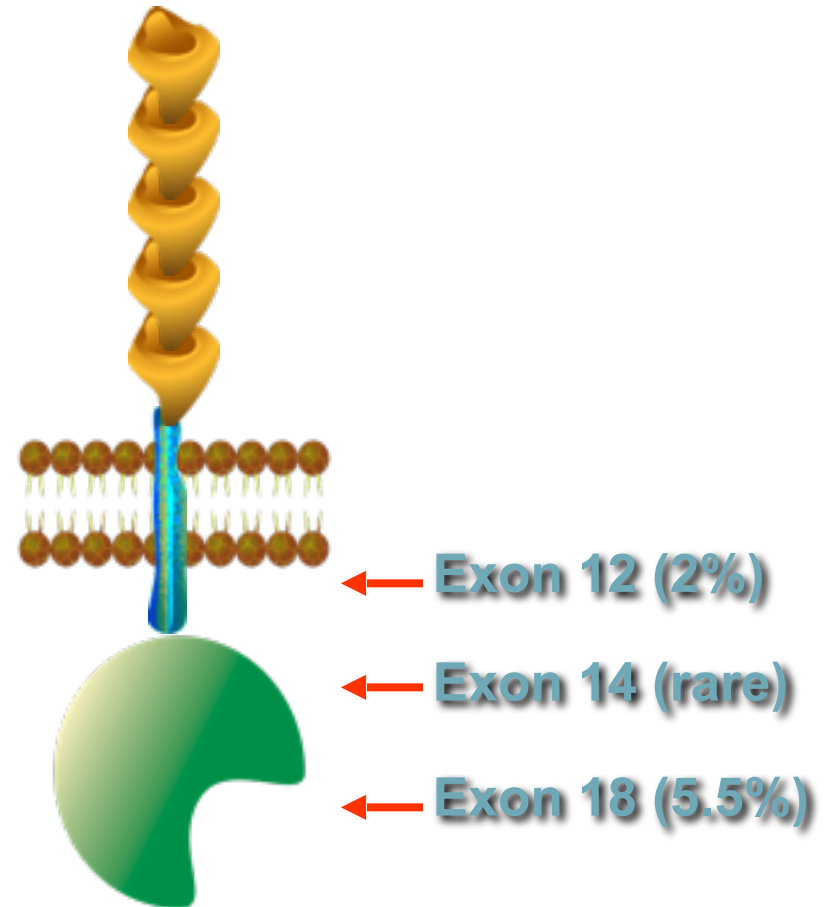
# *KIT* and *PDGFRA* Mutations in >2000 GISTs (Heinrich-Corless)

Overall Mutation Frequency: **86%**

## *KIT* (78.5%)

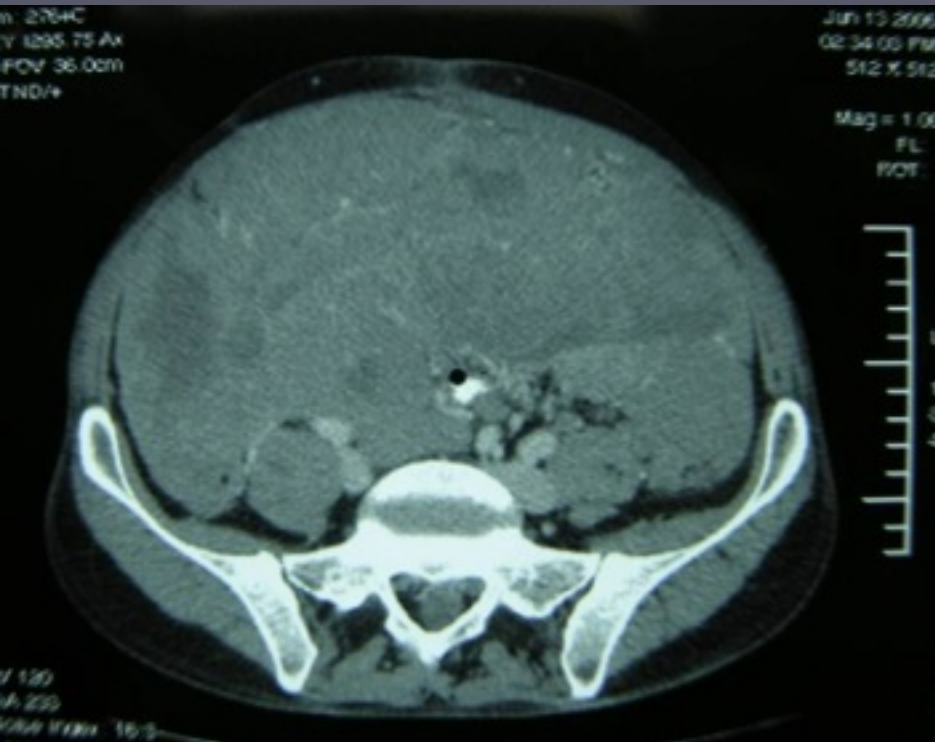


## *PDGFRA* (7.5% total)



# Metastatic GIST

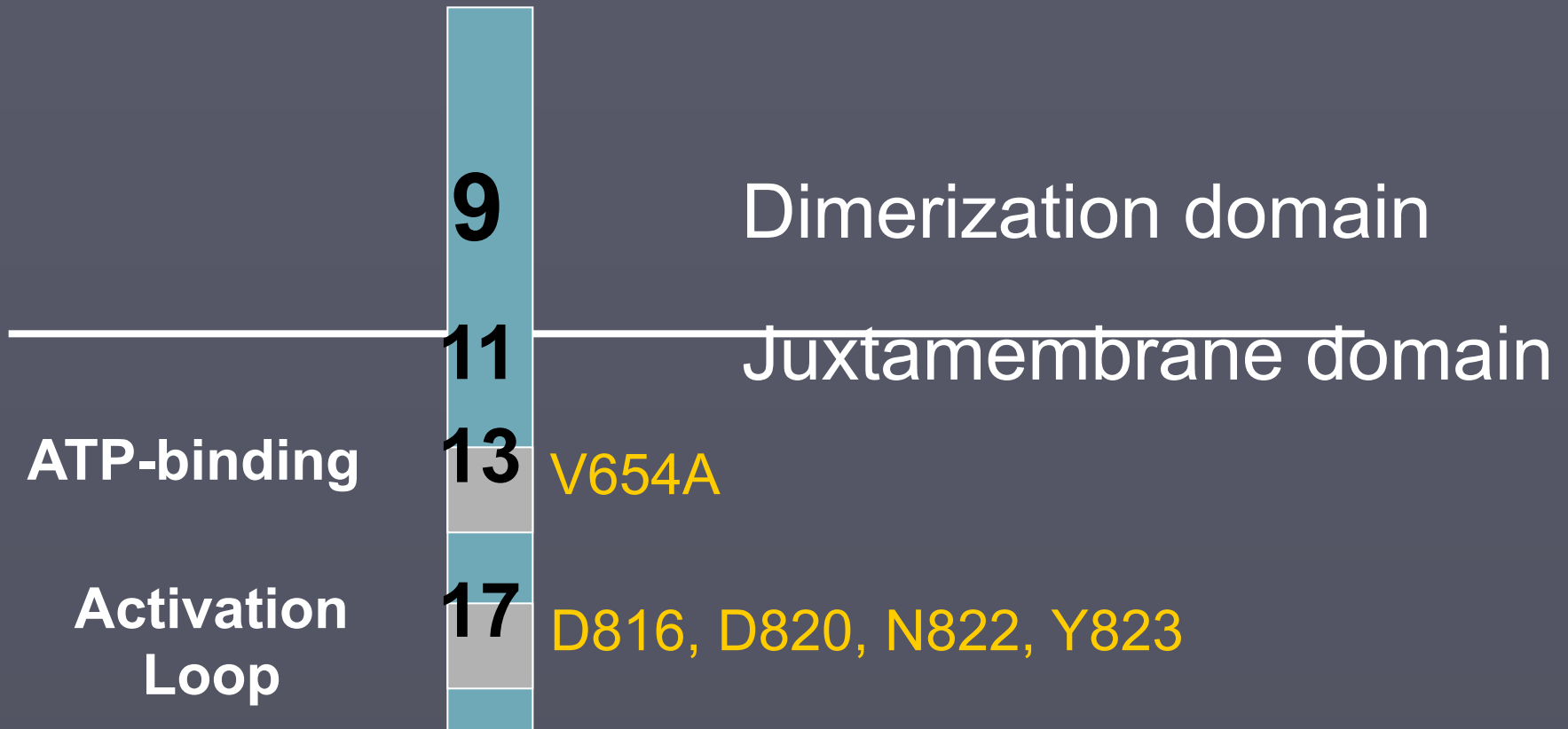
## Major response after 6 months of Imatinib



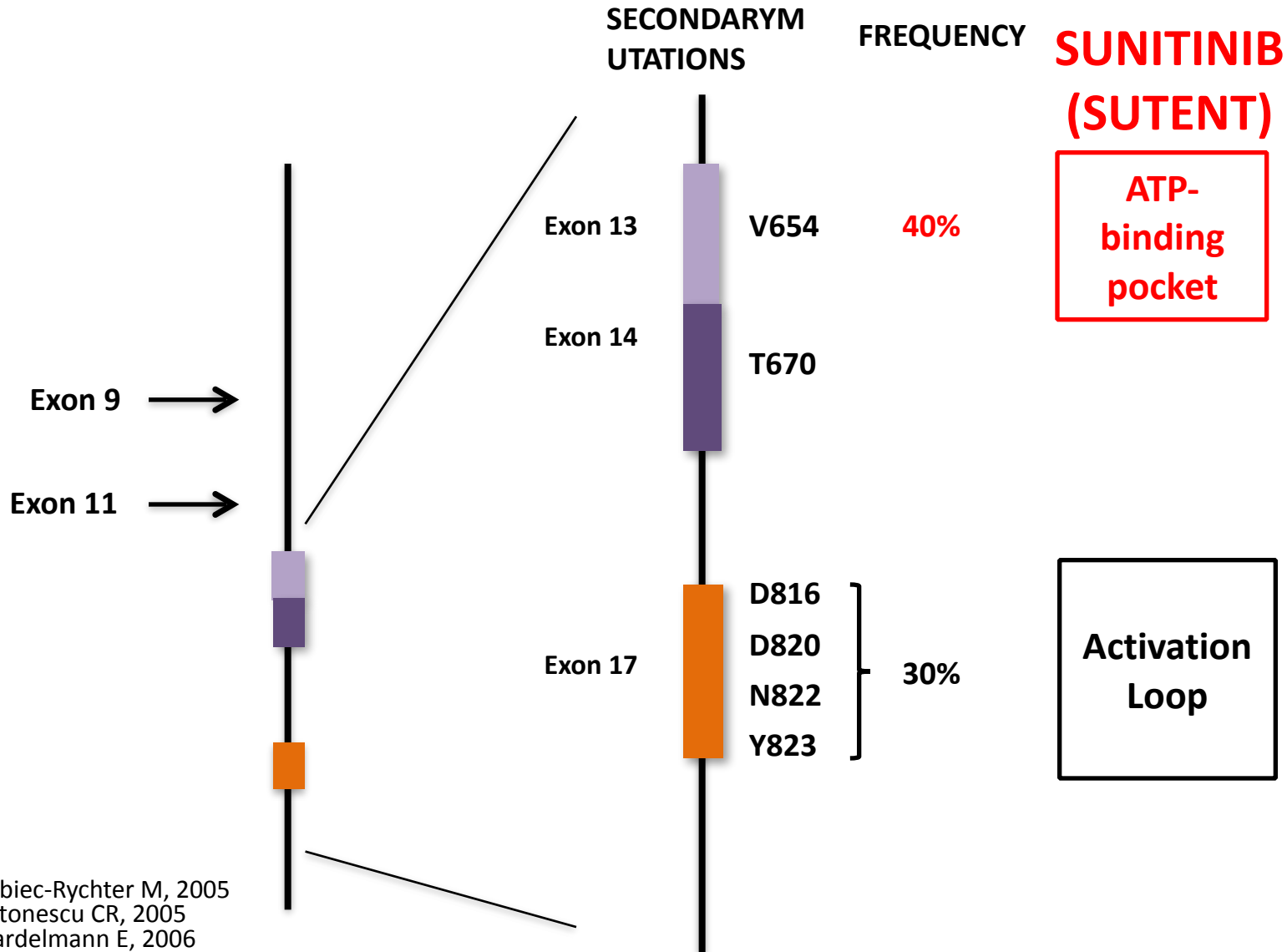
KIT exon 11 mutation



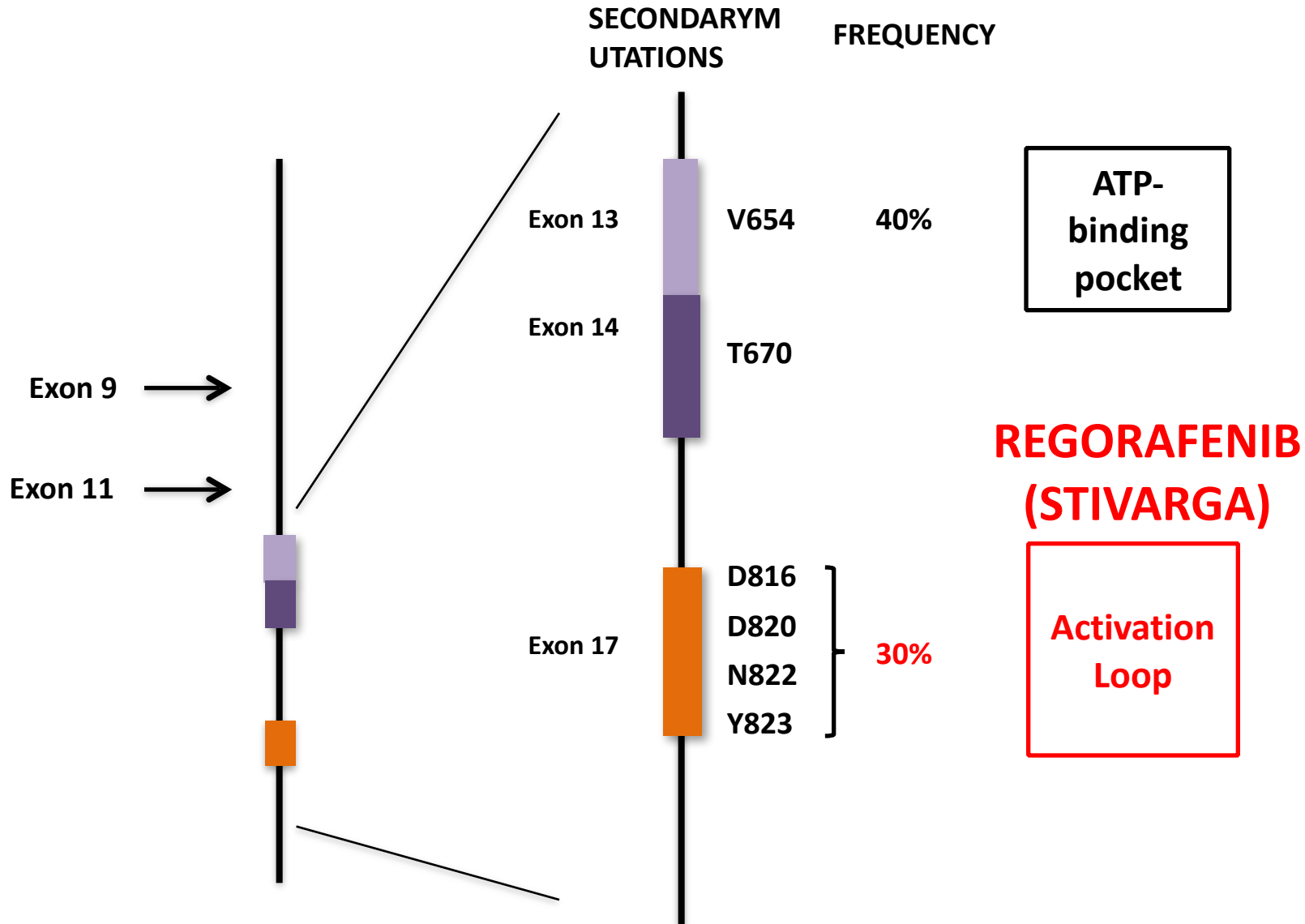
# Secondary imatinib-resistance **KIT** mutations in GIST



# Secondary resistance in GIST



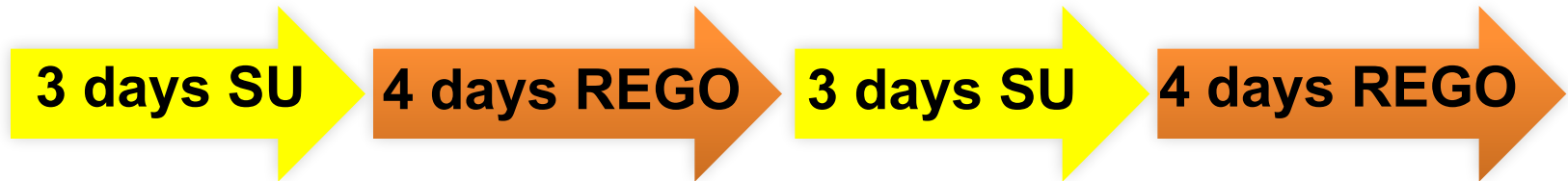
# Secondary resistance in GIST





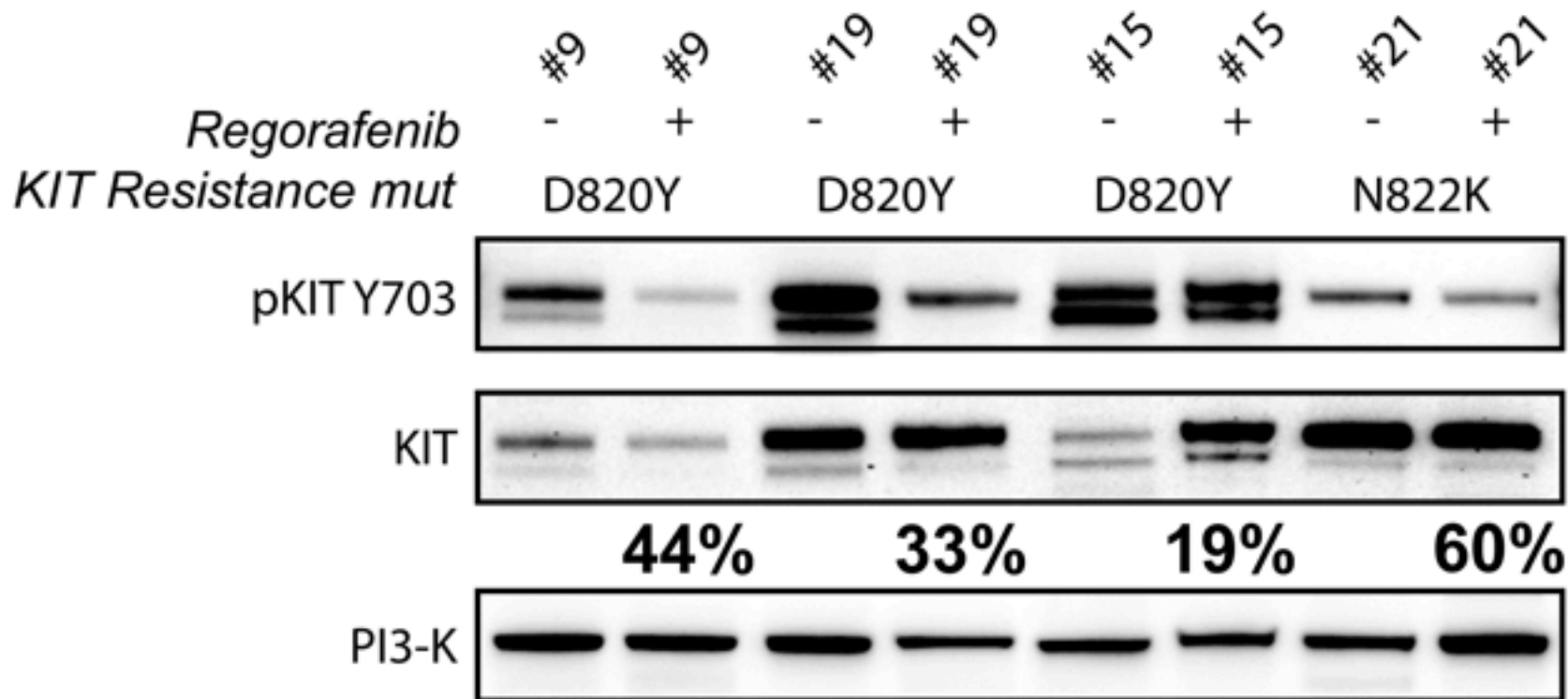
# Rapid alternation regimen

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- ✓ 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)

Correlative studies with KIT



# Mutations activate KIT/PDGFR $\alpha$ , causing GIST cells to grow and survive

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KIT baseline activation  
Normal GIST precursor  
cell

KIT/PDGFR $\alpha$   
Mutation



Increased KIT/PDGFR $\alpha$  activation  
causes GIST to grow



# Imatinib and other kinase inhibitors down-regulate KIT/PDGFR $\alpha$ activation to levels that no longer support cell growth

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**KIT or PDGFR $\alpha$  mutant GIST**



**KIT/PDGFR $\alpha$  activation restored to low levels**

KIT and PDGFRA imatinib-resistance mutations are life-savers for GIST but **at same time they STRESS the cells**

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**Optimal energy-level for GIST**



**2nd Mutation  
Imatinib-  
resistance**



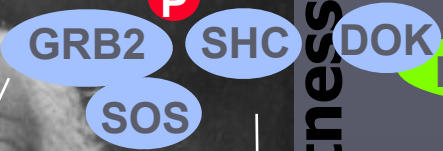
**Destroy GIST by  
selectively STRESSING the  
most Gleevec-resistant cells**



Darwin fittest/fitness - st-rig



Adhesion, motility



Proliferation



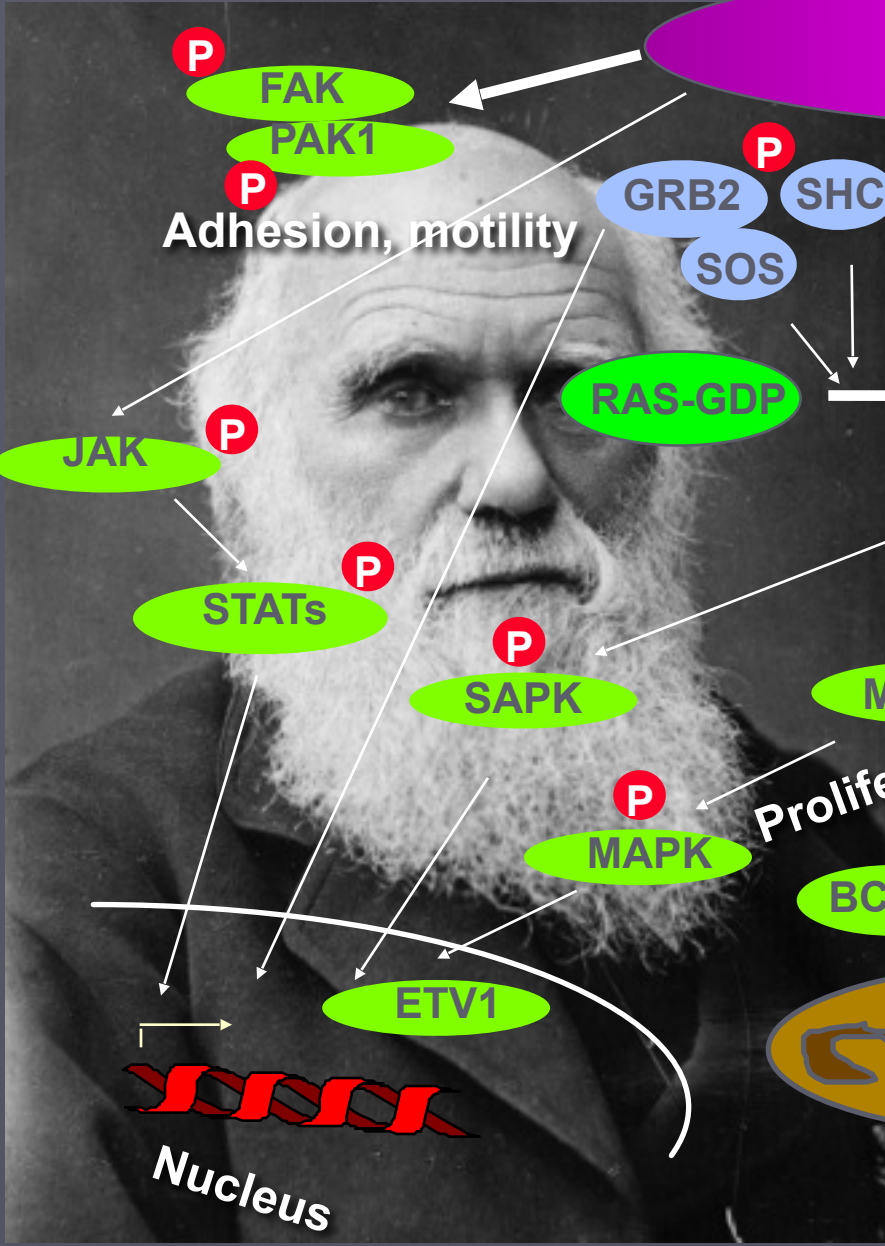
Survival



Mitochondria



Nucleus

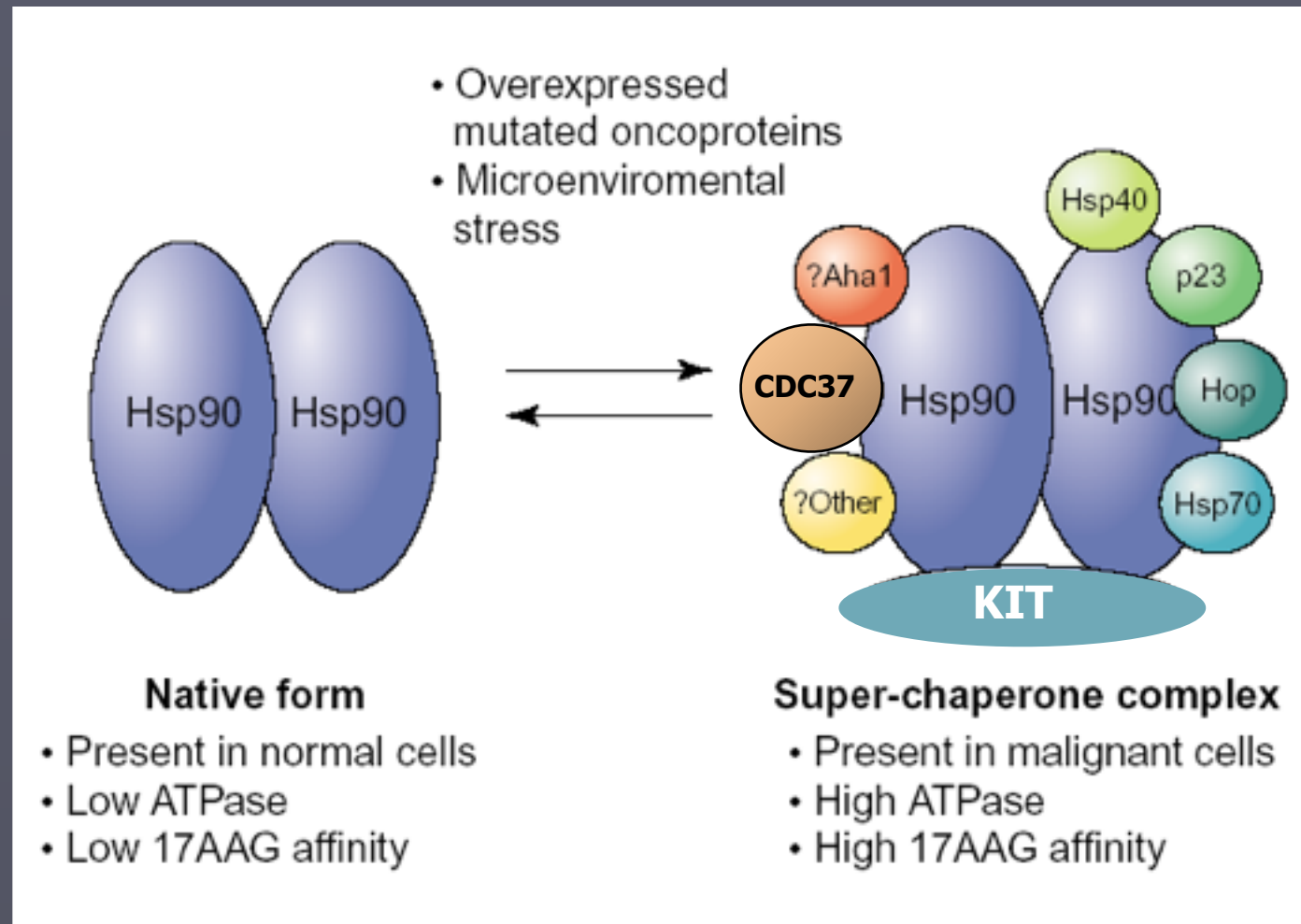




# HSP90: Key KIT oncoprotein chaperone in GIST

## Chaperone family:

- protein folding
- translocation
- stabilization



# Screen 11,000 genes to determine which the GIST cells need most

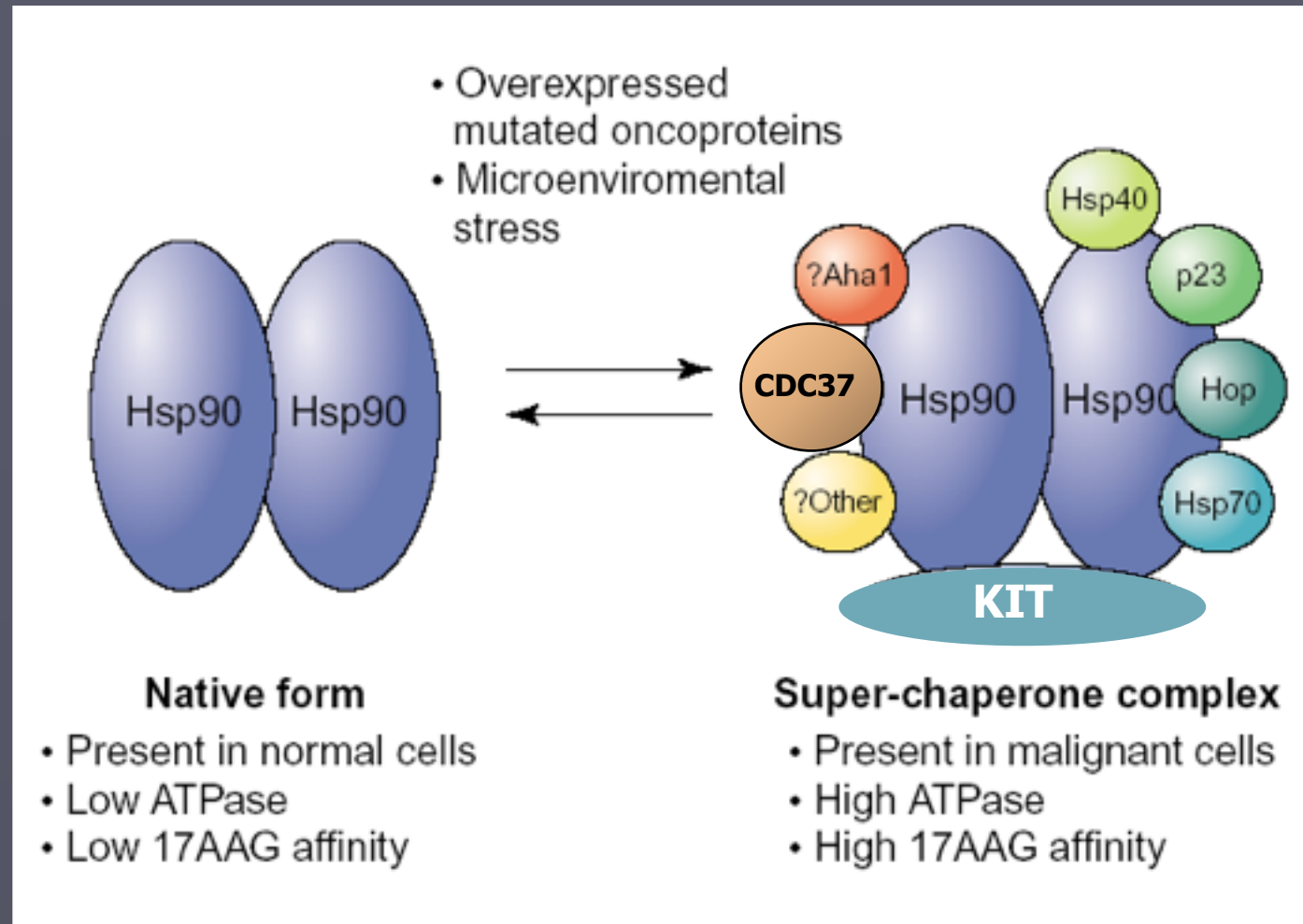
CDC37 = most essential gene among 11,000 genes screened!

NAME	RIGER_RANK	RIGER_SCORE	RIGER_LEV
CDC37:NM_007065	1	-1.82	0.8
VCP:NM_007126	3	-1.81	0.6
PSMC4:NM_006503	2	-1.81	0.8
ZNF206:NM_032805	4	-1.78	0.4
PARN:NM_002582	5	-1.77	0.6
DES:NM_001927	6	-1.77	0.8
EIF5B:NM_015904	7	-1.76	0.75
ZNF207:NM_003457	8	-1.76	0.6
PDHA1:NM_000284	10	-1.75	0.6

# CDC37 targeting 10-fold more selective than HSP90 targeting

## Chaperone family:

- protein folding
- translocation
- stabilization



# shRNA pooled library screen in GIST

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CDC37



Hsp90

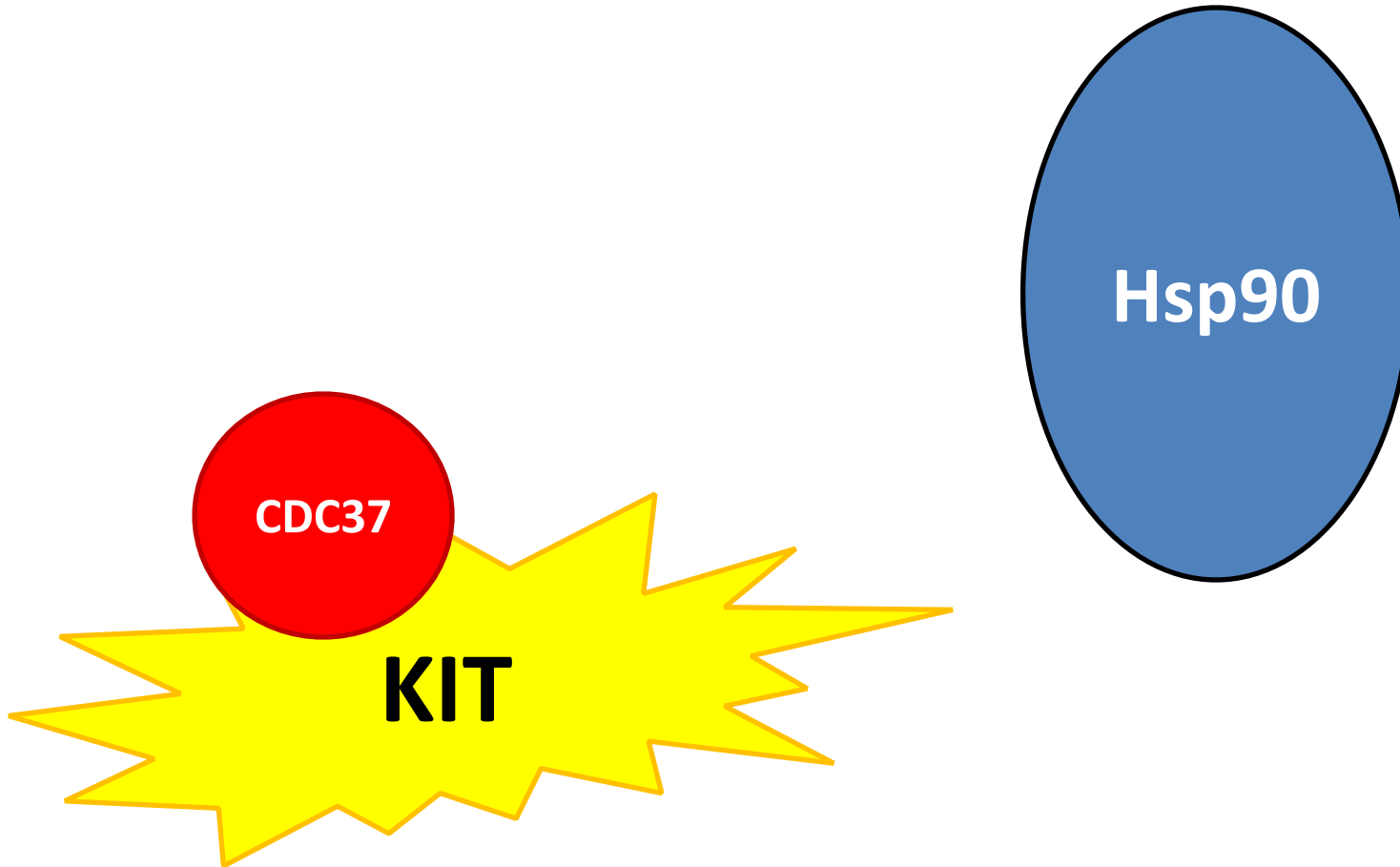


**KIT**



# shRNA pooled library screen in GIST

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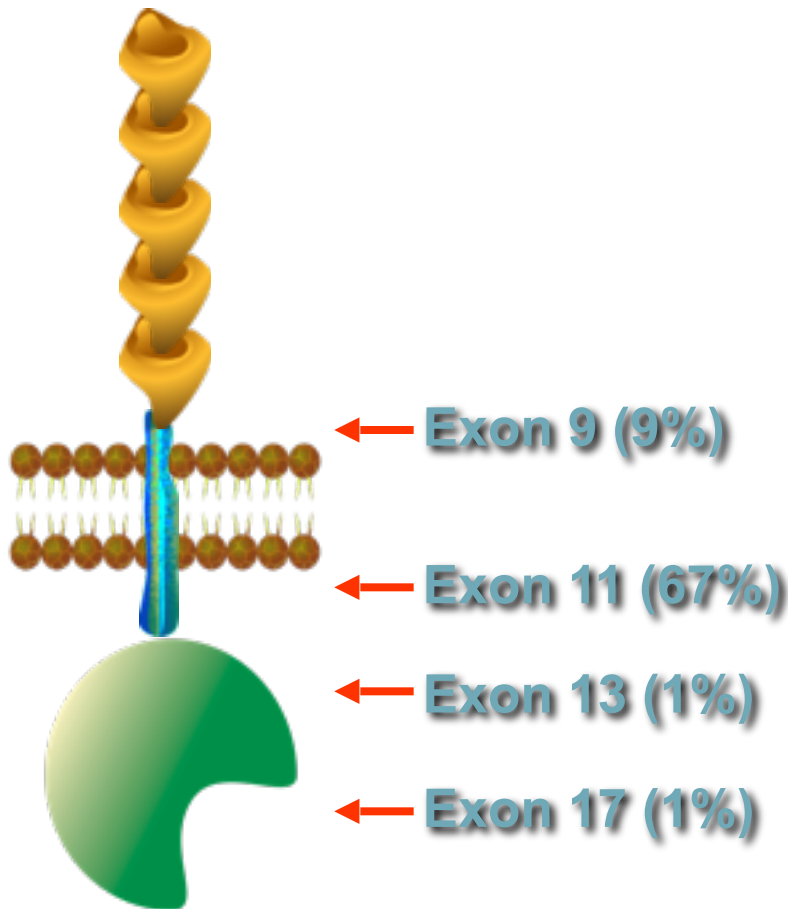




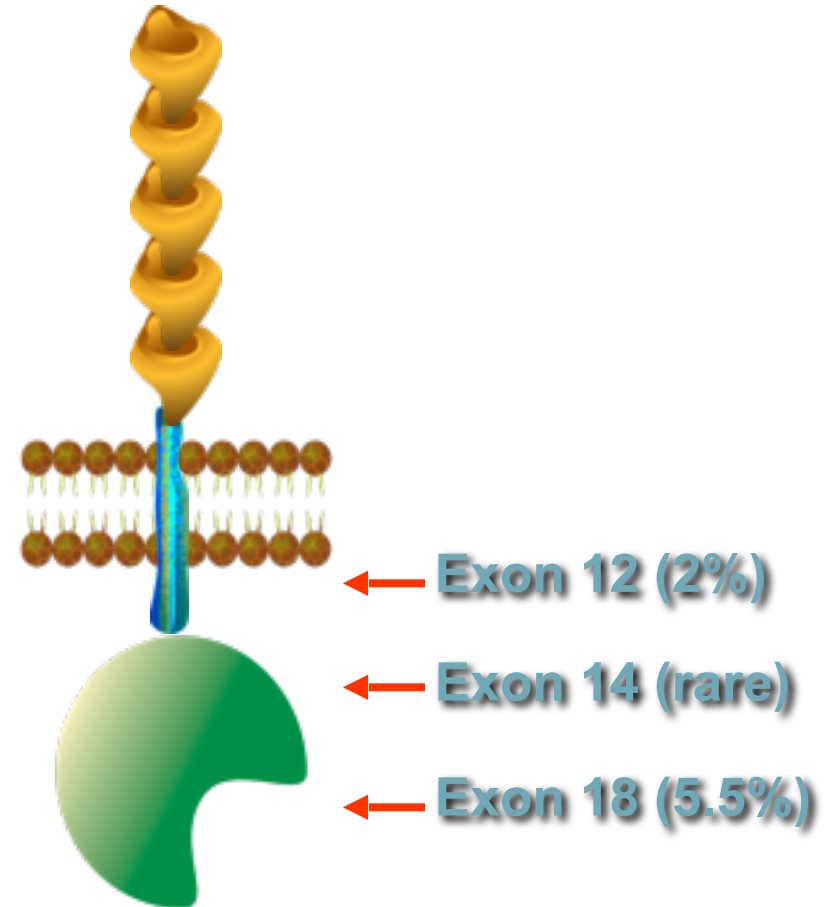
# Can we Target KIT/PDGFRα by Immunotx???

Overall Mutation Frequency: **86%**

**KIT (78.5%)**

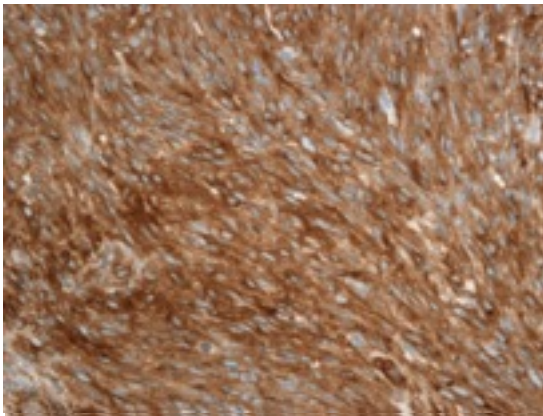
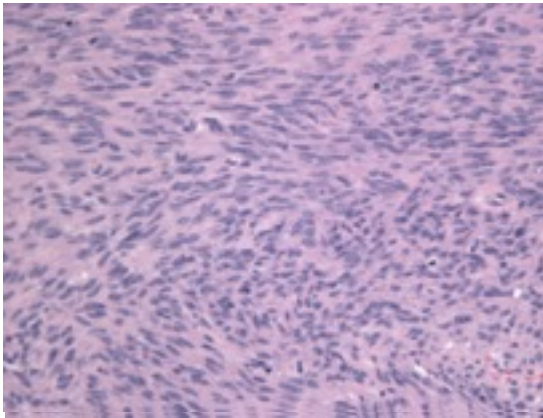


**PDGFRα (7.5% total)**



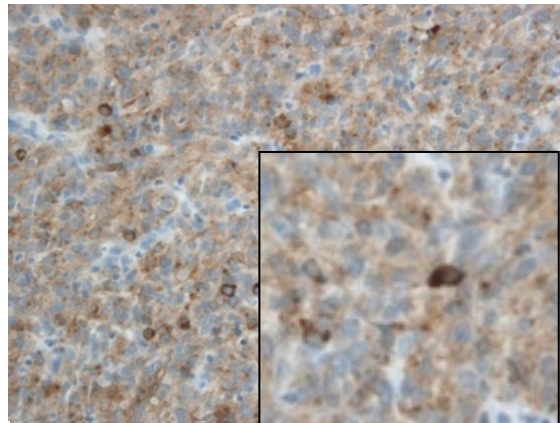
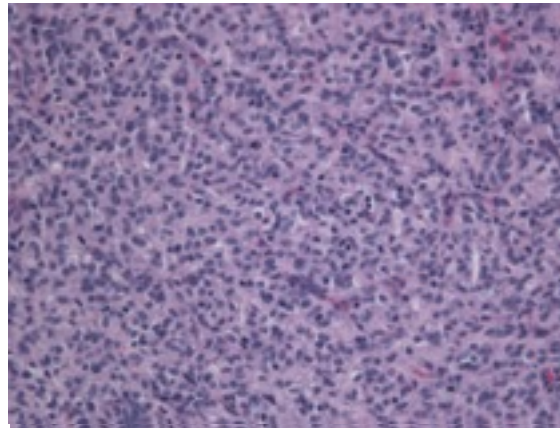
# 3 TKI-resistant GIST metastases (same patient): Varied cytoplasmic **NOT MEMBRANE** oncoprotein target expression

SPINDLE CELL  
KIT: DIFFUSE-STRONG



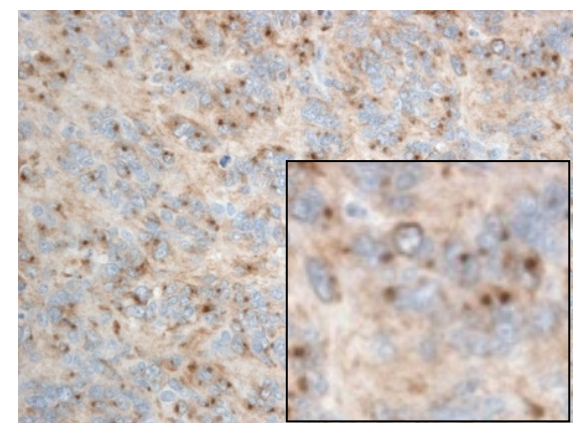
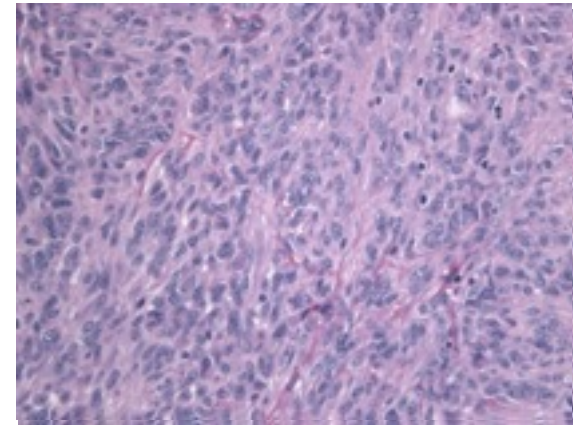
Strong Cytoplasmic

EPITHELIOID  
KIT: WEAK



Variable Cytoplasmic

SHORT SPINDLE CELLS  
KIT: GOLGI PATTERN



Golgi Pattern

# Models: Defining GIST Biology

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## ▶ 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