Novel therapeutic strategies for GIST: Targeting the tumor and treating the whole patient

GIST Patient Summit
MD Anderson Cancer Center, Houston, TX
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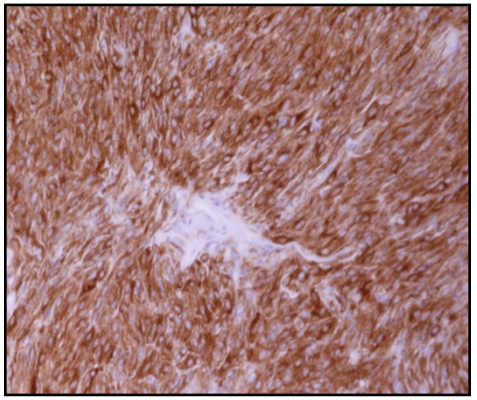
University of Pittsburgh School of Medicine

GISTs are caused by activating *KIT* mutations

- high KIT protein expression
- *KIT* gene mutations (75-85%)
  → gain of function
- *KIT* mutation-negative cases
  - *PDGFRA* (5-7%)
  - "wildtype" (10-15%)



GIST: anti-KIT

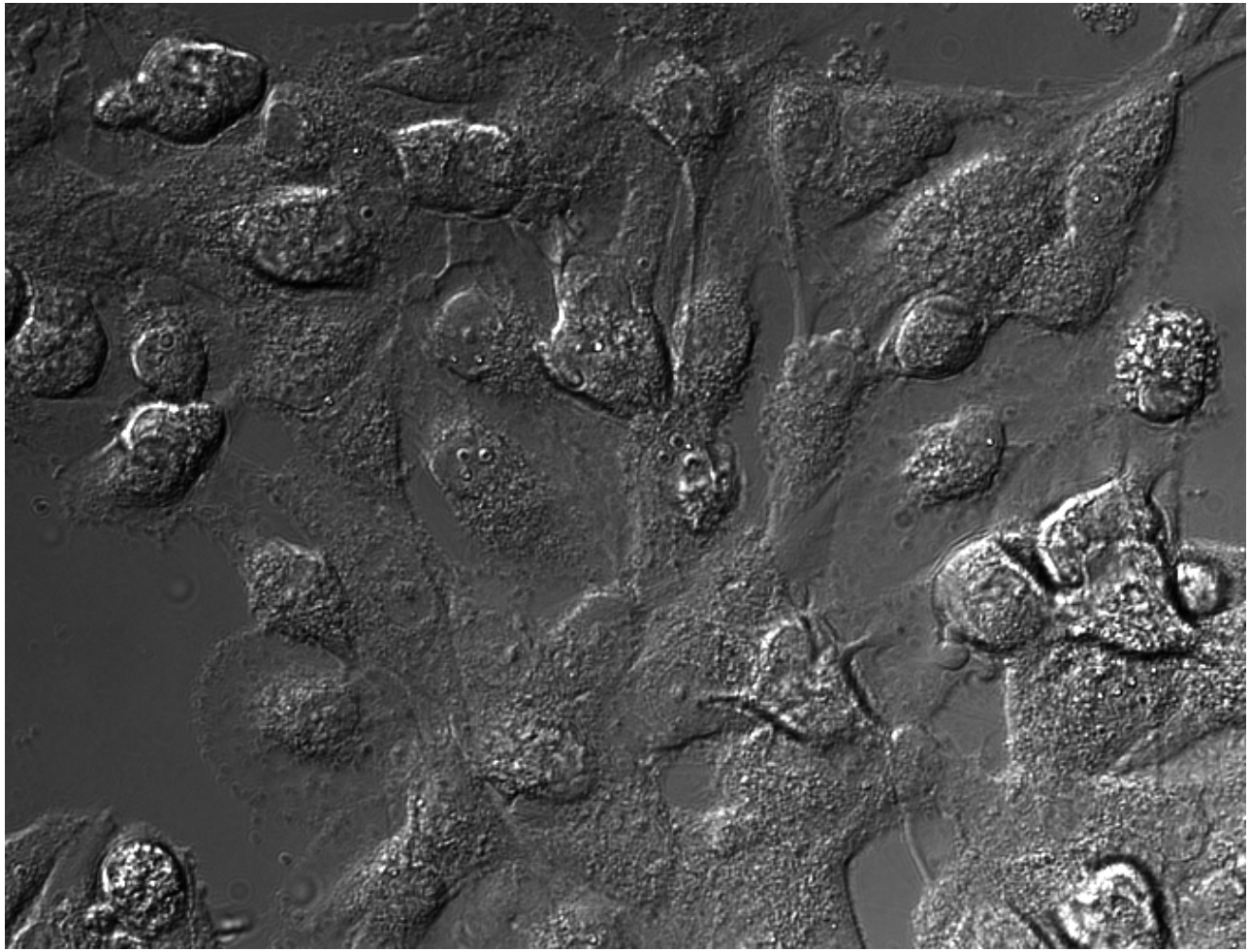
KIT expression and KIT mutations in GIST:

- diagnostic marker

- therapeutic target

Heinrich MC, Corless CL, Duensing A, et al. Science 2003
Duensing A et al. Cancer Res 2004

How does imatinib induce apoptosis in GIST cells?



GIST882:
treated with imatinib
72h incubation
30 min time frames

Problem

incomplete remissions
disease recurrence

new therapies
new therapeutic strategies

to develop new therapies,
we need to know how exactly imatinib works

although imatinib is a pretty good drug,
what are potential flaws that we need to overcome?

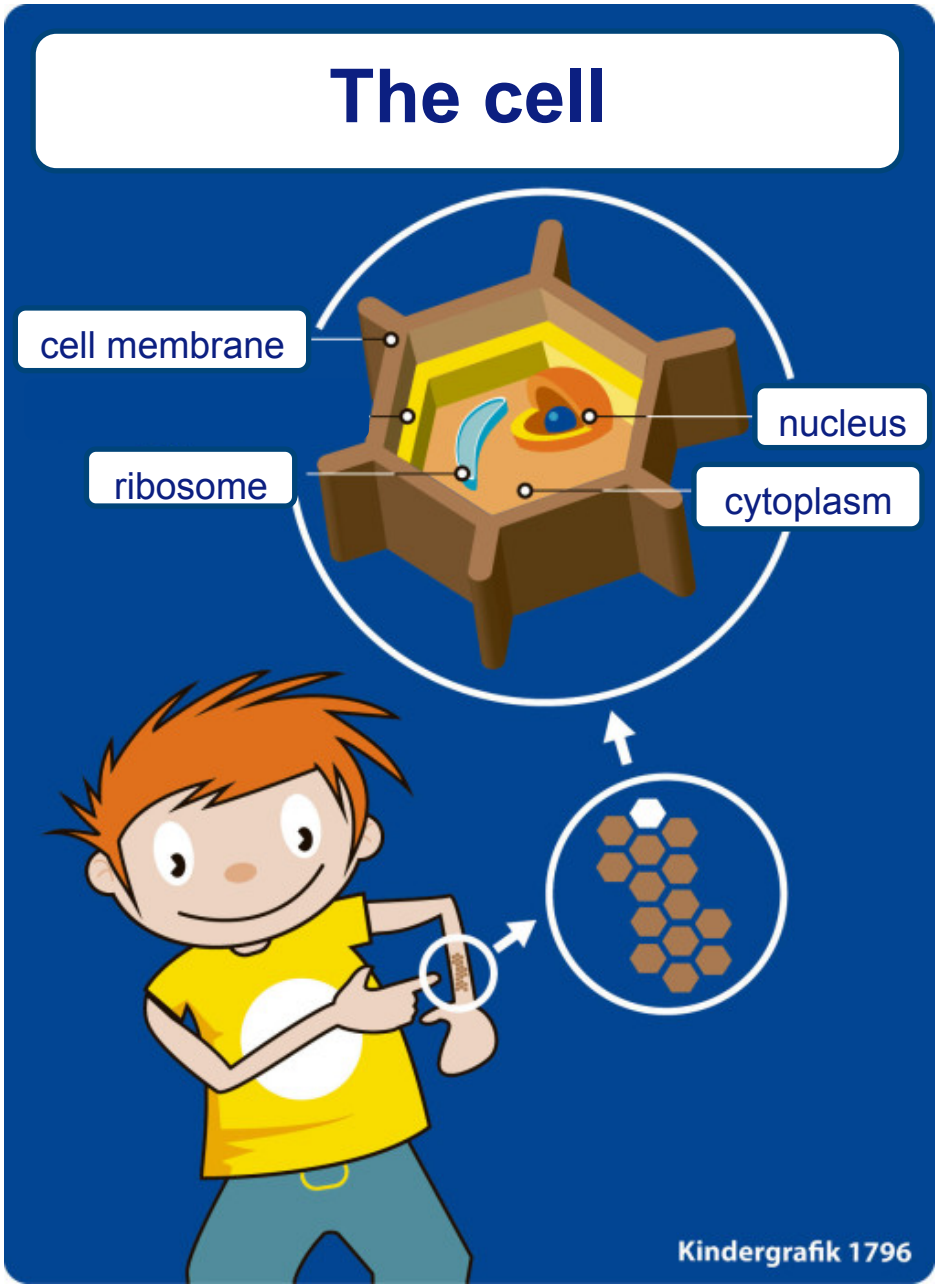
The cell

Kindergrafik 1796

modified from: http://www.ntz.de

The cell

modified from: http://www.ntz.de



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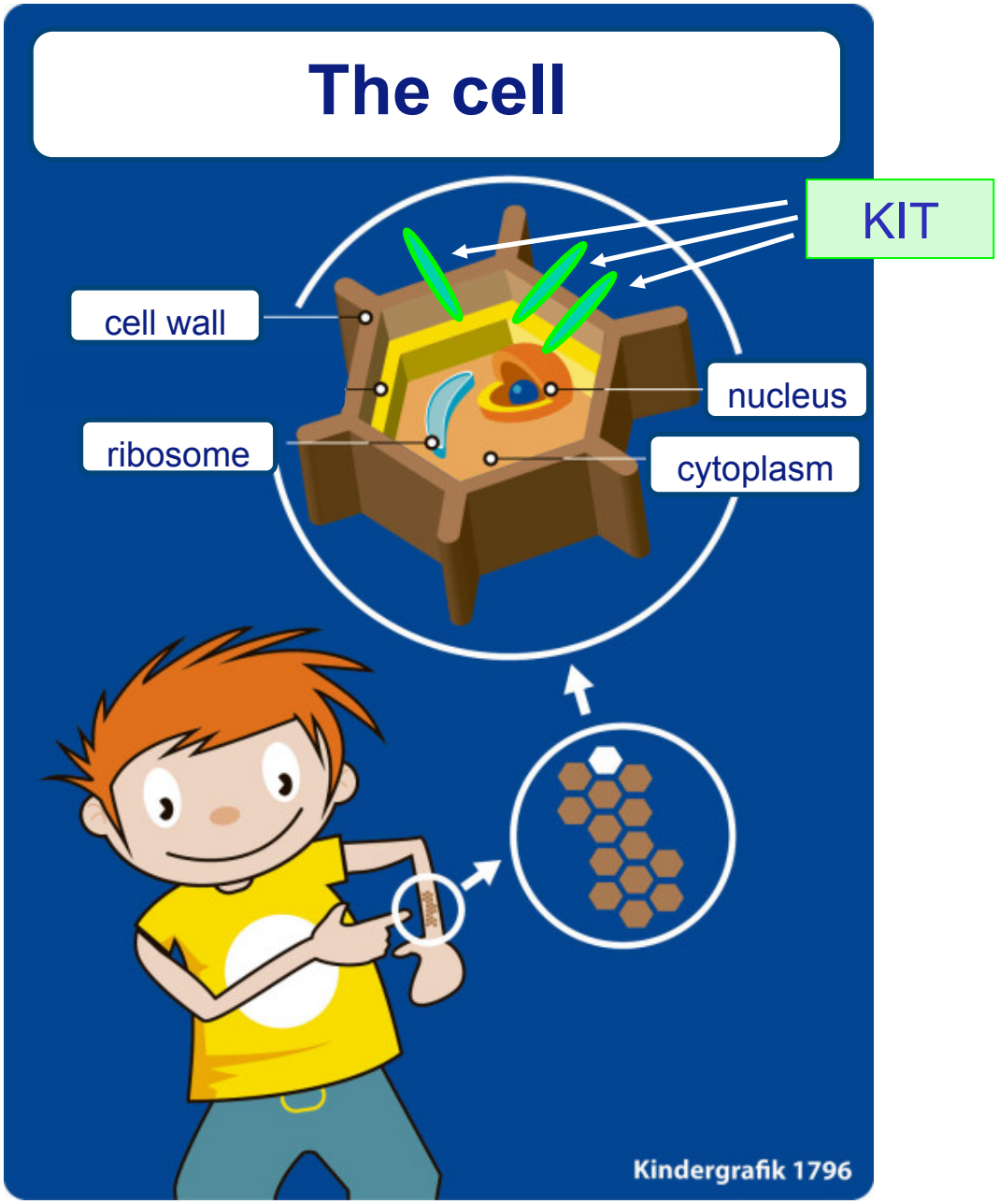

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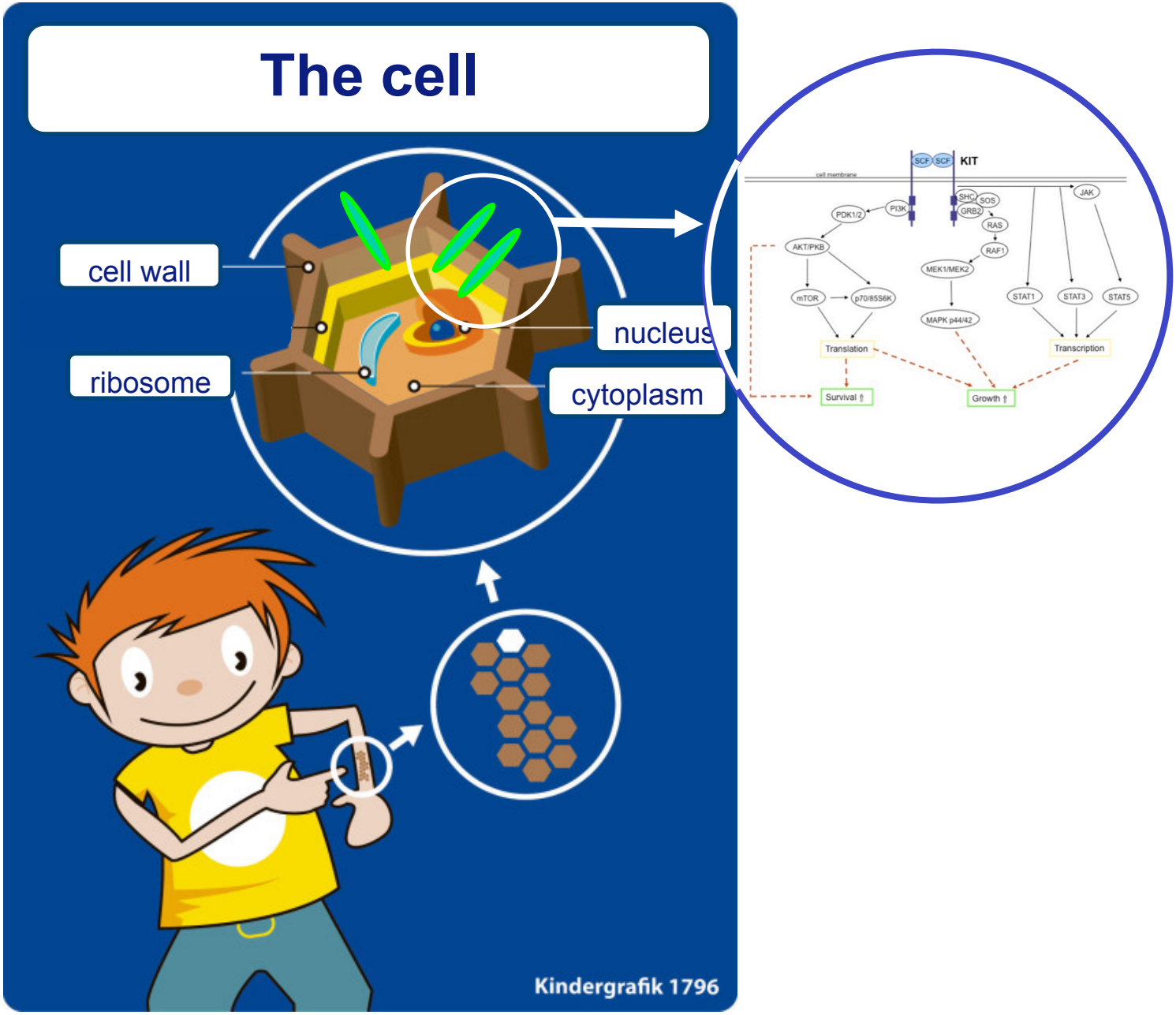

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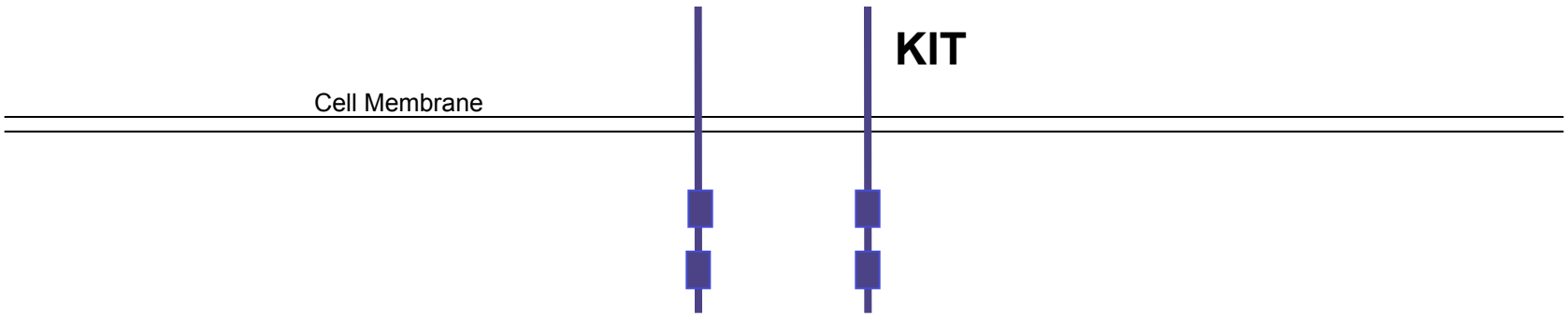
Normal Function of KIT



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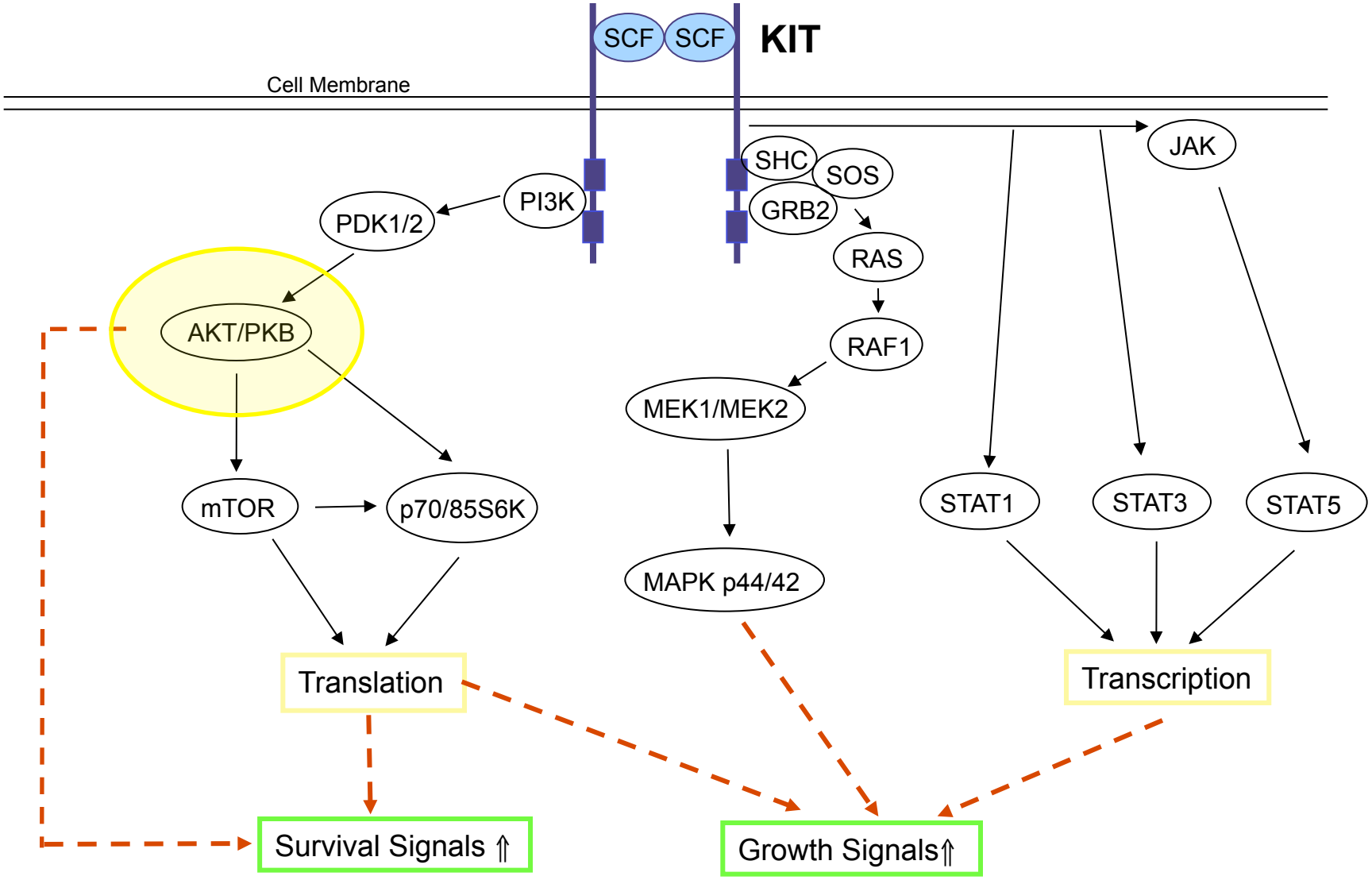

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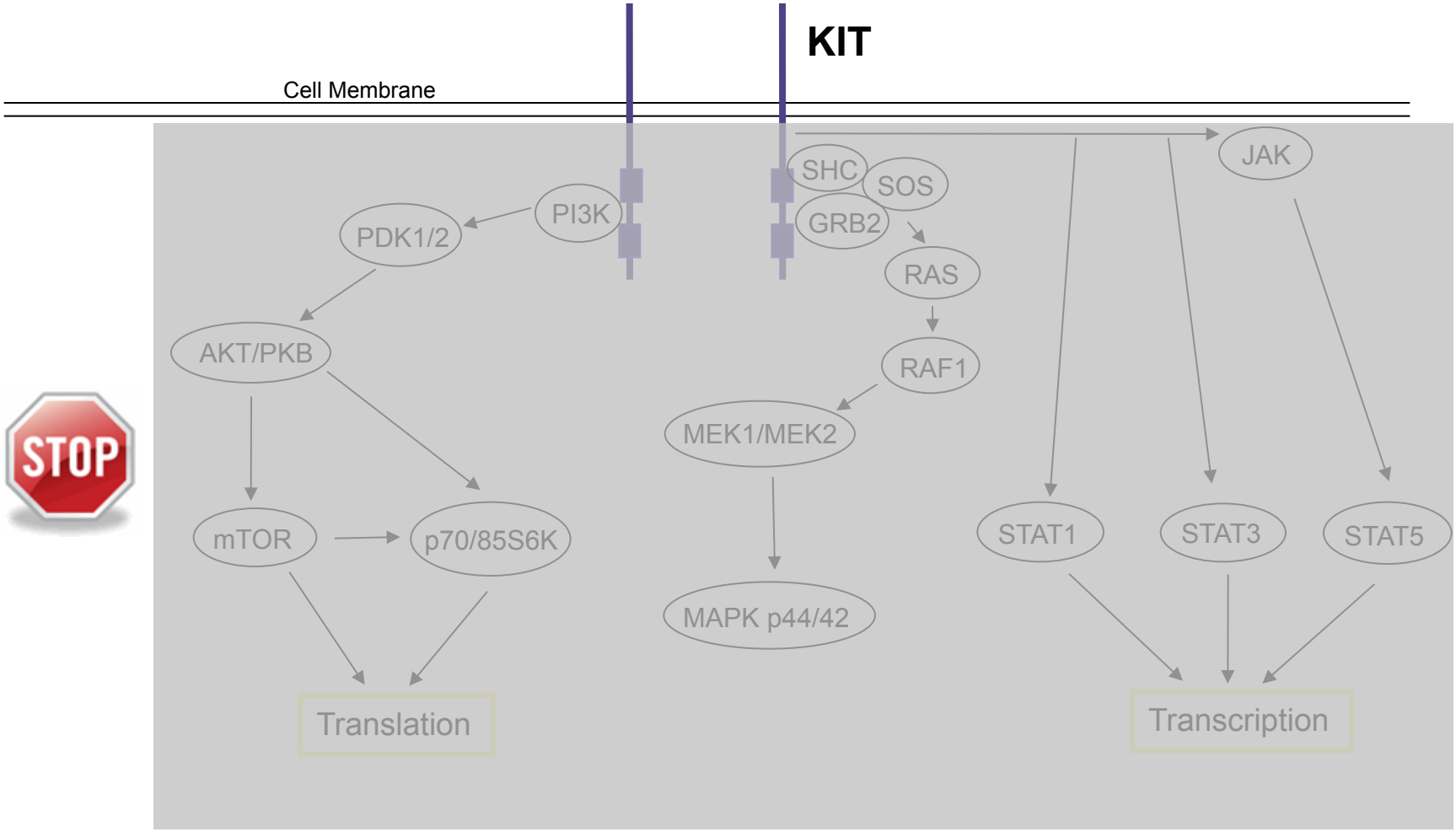
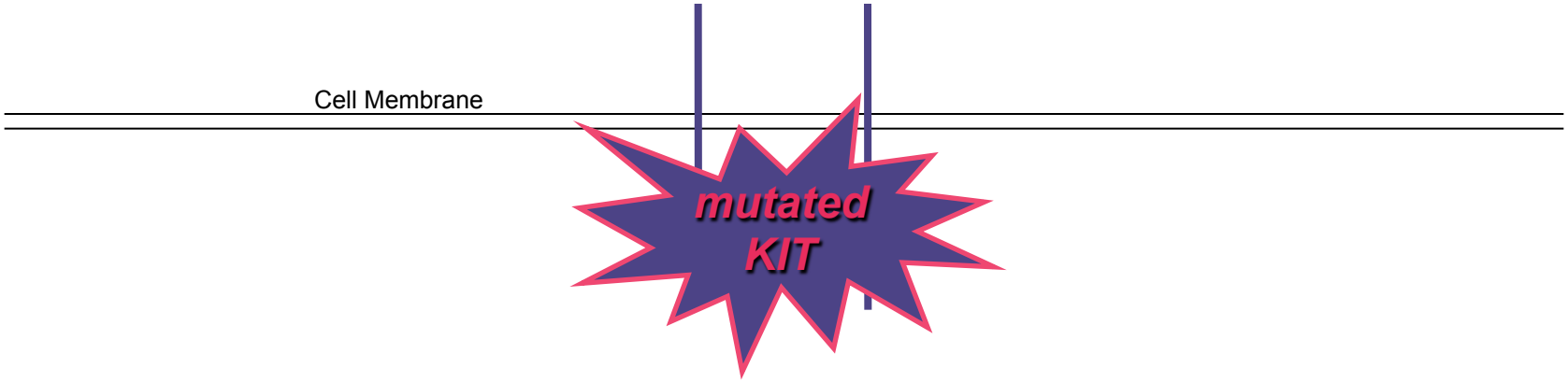


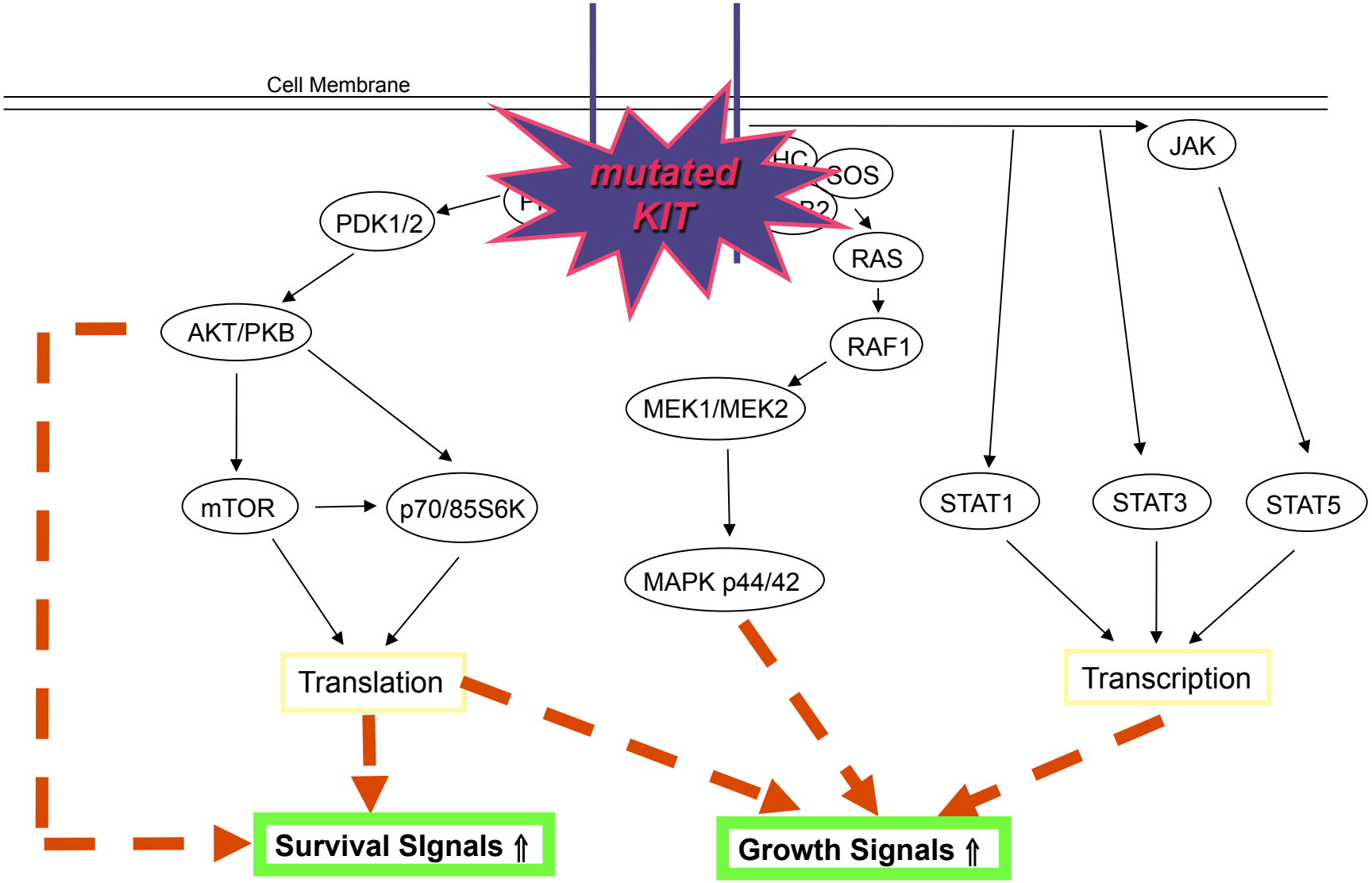
Survival Signals ⇓

Growth Signals ⇓

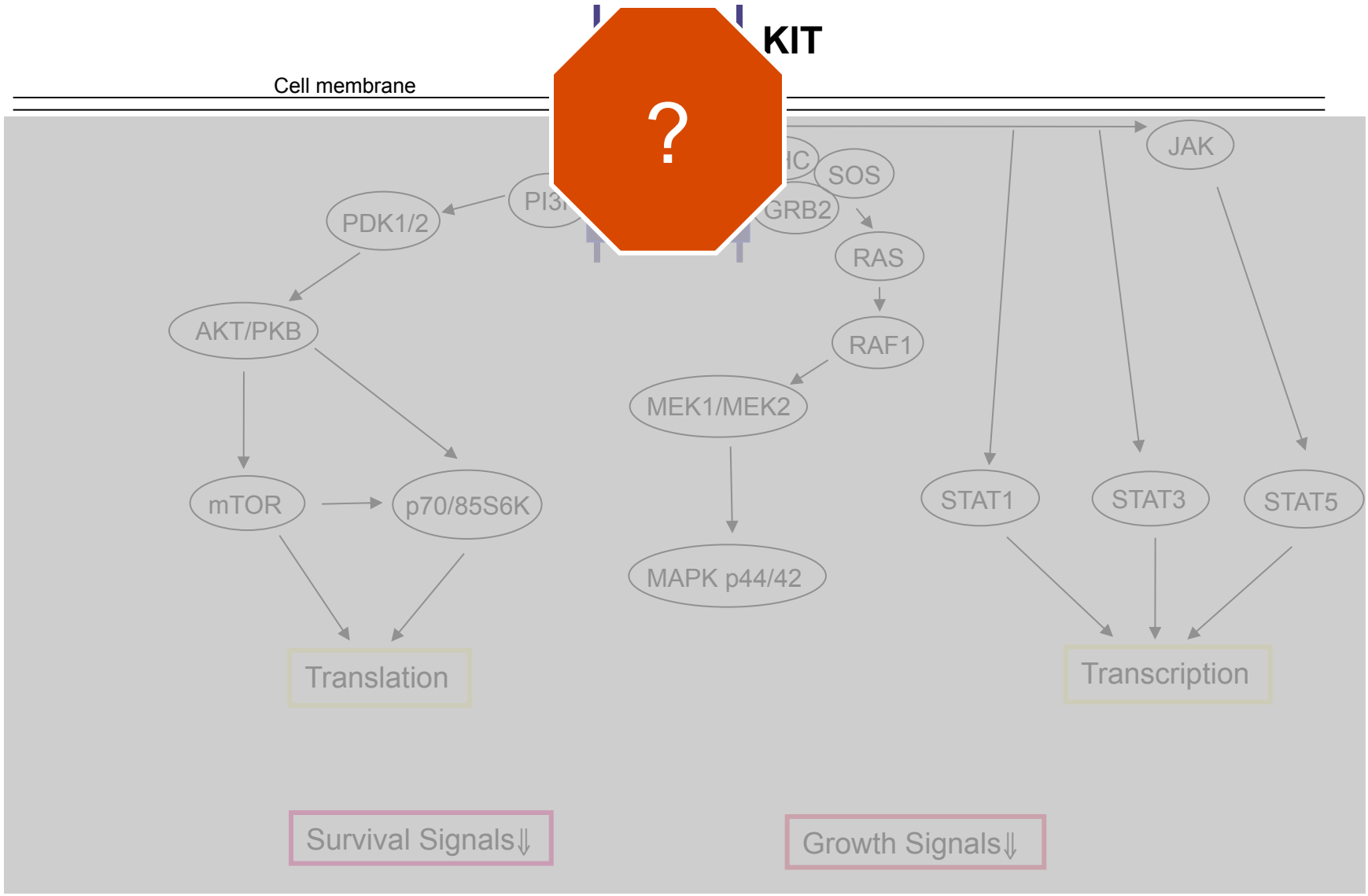
KIT in GIST



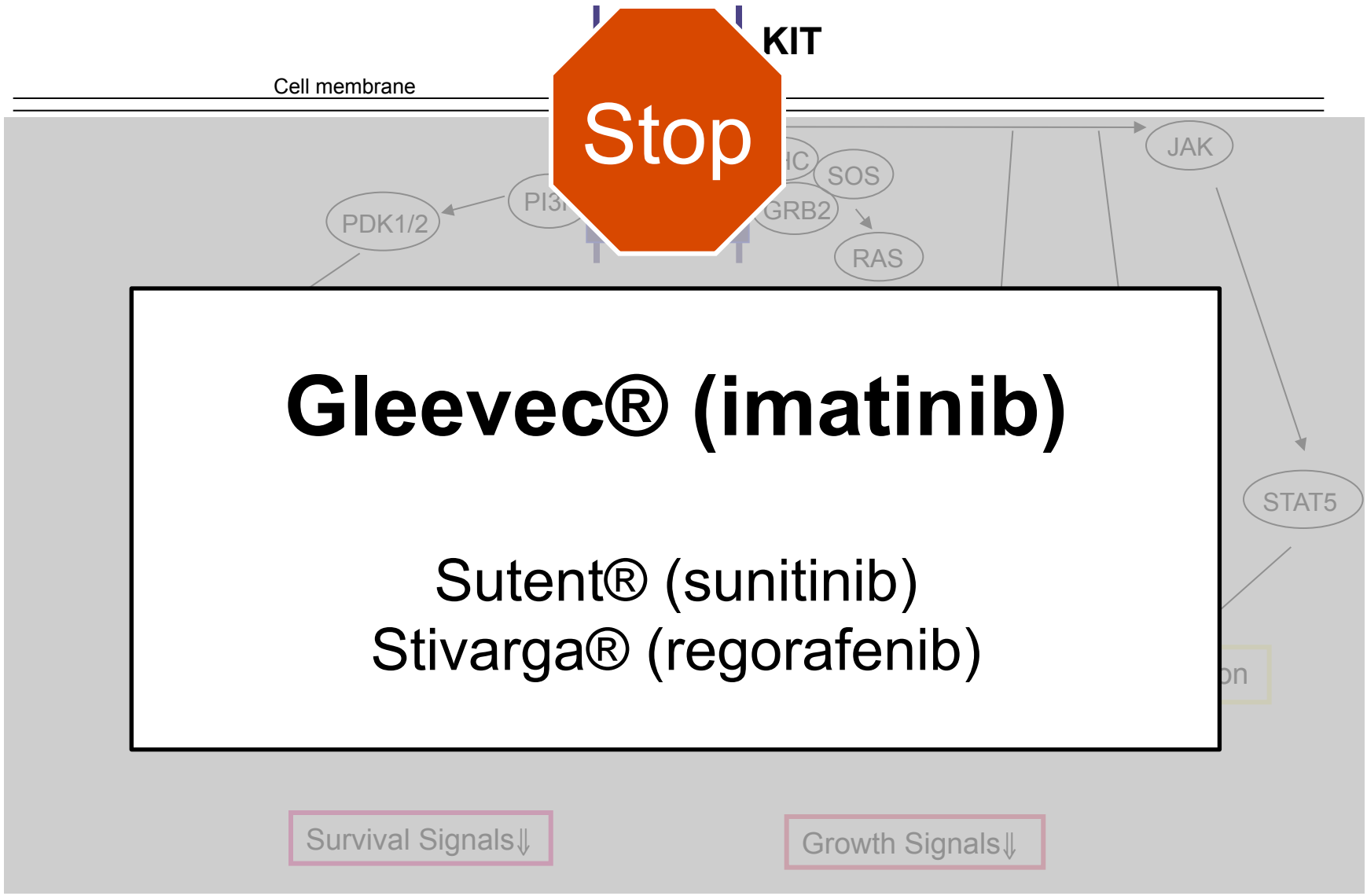
KIT in GIST


Cell Membrane
mutated KIT
PDK1/2
AKT/PKB
mTOR
p70/85S6K
SOS
RAS
RAF1
MEK1/MEK2
MAPK p44/42
JAK
STAT1
STAT3
STAT5
Translation
Transcription
Survival SIgnals ⇑
Growth Signals ⇑

How to stop KIT signaling in GIST?



How to stop KIT signaling in GIST?

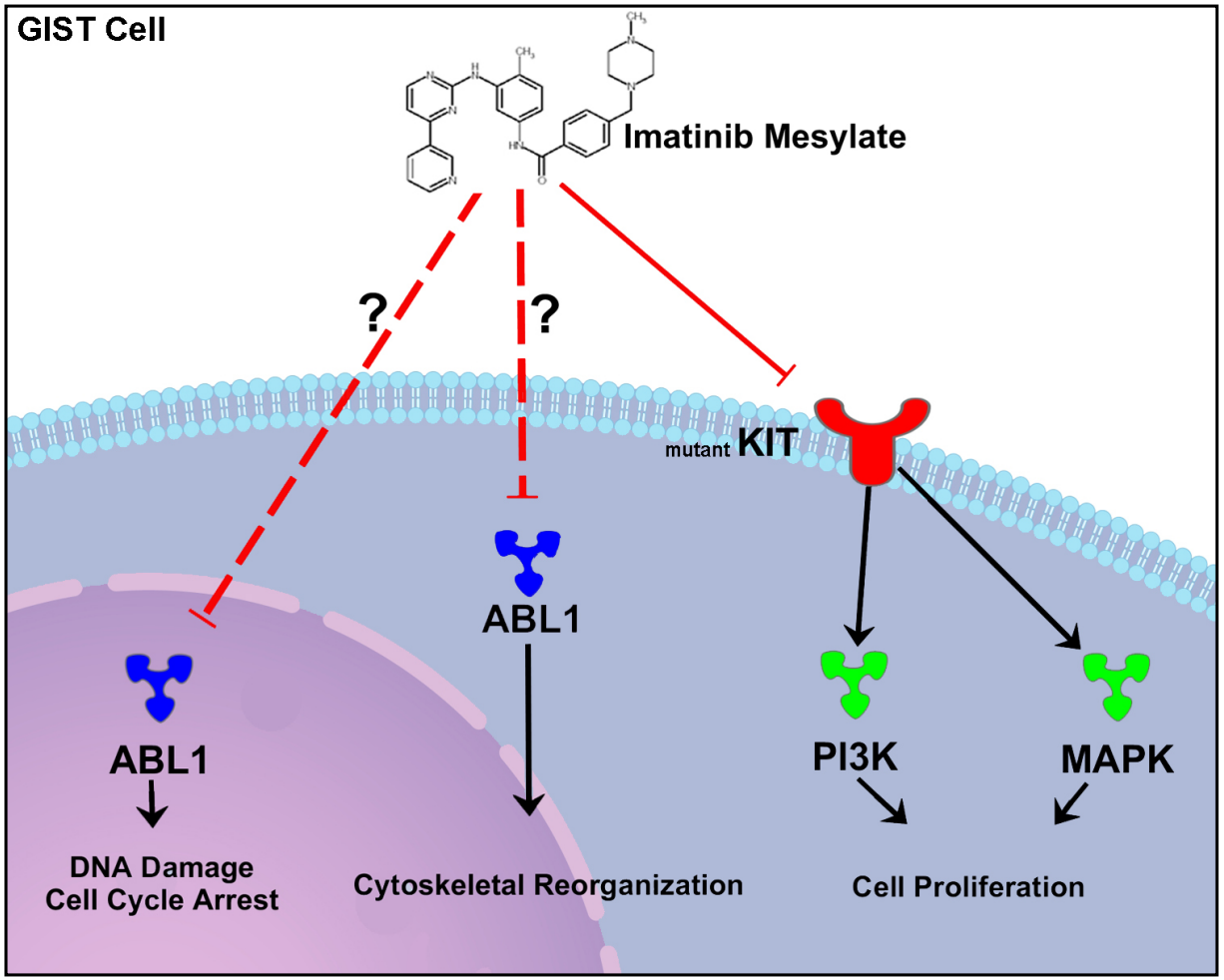


Is inhibition of ABL by imatinib beneficial for GIST treatment?

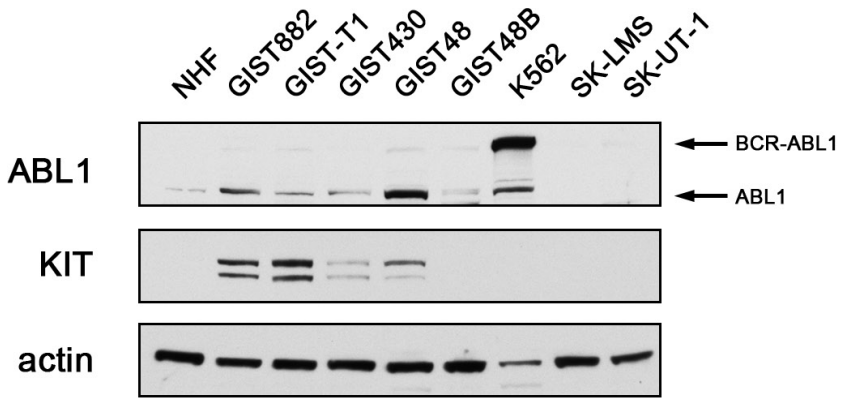
imatinib inhibits:

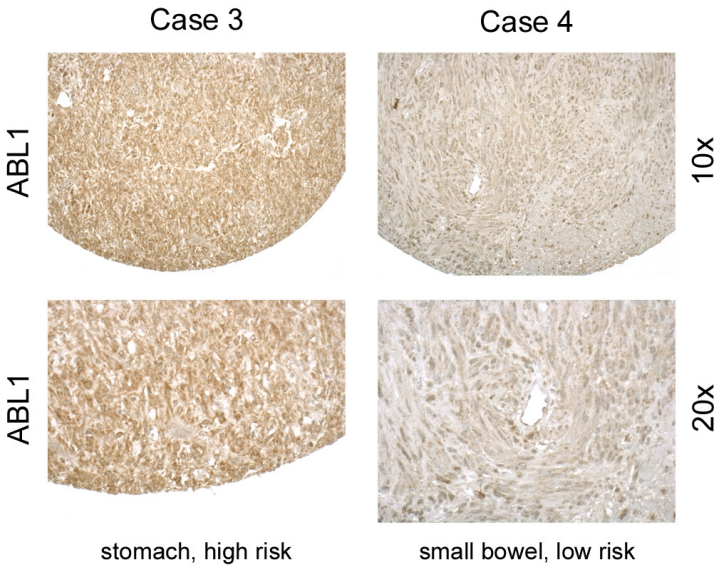
- KIT
- PDGFRA
- PDGFRB
- **BCR-ABL** (chronic myeloid leukemia)
- ABL

normal ABL has various cell protective functions



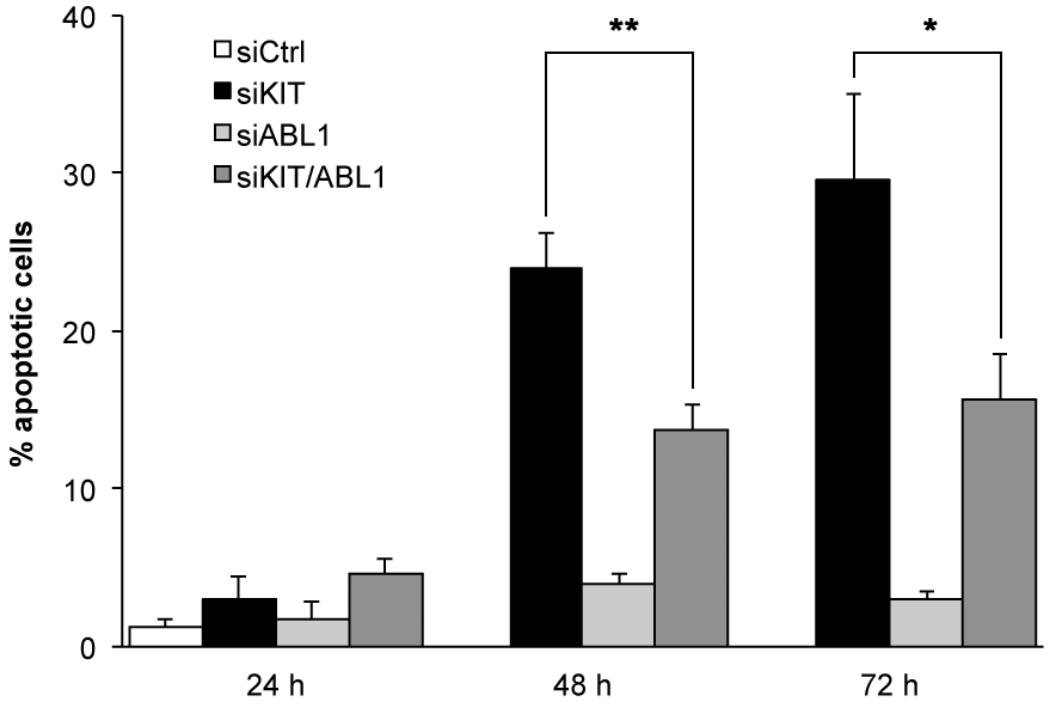
ABL is present in GIST cells





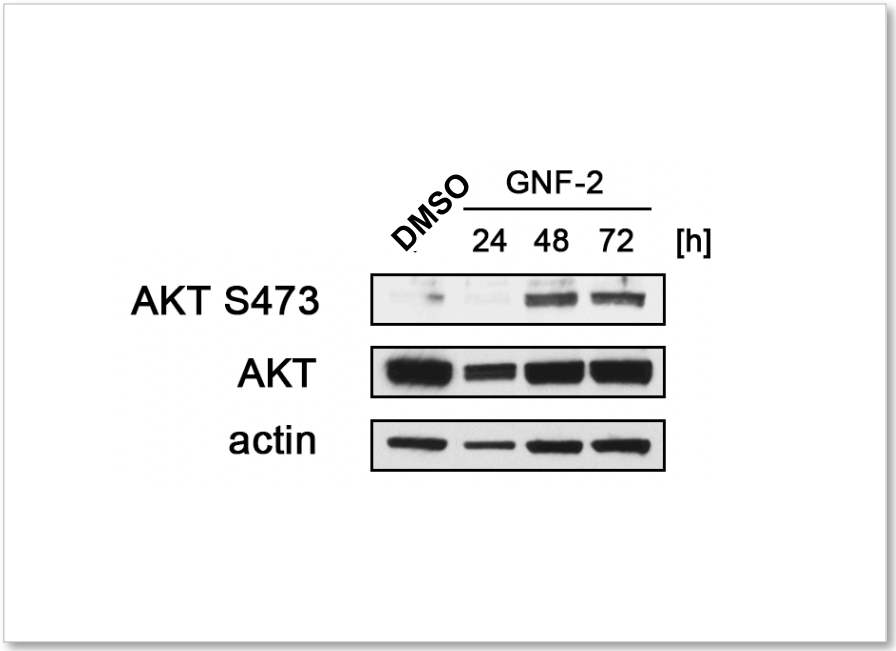
Rausch J, et al. Oncotarget 2017

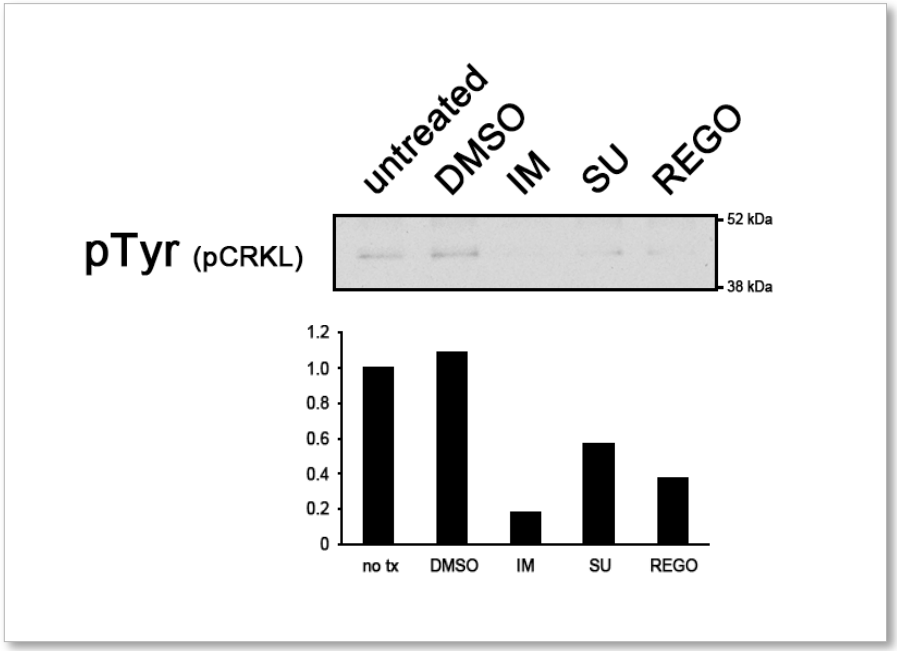
“Inhibiting” KIT *and* ABL kills less GIST cells than “inhibiting” KIT alone



Rausch J, et al. Oncotarget 2017

ABL is a survival factor in GIST cells

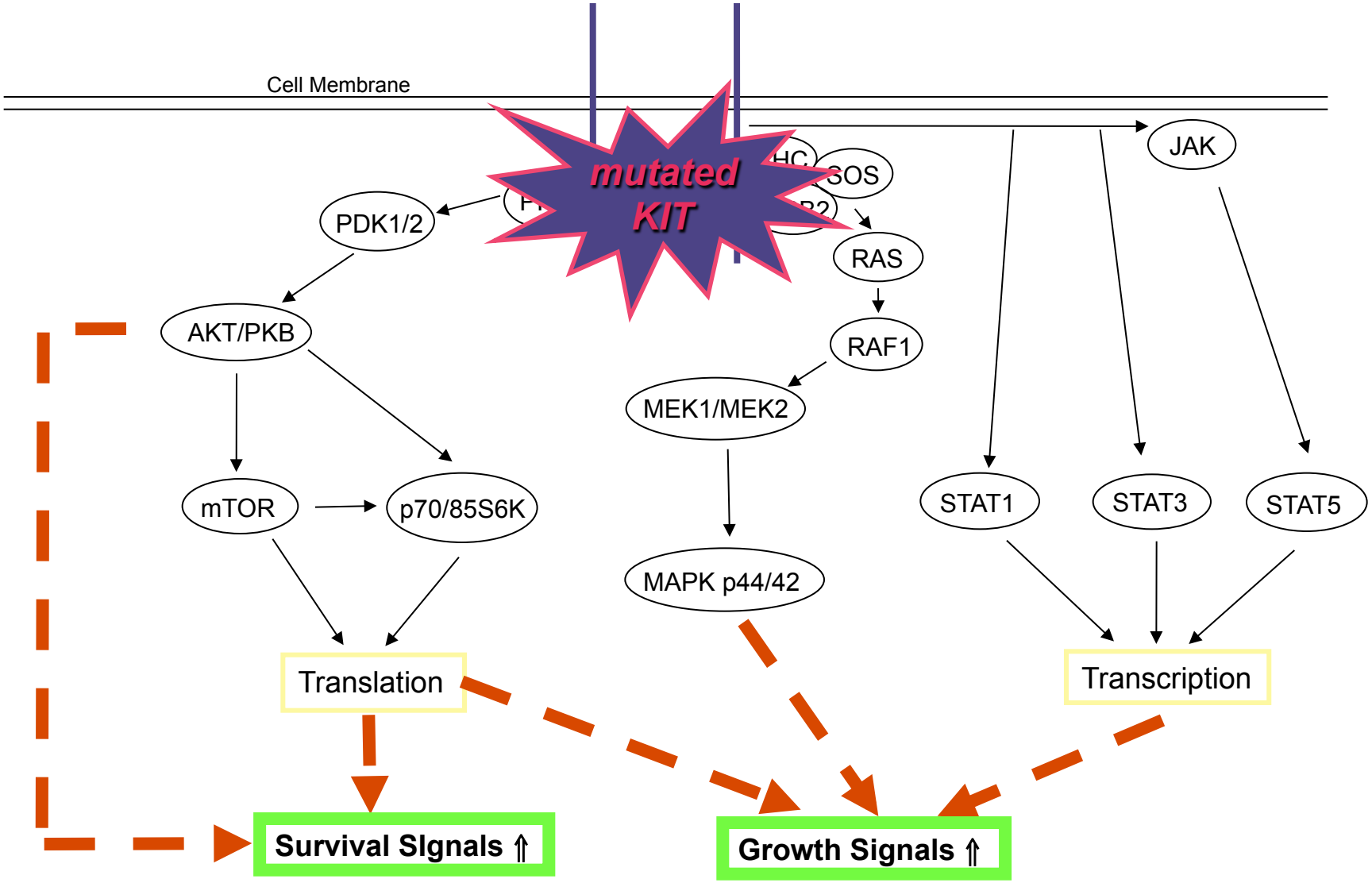




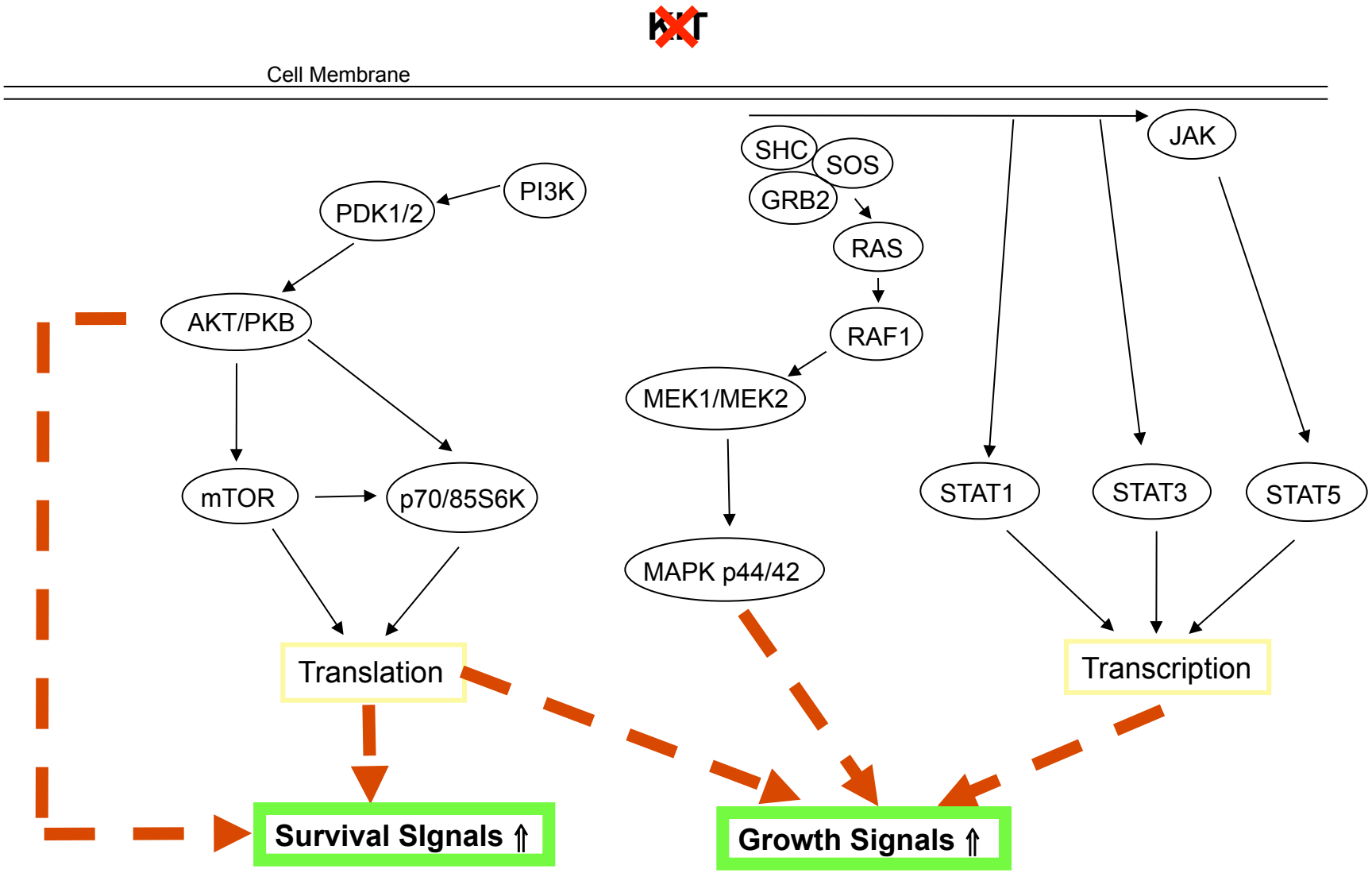
Rausch J, et al. Oncotarget 2017

- new KIT inhibitors for GIST should have increased specificity for KIT and reduced ability to inhibit ABL
- sunitinib, regorafenib → no significant ABL inhibition
- nilotinib, dasatinib → strong ABL inhibition
- BLU-285, DCC-2618

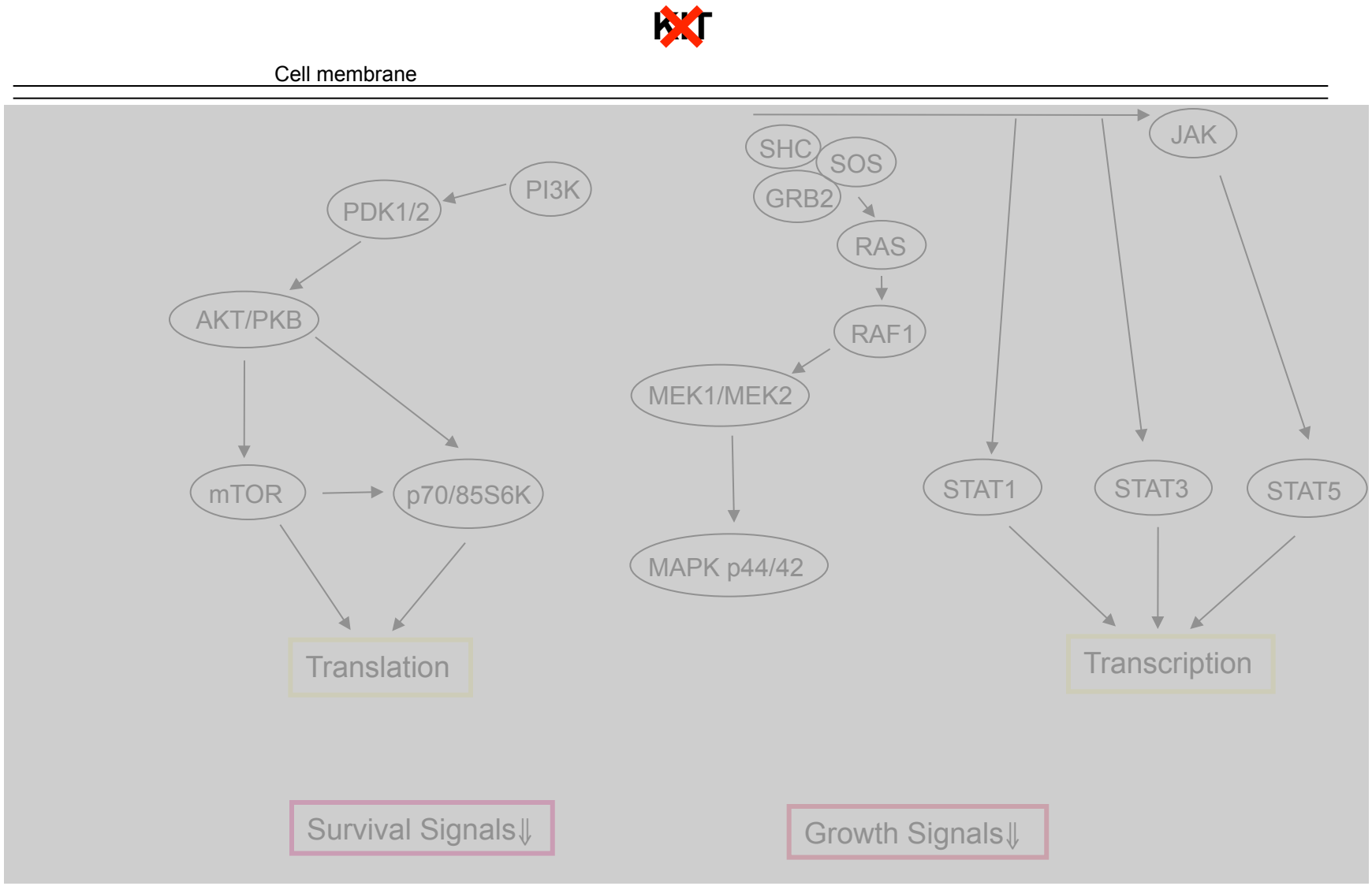
Novel therapeutic strategies in GIST



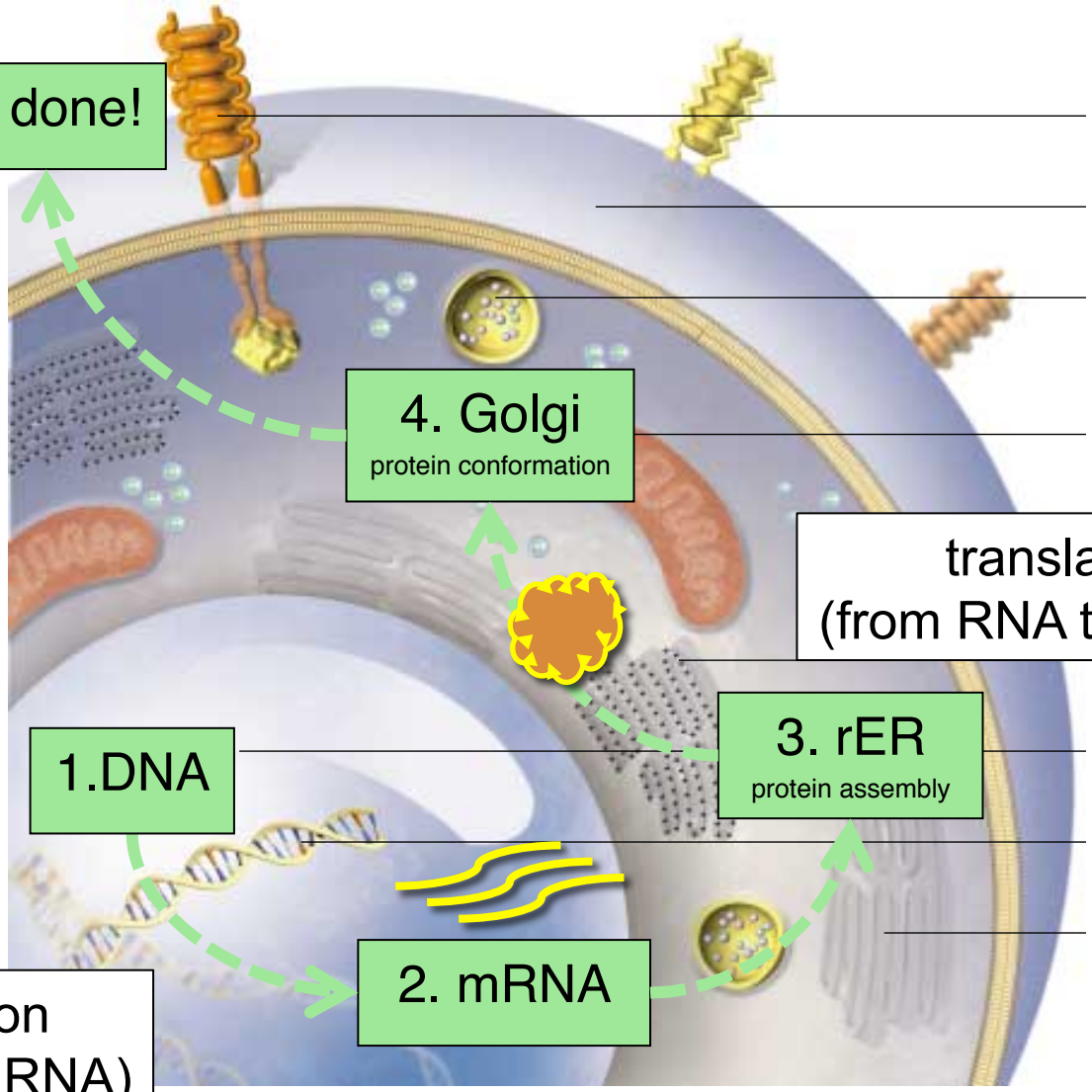
Getting rid of KIT...



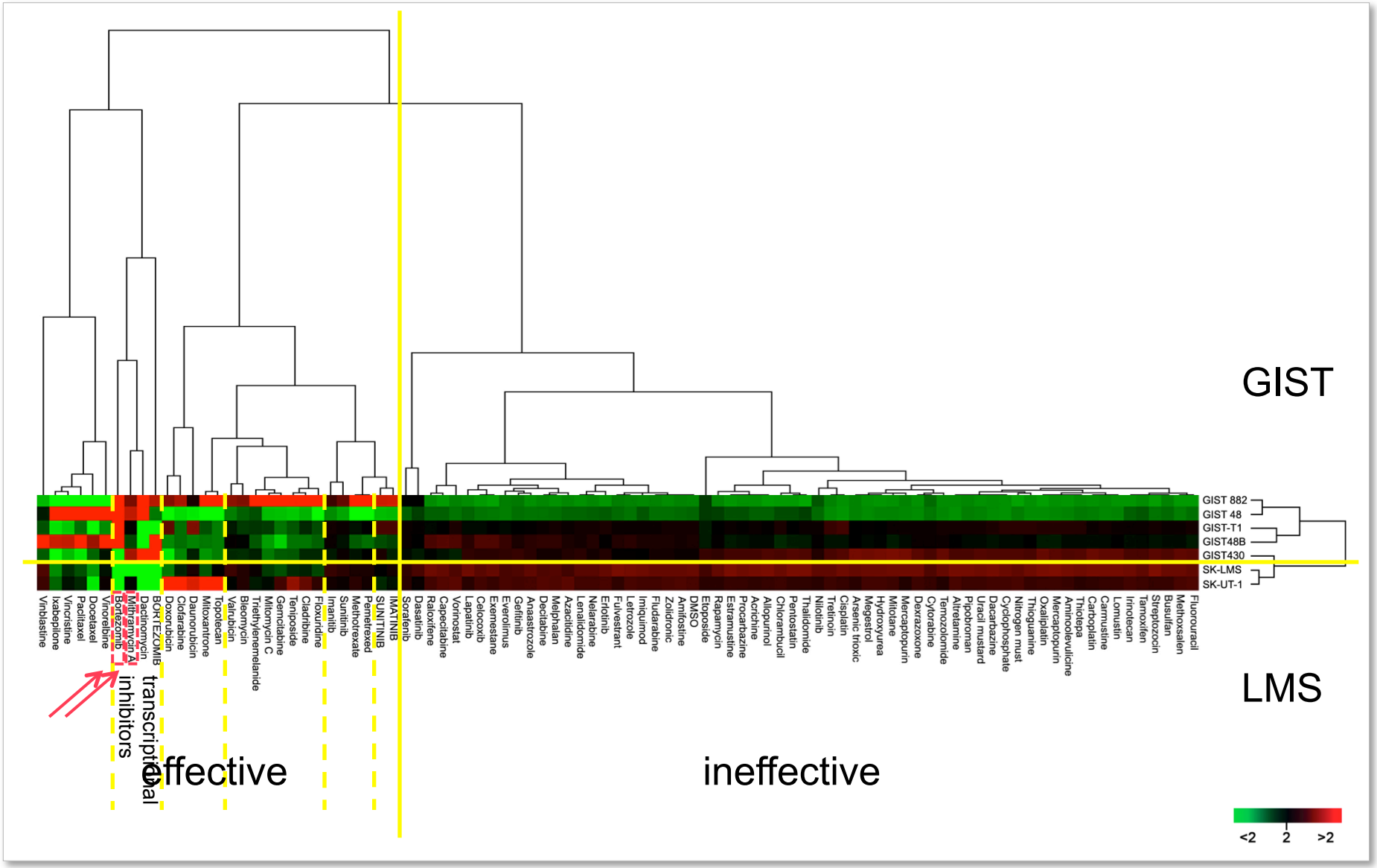
Stops KIT signaling in GIST!



How is KIT made?
(from DNA to protein)

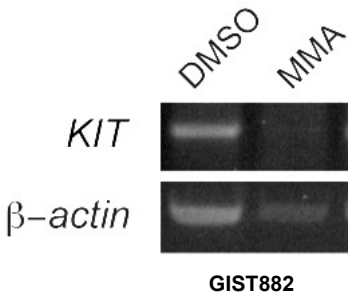


GISTs are sensitive to transcriptional inhibitors

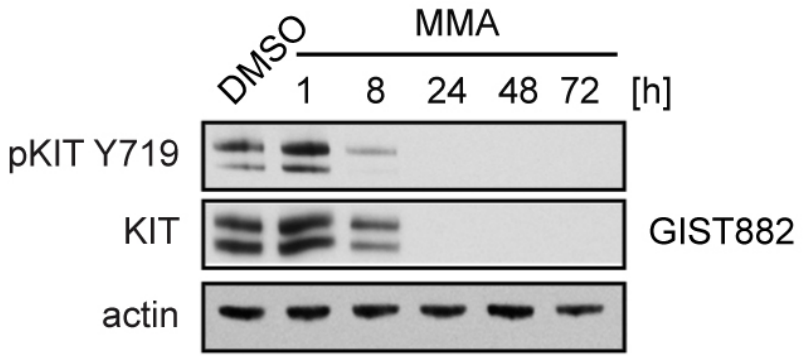


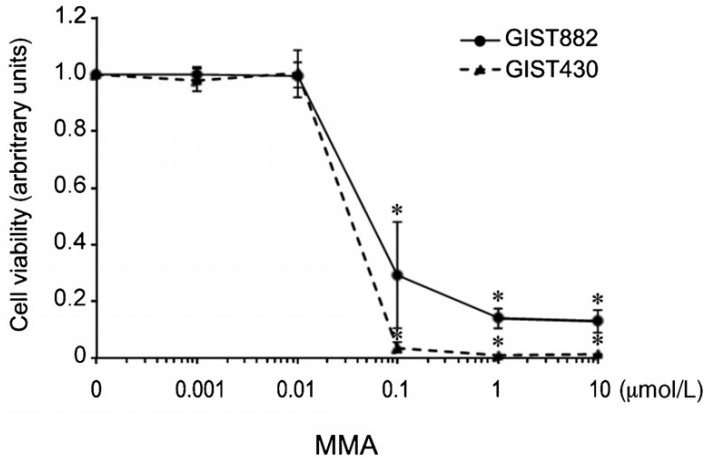
Boichuk S et al., Cancer Research 2014

Mithramycin A: killing GIST cells by inhibiting KIT transcription

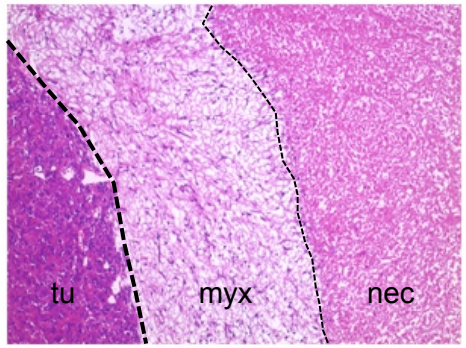


RT-PCR





MMA

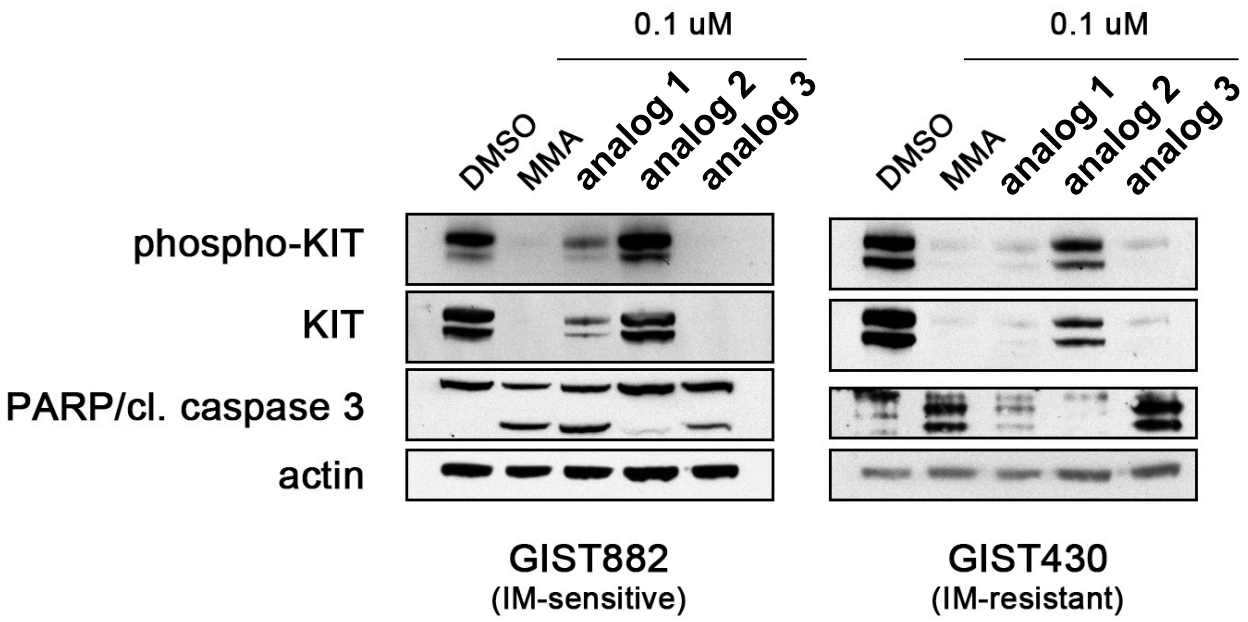


MMA

Boichuk S et al., Cancer Research 2014

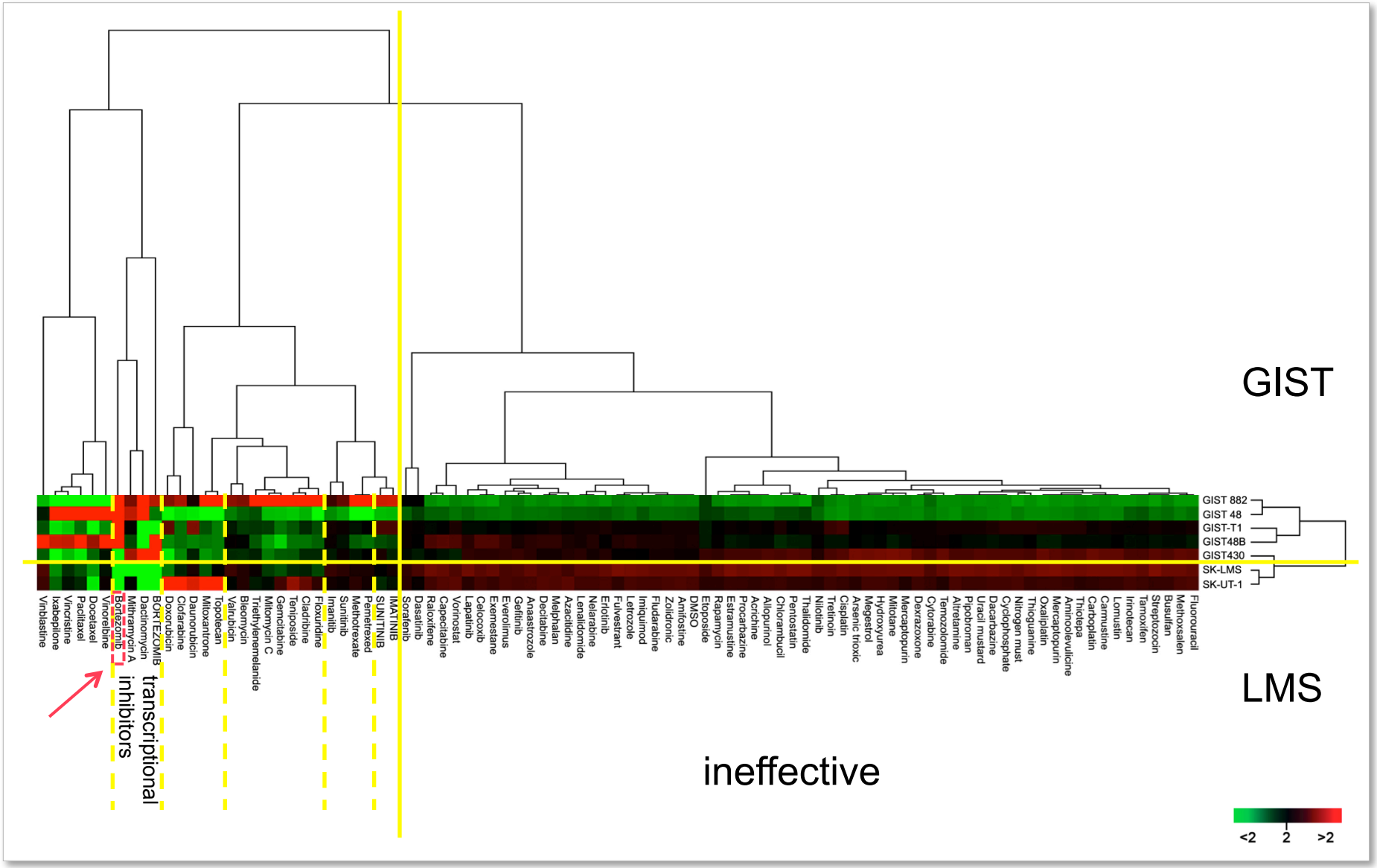
Mithramycin A analogs: same activity, but better toxicity profile

collaboration with EntreChem, Ovieda, Spain



Jessica Rausch - unpublished

GISTs are sensitive to transcriptional inhibitors

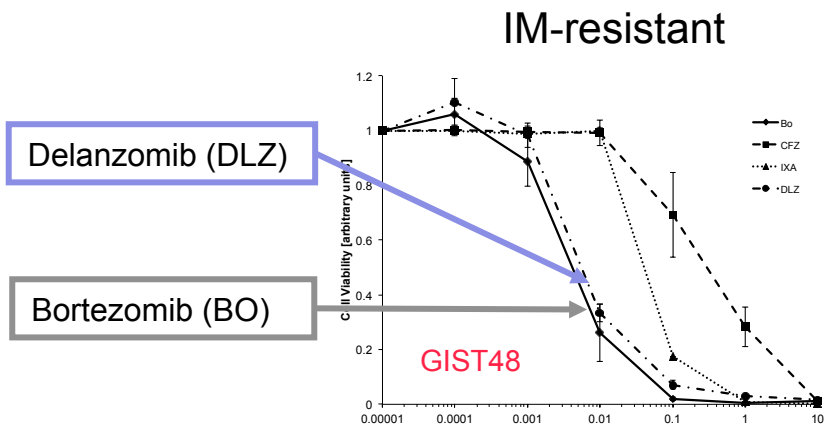


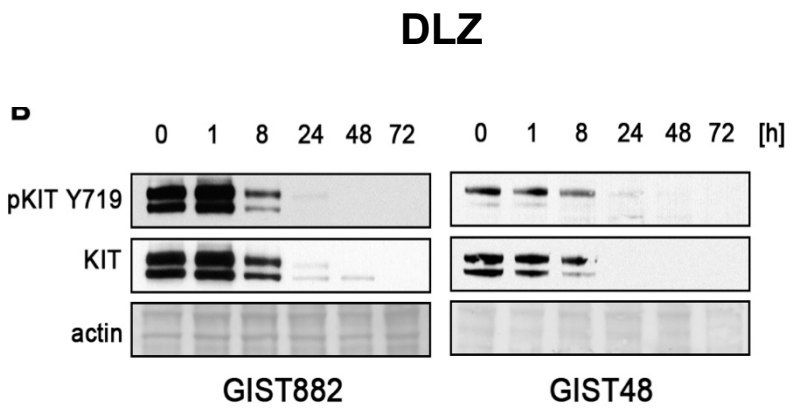
Boichuk S et al., Cancer Research 2014

Second generation inhibitors of the 26S proteosome

Bortezomib (Velcade)	**Carfilzomib (Kyprolis, PR-171)**	**Ixazomib (MLN-9708)**	**Delanzomib (CEP-18770)**
Millennium	Onyx Pharmaceuticals	Millennium	Cephalon
26S (reversible)	26S (irreversible)	26S (reversible)	26S (reversible)
i.v.	i.v.	oral	oral
FDA-approved (multiple myeloma, mantle cell lymphoma)	FDA-approved (multiple myeloma)	FDA-approved (multiple myeloma)	Phase II/III (multiple myeloma)

Inhibitors of the 26S proteasome inhibit KIT transcription similar to bortezomib



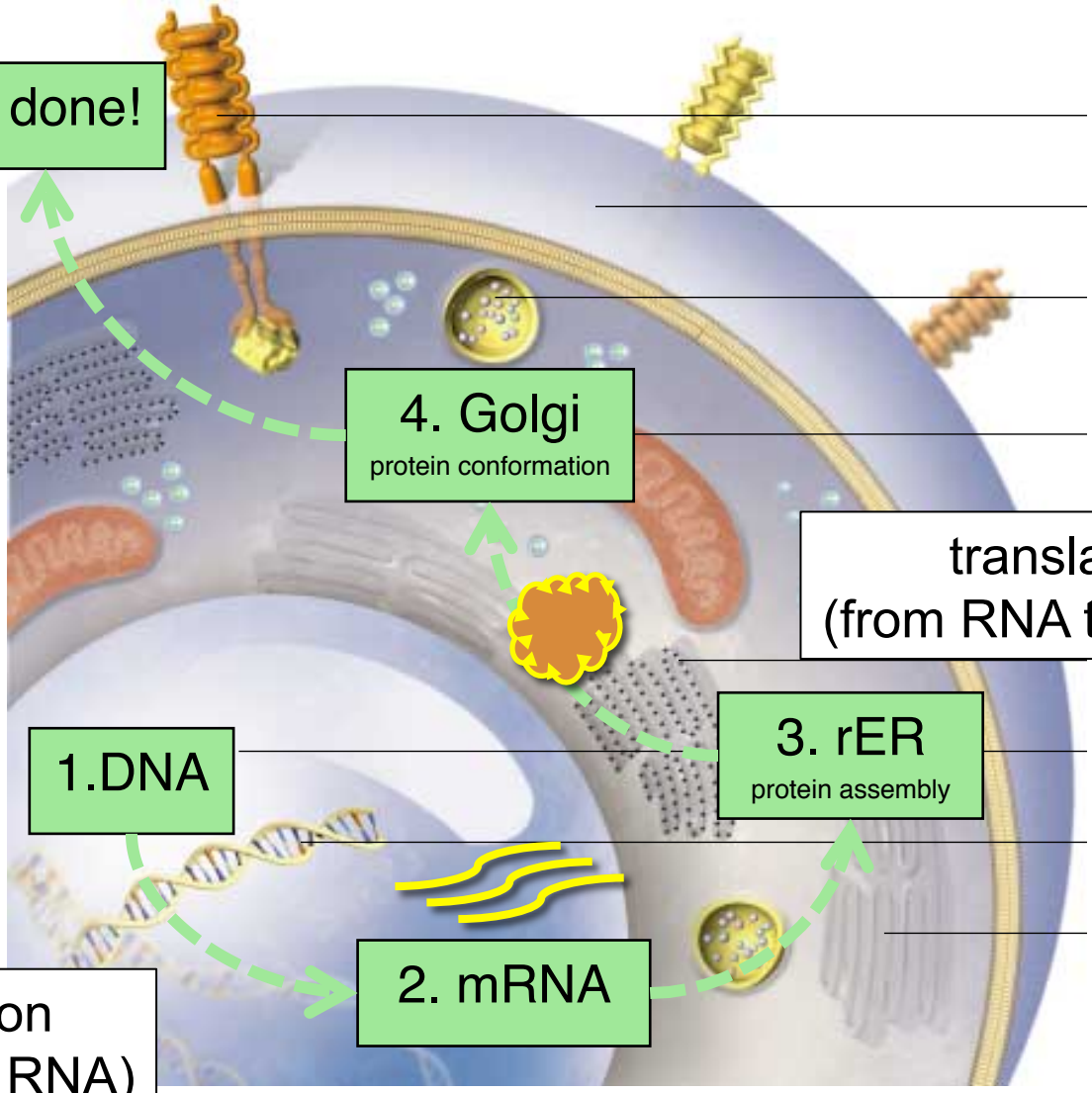


IC50:		IM-resistant
• Bortezomib:	15 nM	**(10 nM)**
• Delanzomib:	20 nM	**(11 nM)**
• Ixazomib:	90 nM	**(50 nM)**
• Carfilzomib:	500 nM	(130 nM)

- second-generation 26S proteasome inhibitors are
  - effective in GIST
  - have the same mechanism of action as bortezomib
- planning clinical trial through NCI CTEP

Rausch JL et al, CTOS 2014

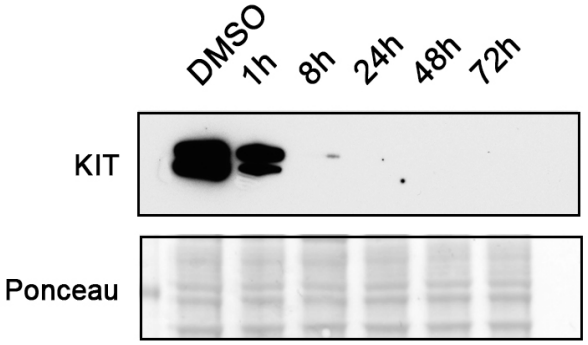
How is KIT made?
(from DNA to protein)



Das Lebenshaus

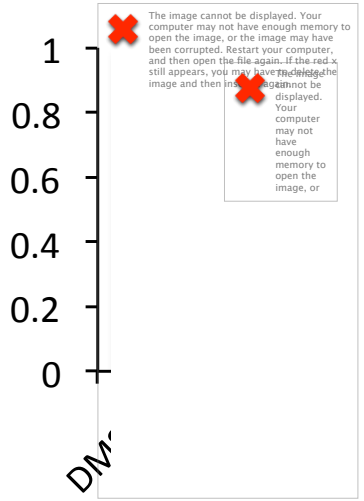
Inhibition of translation leads to loss of KIT and effectively kills GIST cells

www.sigmaaldrich.com



IM-resistant
(GIST430)

inhibition of protein synthesis



Patil SS et al, CTOS 2016

Homoharringtonine (Synribo®)

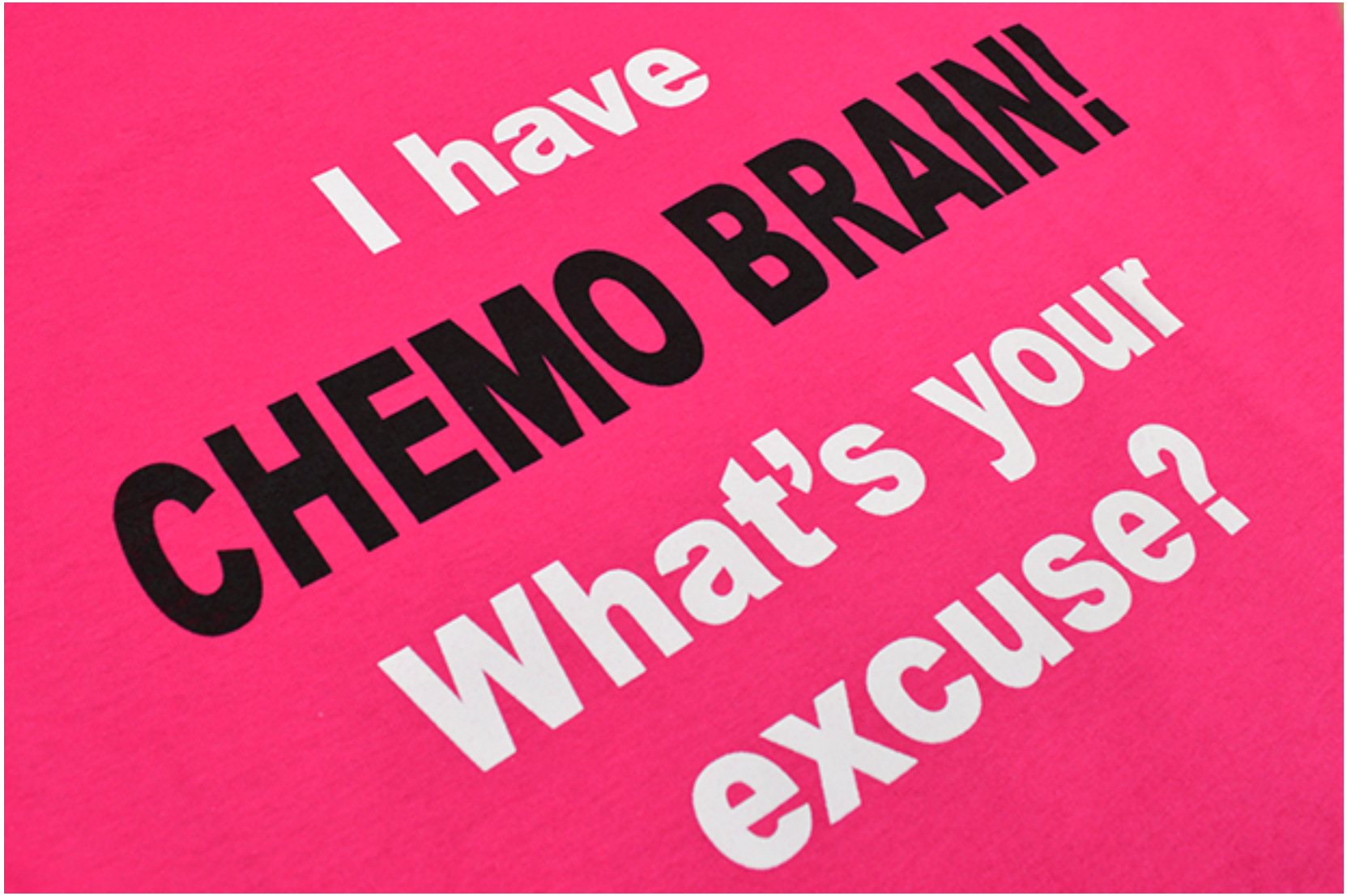
- inhibitor of protein translation
- FDA-approved for treatment of imatinib-resistant chronic myeloid leukemia

Take-home messages (Part I)

- development of KIT kinase inhibitors to target GIST should include reducing their ability to inhibit the ABL kinase

- eliminating KIT protein expression via
  - inhibition of DNA transcription or
  - inhibition of protein translation

  are promising treatment strategies for TKI-resistant GIST



choosehope.com

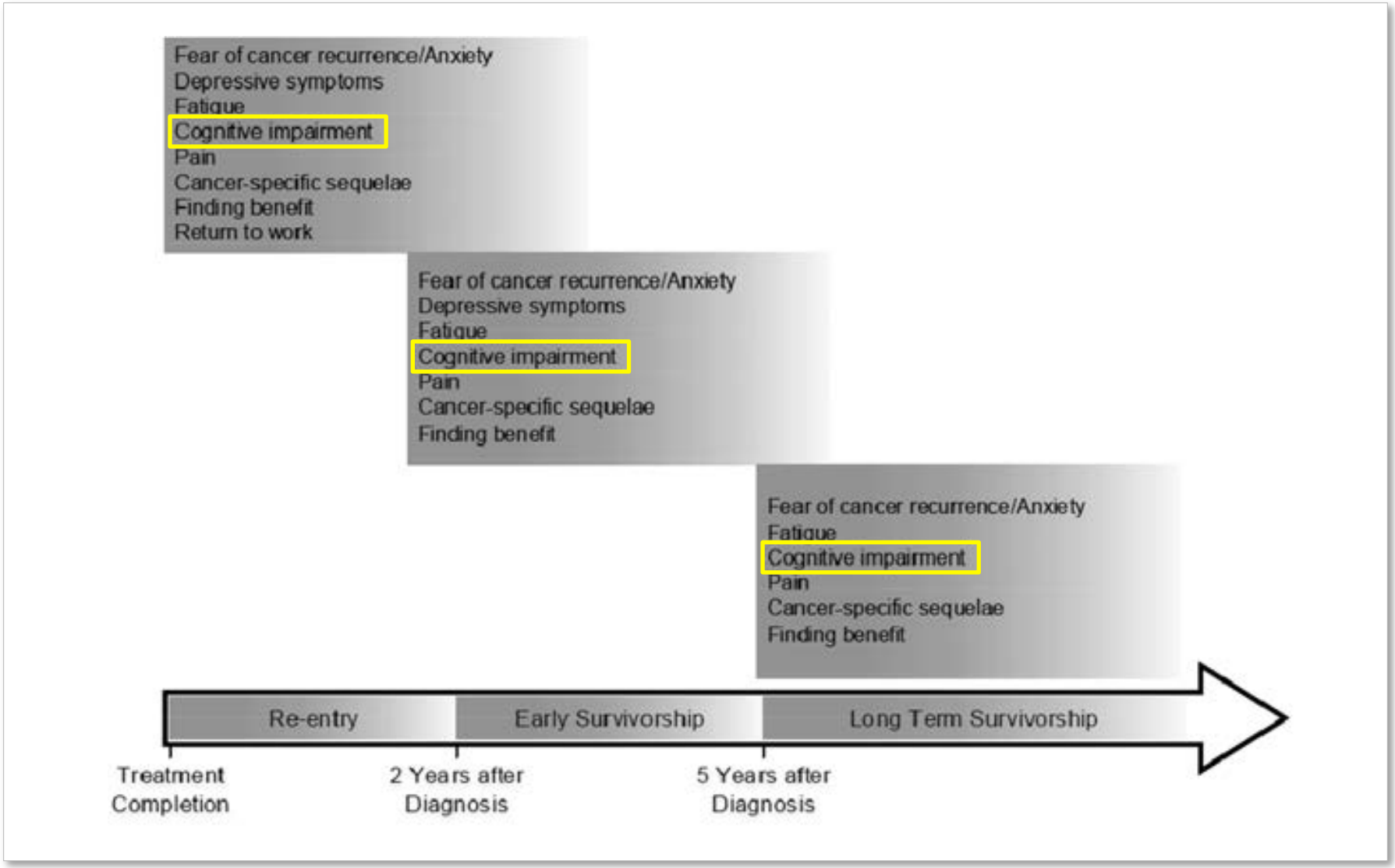
To Do:

- Buy fresh lime for the fiesta tonight
- pick up the cat's medicine at the vet's
- Buy a new bike helmet for Jr.

“Chemo-brain”
(Chemotherapy-related cognitive dysfunction)

- first described in the 1980s:
  ”Chemotherapy is associated with measurable decrements in neuropsychological test performance” (Silberfarb et al.)
- Prevalence: ~15-80% depending on study
- what is affected?
  - verbal memory, working memory, visual-motor processing speed
- usually mild, not progressive impairments
- often confounded by
  - age, education, IQ, pre-morbid neurologic impairment, depression, anxiety fatigue, substance use

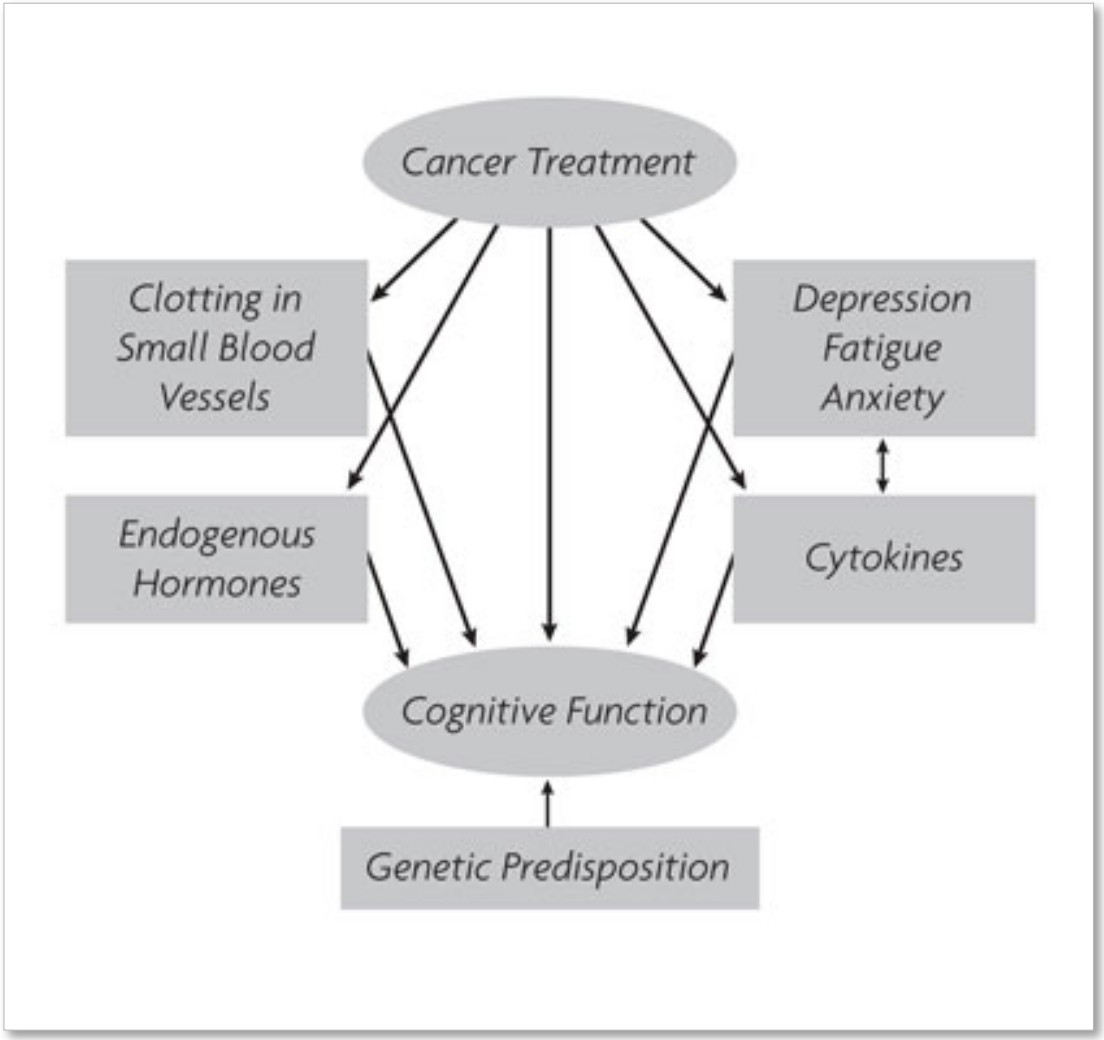
Life after diagnosis and treatment of cancer in adulthood



Stanton A, Rowland JH, Ganz PA, American Psychologist, 70, 159-174

What causes chemo-brain? (And why does not everyone get it?)

- widely varying hypothesized mechanisms
- direct neurotoxicity and cell death
- white matter degradation
- pro-inflammatory cytokines (“the immune system”)
- estrogen suppression − hormone therapy
- stress?

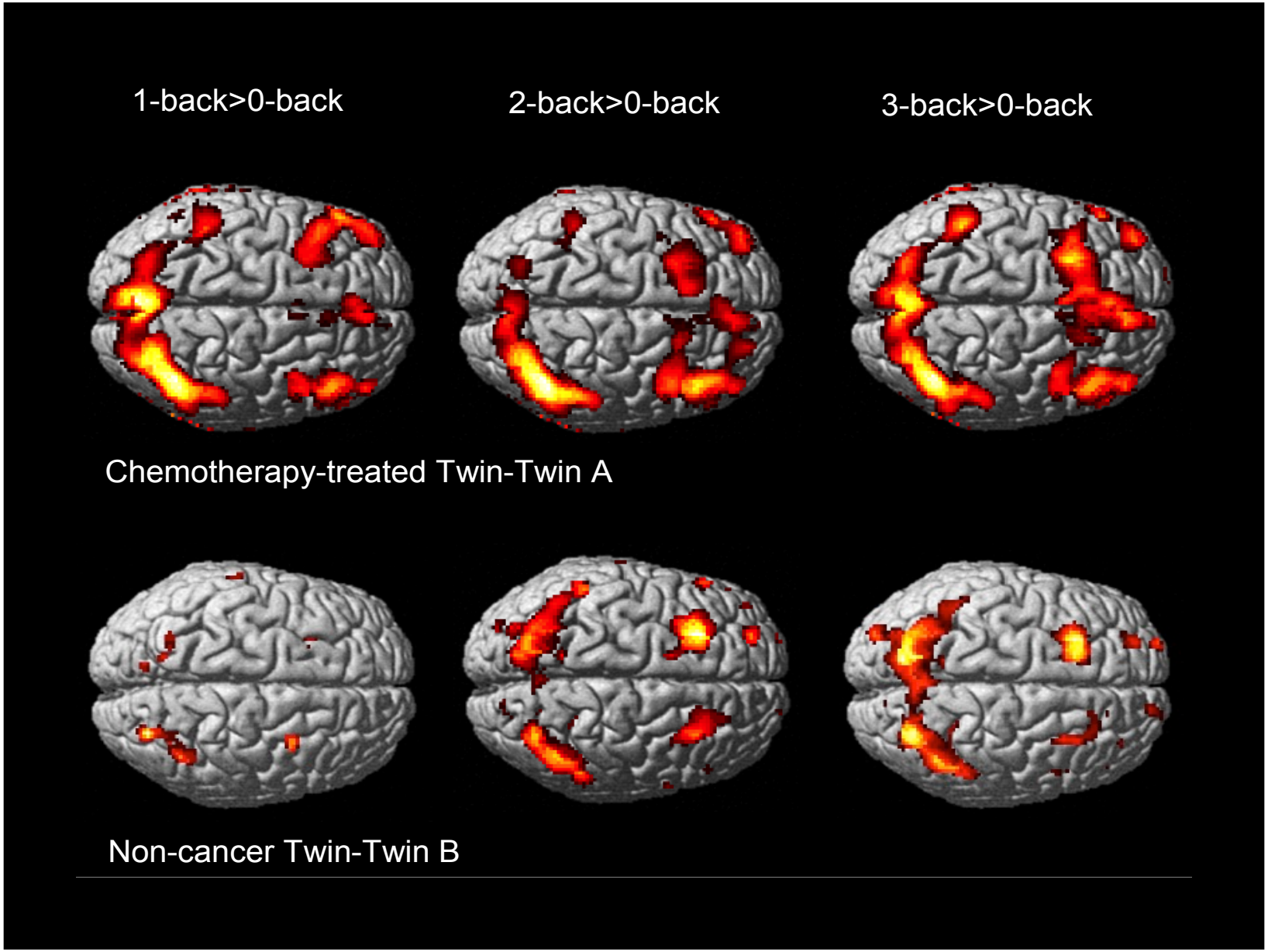


Pine Street Foundation, Becoming Your Own Advocate Newsletter, 2005

So, chemo-brain is real. But…

Why do many patients still have normal neuropsychological testing scores?

Where is the impairment?!



Ferguson RJ et al., Journal of Clinical Oncology, 2007

The chemo-brain (has to) work harder to get things done.

What are the consequences?

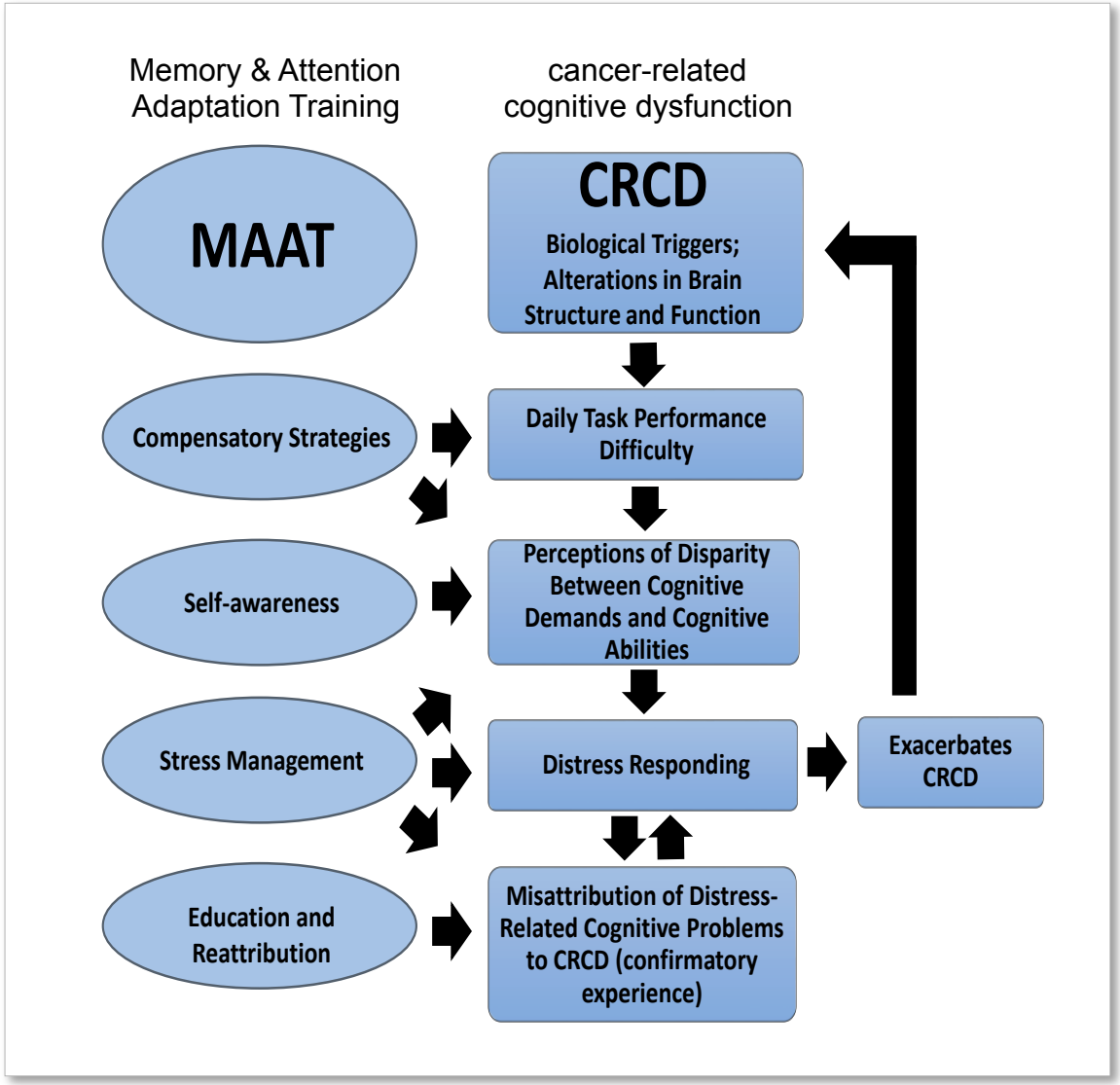
social life, family, employment…

And what to do about it?!

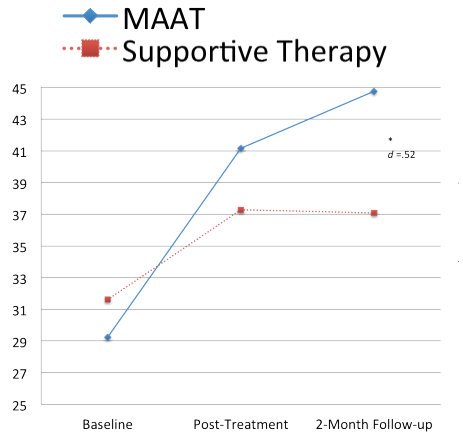
MAAT – Memory & Attention Adaptation Training

4 treatment components

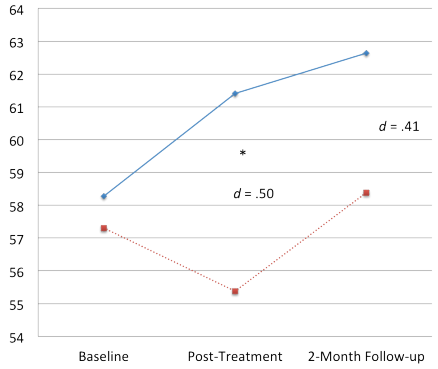
- Education and "memory failure reattribution"
- Self-awareness training
- Self-regulation and stress management
- Cognitive Compensatory strategies



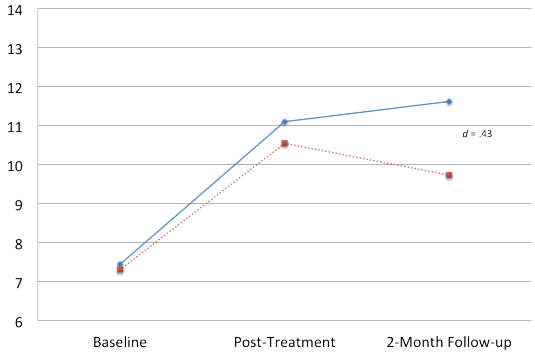
It works!



cognitive impairments



neurocognitive processing speed



quality of life

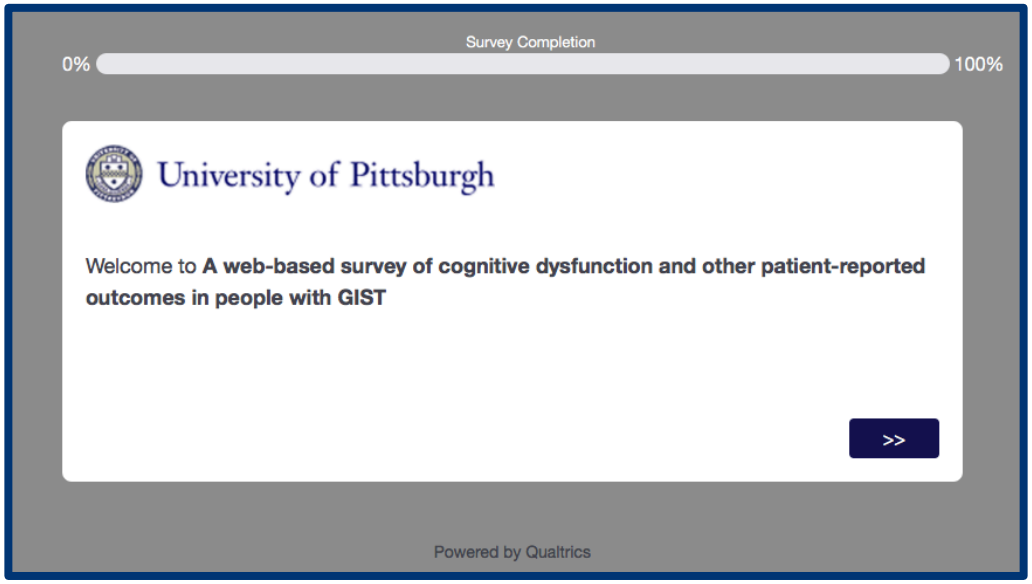
Treatment Satisfaction	Post Treatment	2-Month Follow Up
ITEM (higher = more satisfaction)	**0-8 (*sd*)**	**0-8 (*sd*)**
1. Rate how satisfied you were in general with the treatment program		
Supportive Therapy	5.5 (2.3)	5.7 (2.0)
MAAT	6.9 (.8)	6.9 (1.1)
2. Rate how helpful the treatment program was with *improving* problems of attention and memory		
Supportive Therapy	3.2 (2.5)	3.3 (2.1)
MAAT	5.5 (1.5)	5.4 (1.6)
3. Rate how helpful the treatment program was with helping you *compensate for and handle* memory or attention problems when they arise		
Supportive Therapy	4.8 (2.0)	4.7 (2.7)
MAAT	6.2 (1.4)	6.3 (1.7)

Nothing is known…

… about cognitive dysfunction in patients on long-term tyrosine kinase inhibitor therapy.

Like you!

A web-based survey of cognitive dysfunction and other patient-reported outcomes in people with GIST



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Dr. Dana Bovbjerg, PhD

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University of Pittsburgh School of Medicine

Dr. Beth E. Snitz, PhD

Department of Neurology
University of Pittsburgh School of Medicine

What were the 3 items that you were assigned to remember?

What is our survey about?
What will we ask?

1. some basic questions:

   - basic demographics
   - basic clinical and treatment history

2. standardized questionnaires asking about:

   - general health
   - perceived cognitive impairments
   - fatigue
   - sleep disturbance
   - emotional distress – depression
   - pain

Important to know...

- validated, widely used questionnaires with strong psychometric properties
- PROMIS
  (patient-reported outcomes measurement information system)
  - library for health care researchers to measure health with valid and reliable questionnaires about symptoms, function and quality of life
  - access for researchers through credentialed registration process
  - limits spread of questionnaires and copyright violations
- standardized reference populations
  - normed on thousands of patients and healthy individuals
- numerical rating scale

Important to know...

- completely anonymous
- no personal or private health information is being asked
- nobody can be identified

WE WANT YOU

to directly participate in our research!

Now! (And later...)

- take our survey (once it goes live...)
- will be posted on GSI listserv and GSI Facebook page

- let us know if we missed something
- fill out form in your conference package
- leave with me or the conference organizers (Ginger, Marina...)
- or: email me with suggestions: aduensin@pitt.edu

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Conclusions
NEED TO REVISE TO INCLUDE ALL OF THE PREVIOUS CHEMO BRAIN

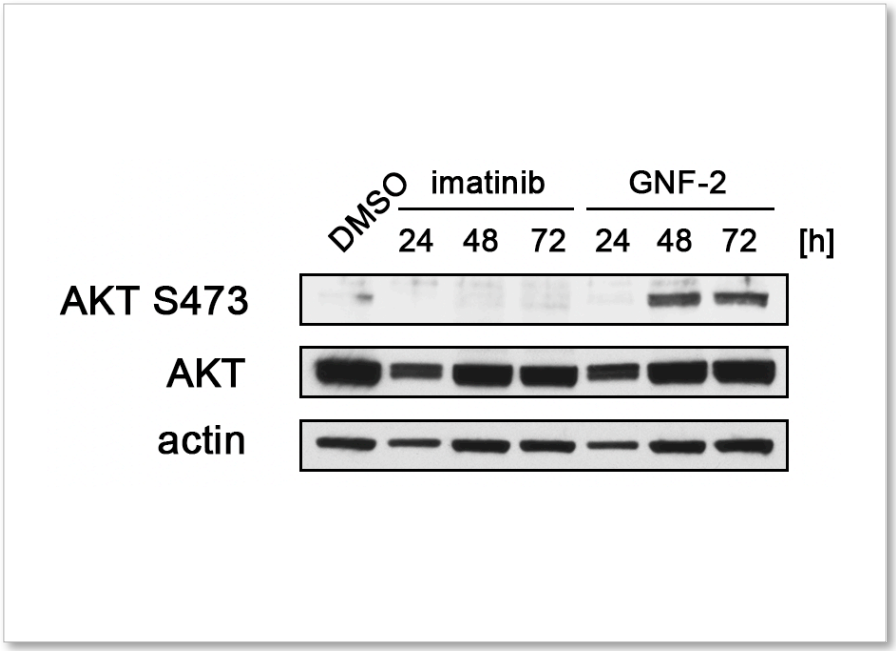
- MAAT appears to be more effective than other cognitive behavioral therapy.

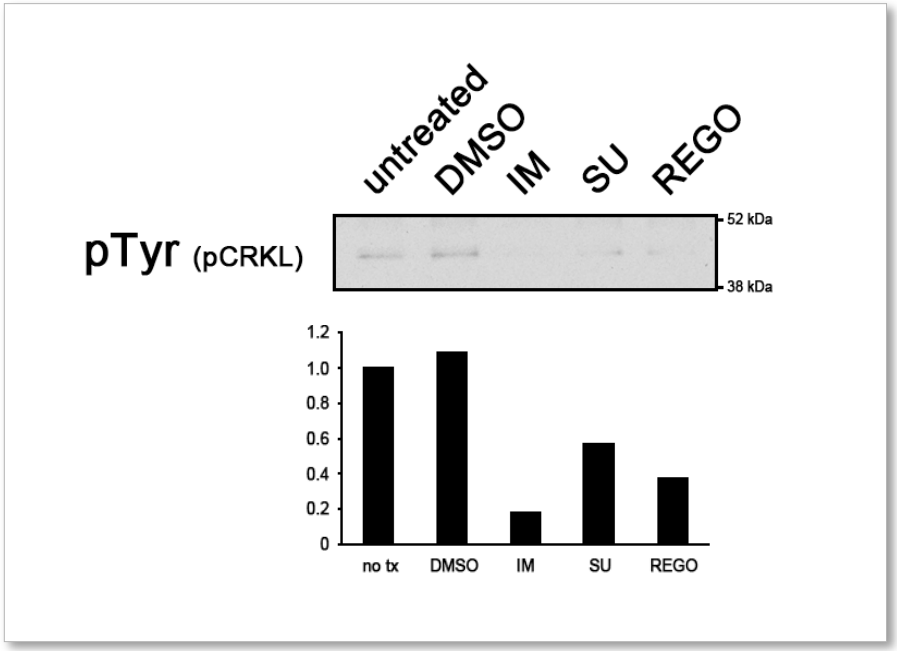
- MAAT likely has positive sustained effects on quality of life (less anxiety about cognitive failures).

- It can readily be delivered electronically with high survivor satisfaction.

WE WANT YOU

ABL is a survival factor in GIST cells





Rausch J, et al. Oncotarget 2017

- new KIT inhibitors for GIST should have increased specificity for KIT and reduced ability to inhibit ABL
- sunitinib, regorafenib → no significant ABL inhibition
- nilotinib, dasatinib → strong ABL inhibition
- BLU-285, DCC-2618