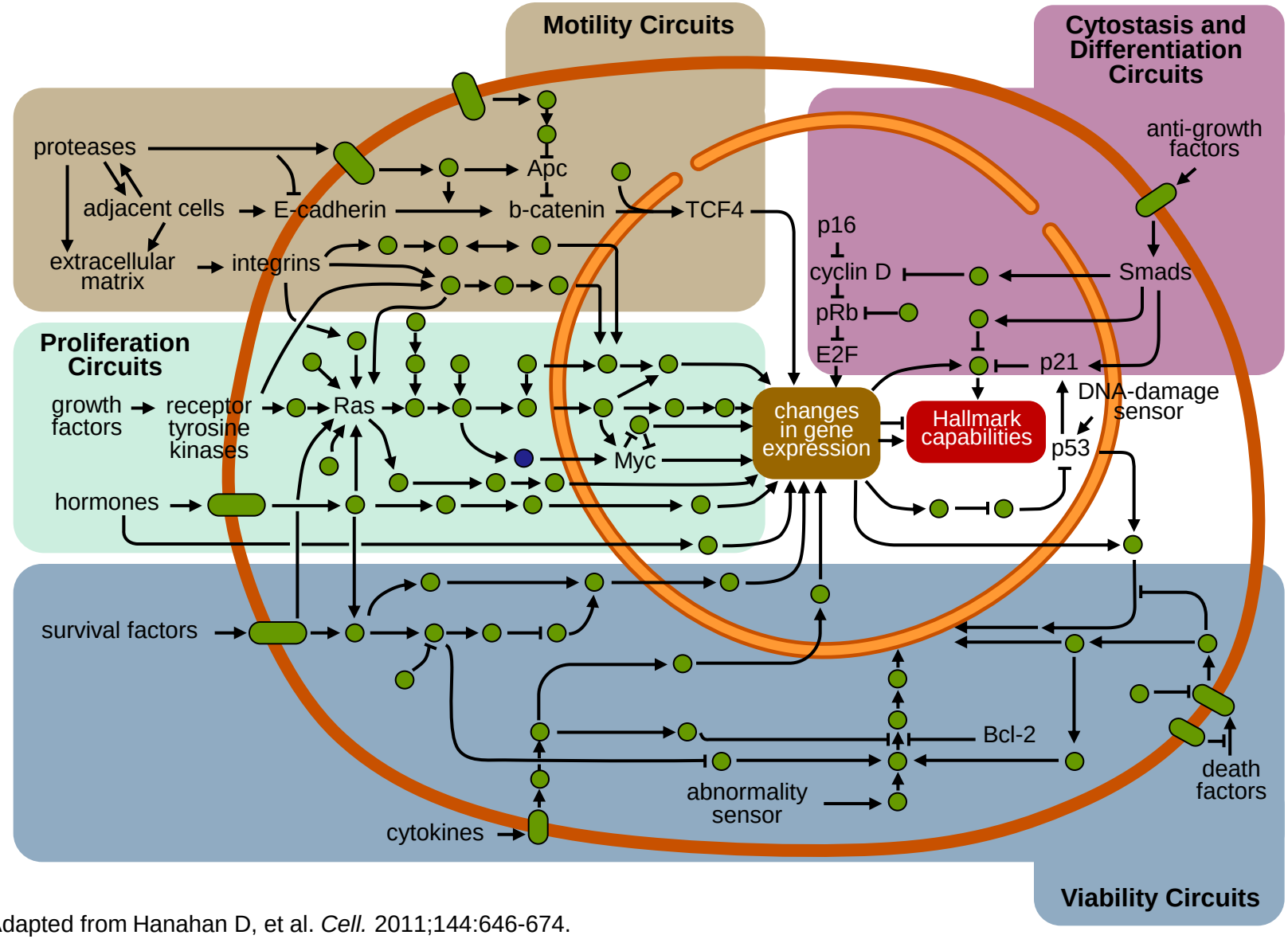
Genomic Landscape of mCRC and GIST

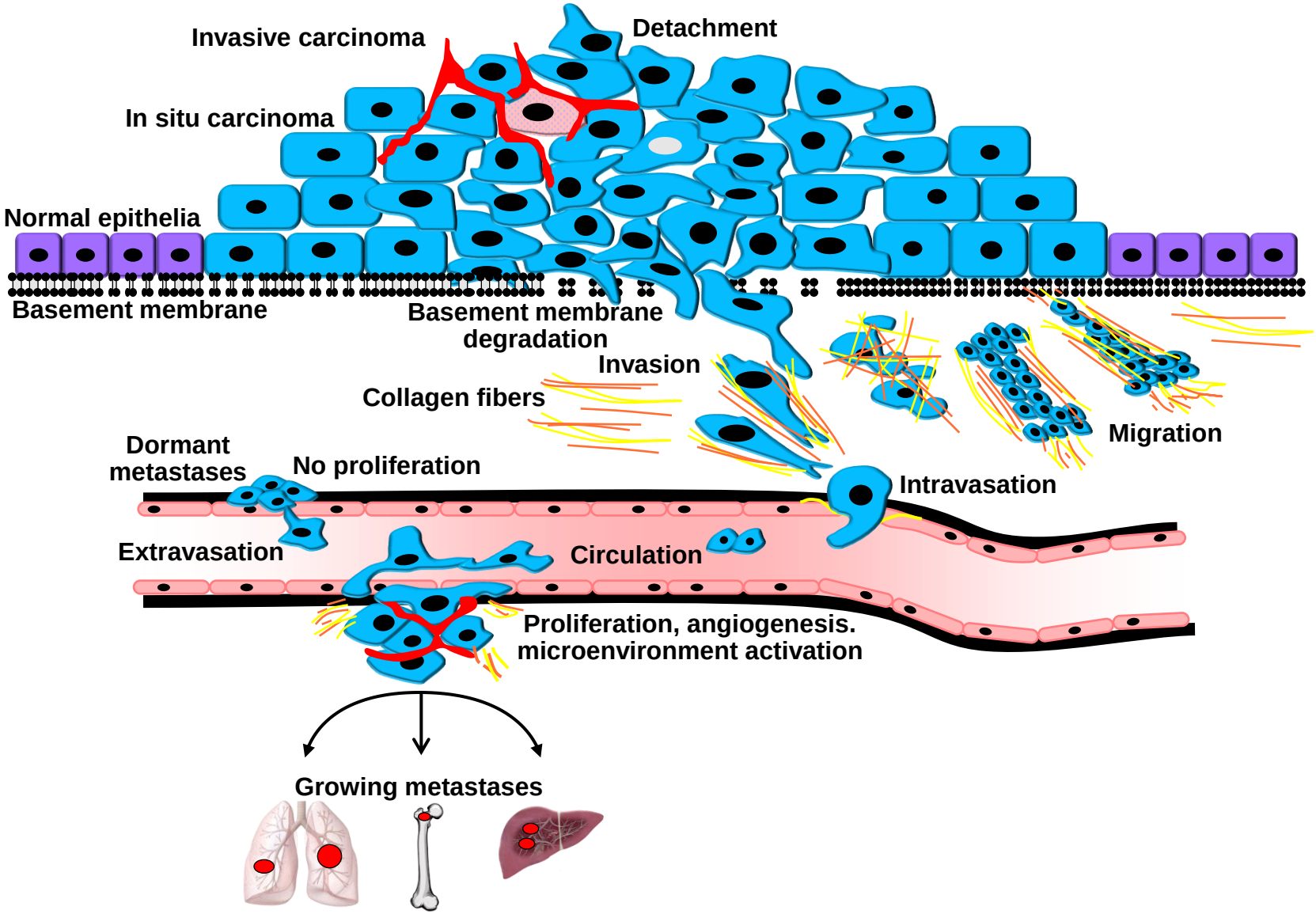
Heinz-Josef Lenz, MD
University of Southern California
Norris Comprehensive Cancer Center
Los Angeles, California

Intracellular Signaling Networks Within Cancer Cells



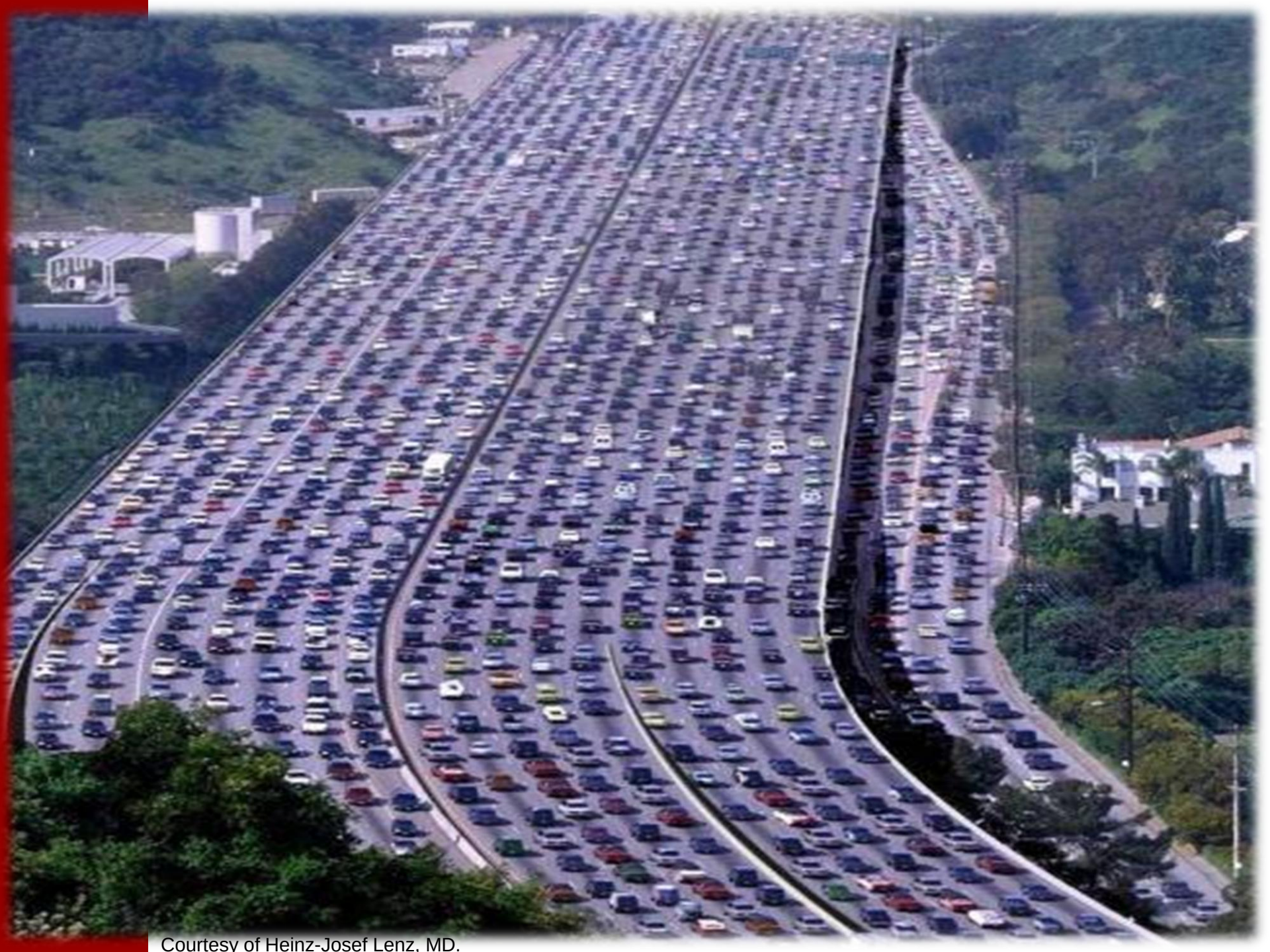
Adapted from Hanahan D, et al. *Cell.* 2011;144:646-674.

Metastatic Cancer Cell



Bacac M, et al. *Annu Rev Pathol Mech Dis*. 2008;3:221-247.

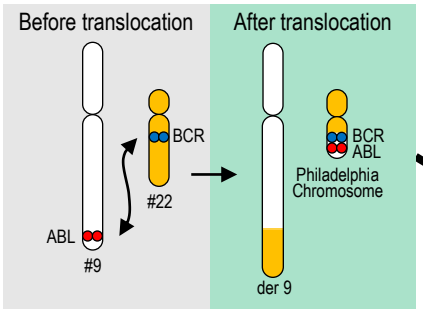
The Driver and the Passenger



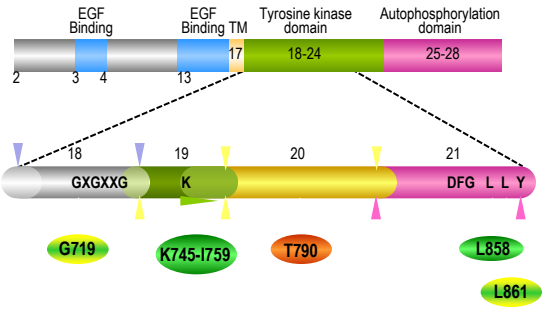
Courtesy of Heinz-Josef Lenz, MD.

Courtesy of Heinz-Josef Lenz, MD.

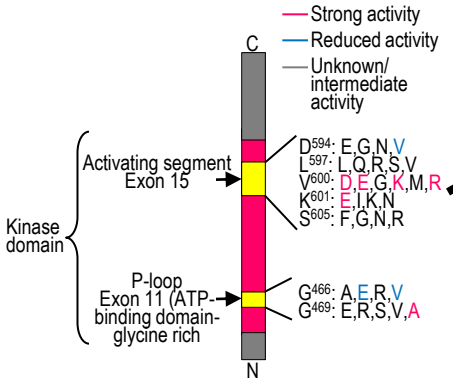
The Drivers We Know Well



BCR-ABL



EGFR



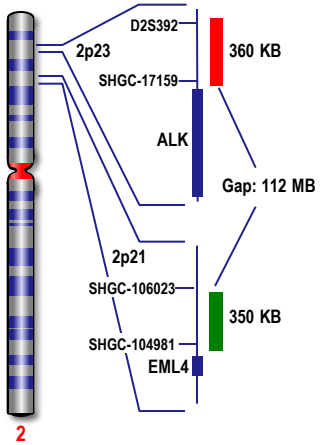
BRAF-V600E

CML

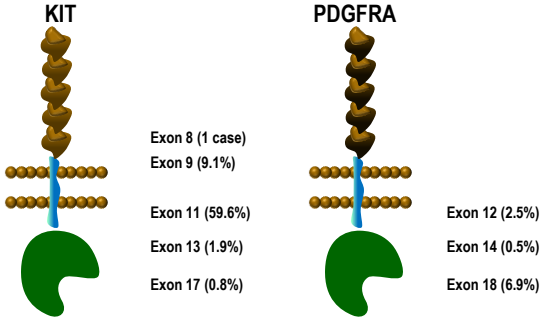
Melanoma

NSCLC

GIST



EML4-ALK



KIT / PDGFRA

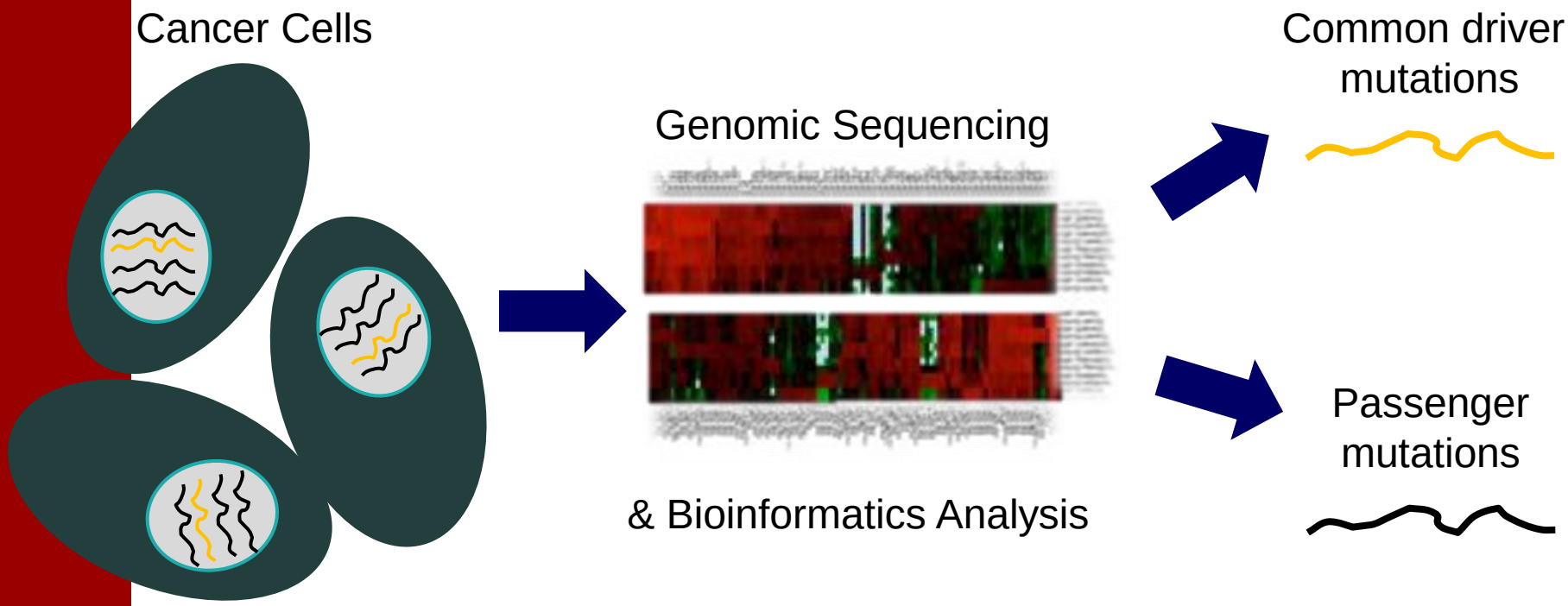
Adapted from: 1. Arkenau H-T, et al. *Br J Cancer*. 2011;104:392-398; 2. Haslam S. *Core Evid*. 2005;1:1-12; 3. SM-EGFR-DB. http://www.somaticmutations-egfr.info/NSCLC.html. Accessed September 11, 2012; 4. GIST Support International. http://www.gistsupport.org/ask-the-professional/gist-with-pdgfr-alpha-mutations.php. Accessed September 11, 2012; 5. KREATECH Diagnostics. http://www.kreatech.com/?id=368. Accessed September 11, 2012.

Difference Between mCRC and GIST Driver vs Passenger Mutations

- Somatic mutations found in cancers are either “drivers” or “passengers”
  - Driver mutations are causally involved in the neoplastic process and are positively selected for during tumorigenesis (cKIT in GIST)
  - Passenger mutations provide no positive or negative selective advantage to the tumor but are retained by chance during repeated rounds of cell division and clonal expansion (Kras mutation in mCRC)

Wood LD, et al. *Science*. 2007;318:1108-1113.

Identification of Driver Mutations

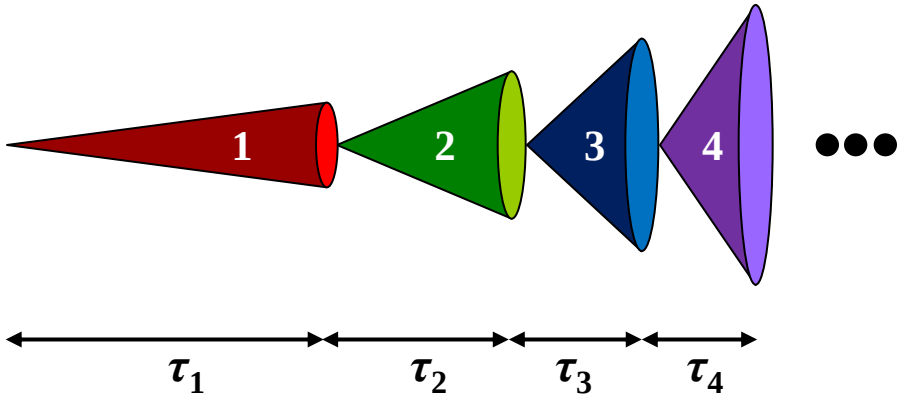


Sjoblom T, et al. *Science.* 2006;314:268-274.

Distinguishing the Drivers from the Passengers

- Largely driven by modeling[1,2]
- Solid tumors typically contain 40-100 coding gene alterations, including 5-10 driver mutations[2]
- Driver mutations promote tumor expansion and similarly arise in a tumor of growing size[2]

Clonal Expansion with Cumulative Driver Mutations[2]



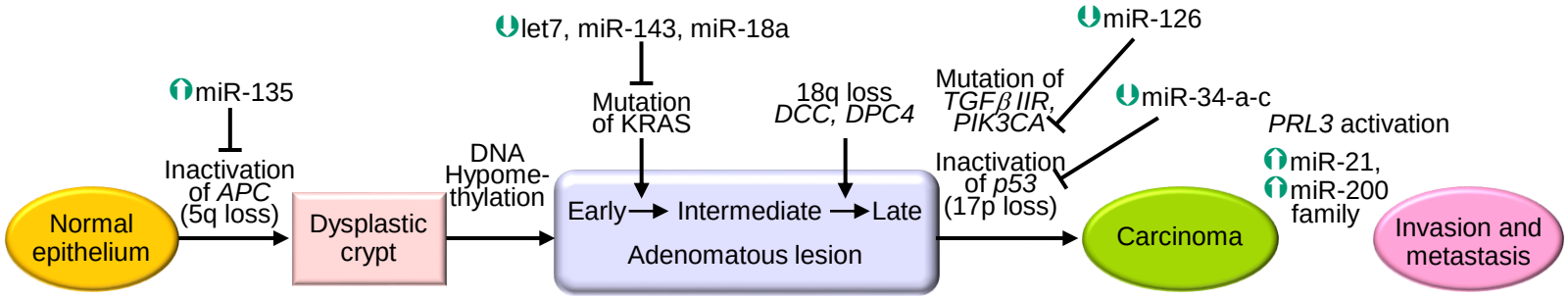
τ_1 is the average time it takes the lineage of the founder cell to produce a successful cell with two driver mutations

- Analysis of growth rate, average cell division time in a given tumor, expected number of driver versus passenger mutations, and validation screening of identified mutations ⟶ isolation of probable drivers[2]

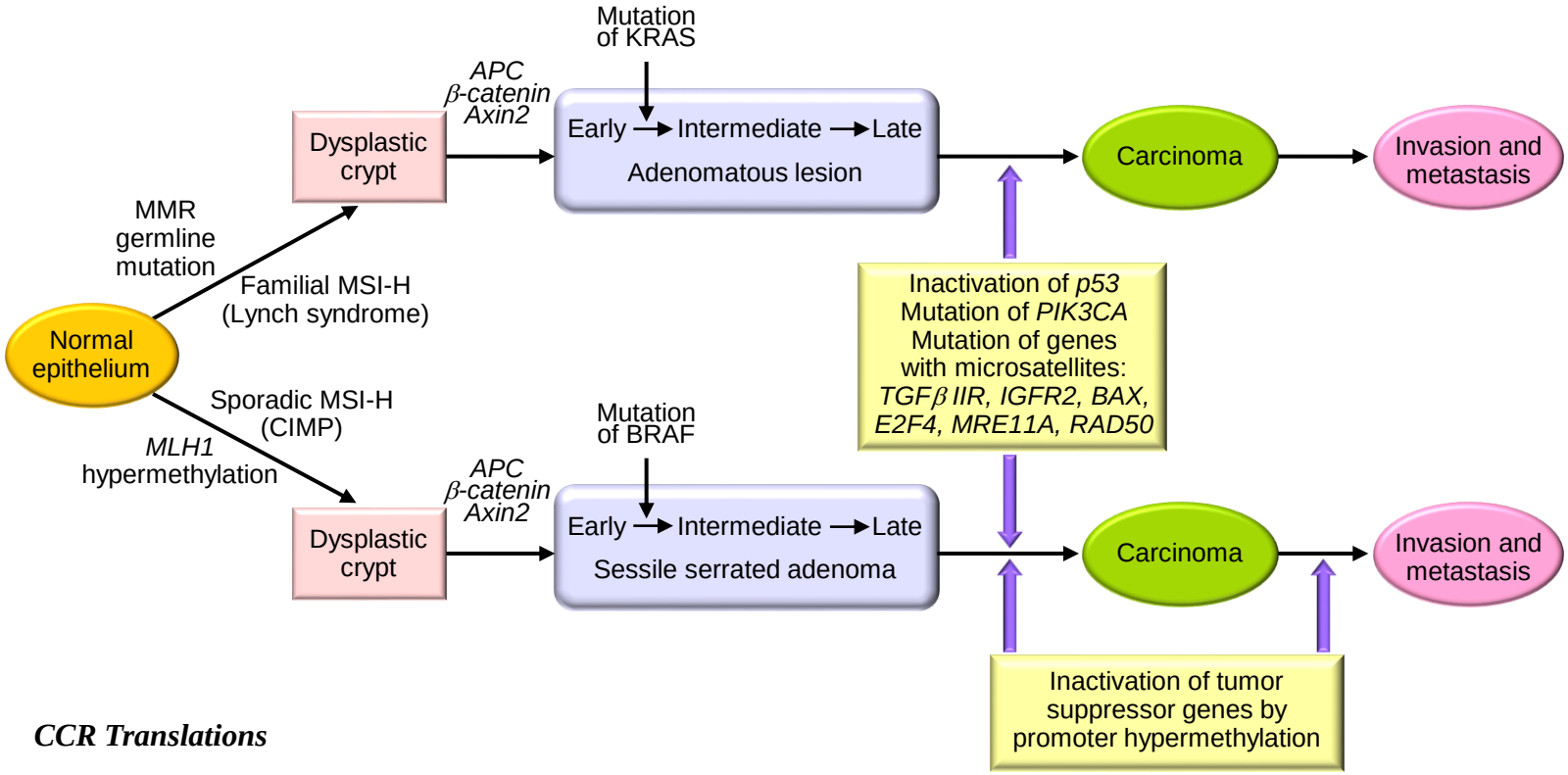
1. Sjoblom T, et al. *Science.* 2006;314:268-274; 2. Bozic I, et al. *Proc Natl Acad Sci U S A*. 2010;107(43):18545-18550.

mCRC and GIST: Transformation Process and Therapeutic Targeting

MSS – Chromosomal Instability Pathway



MSI – Mutator Phenotype Pathway

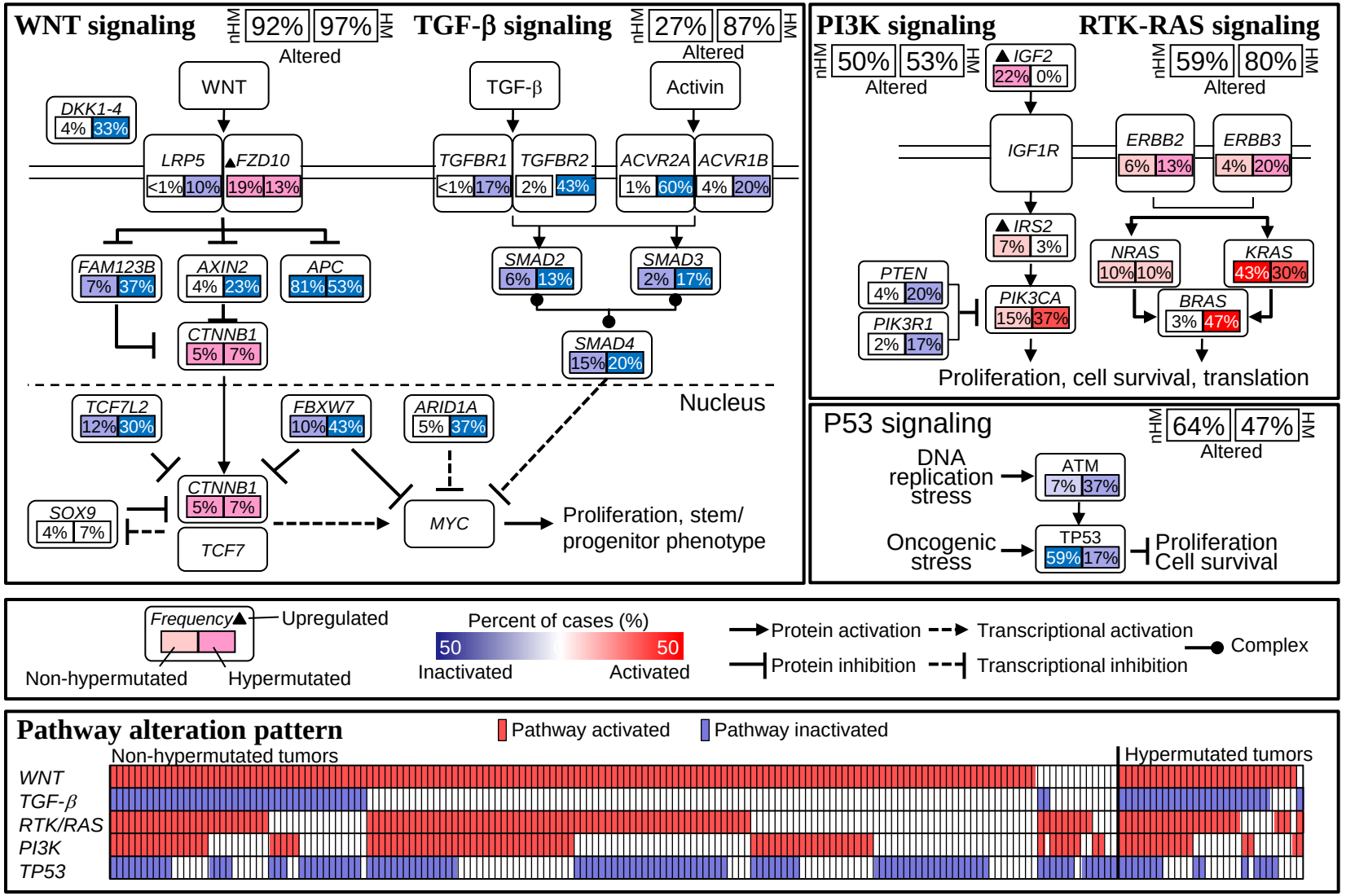


CCR Translations

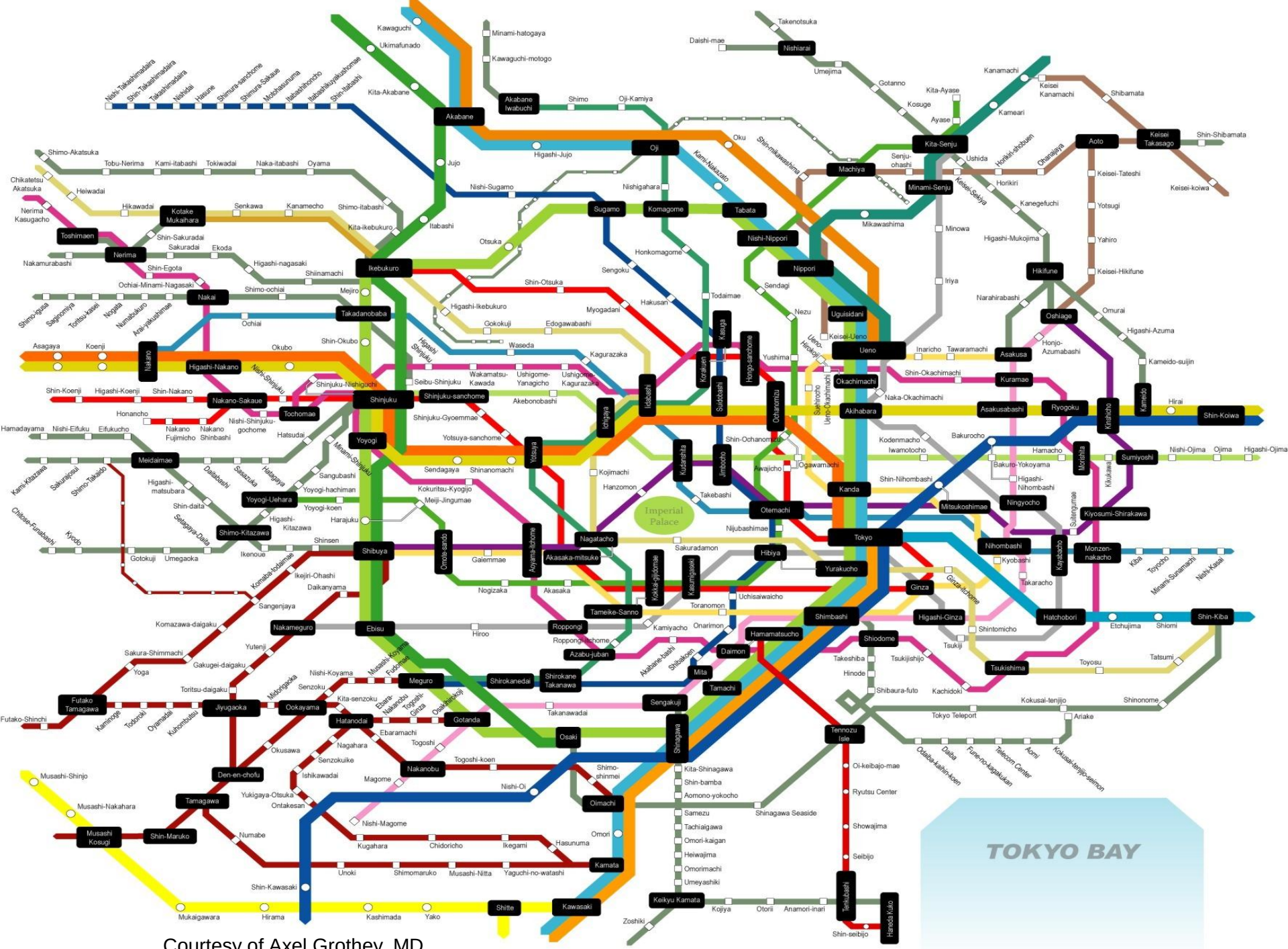
Vilar E, et al. *Clin Cancer Res.* 2011;17:7207-7209.

Clinical Cancer Research

Genetic Changes in CRC

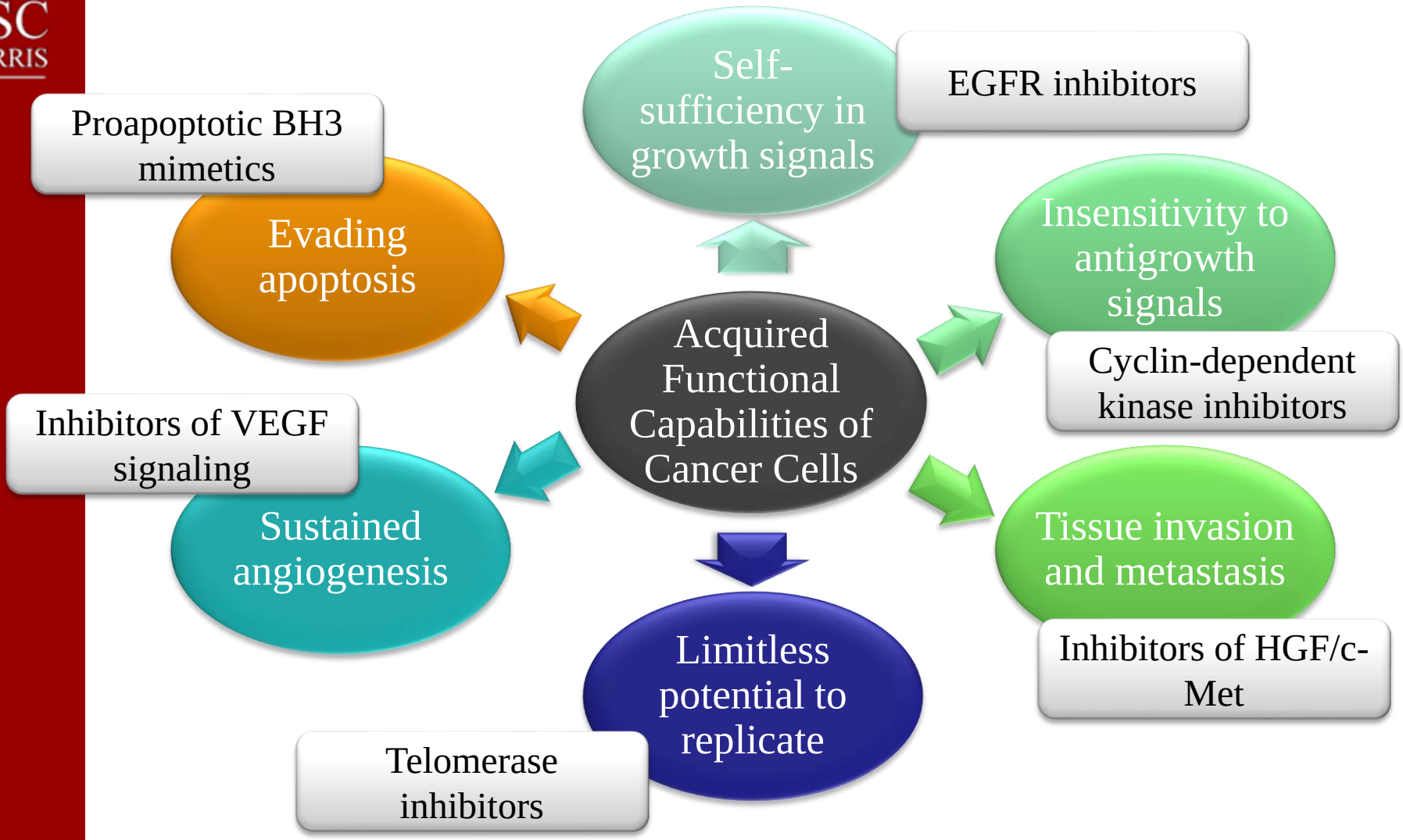


Cancer Genome Atlas Network. *Nature.* 2012;487:330-337.



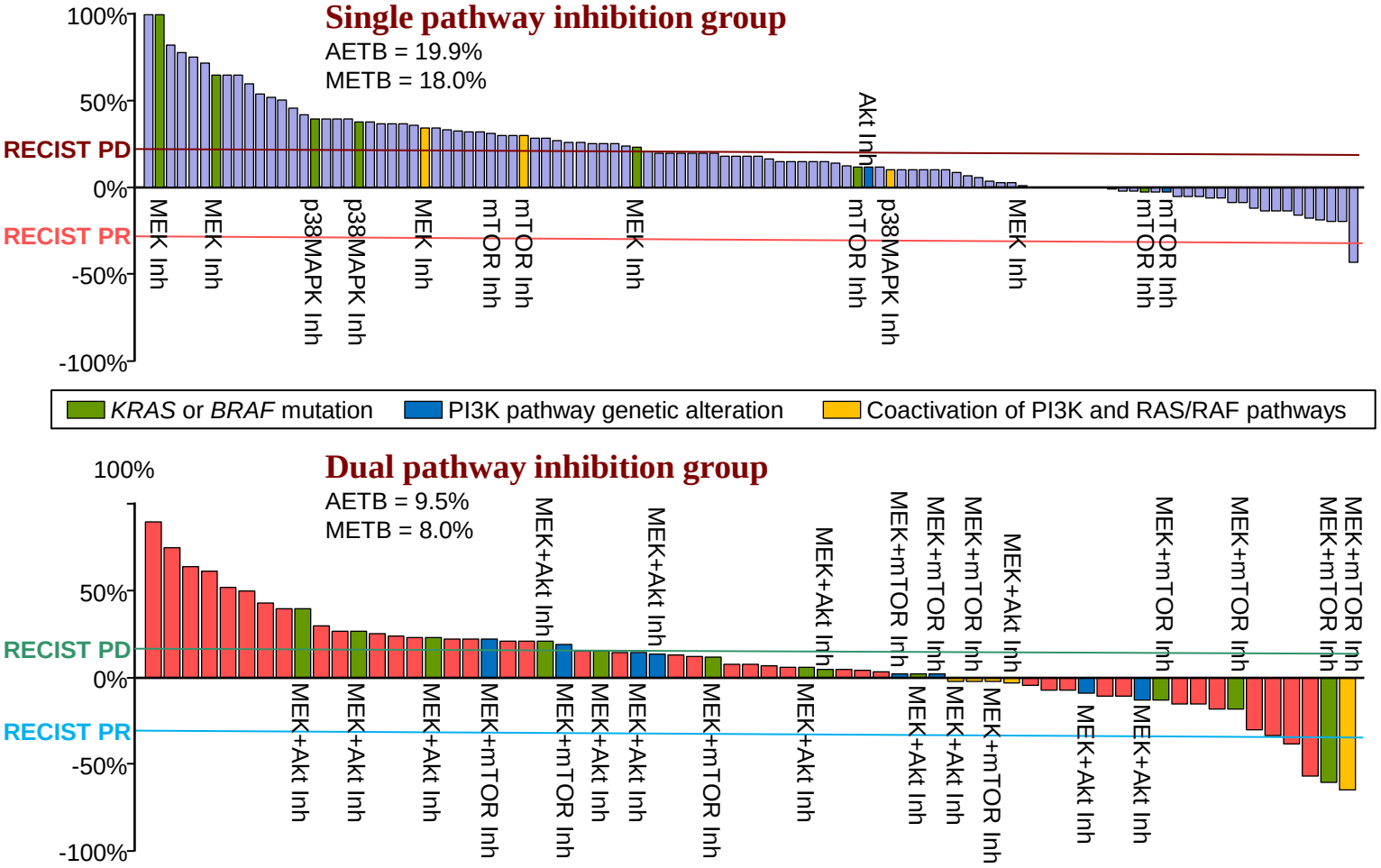
Courtesy of Axel Grothey, MD.

Hallmarks of Cancer – Therapeutic Targeting



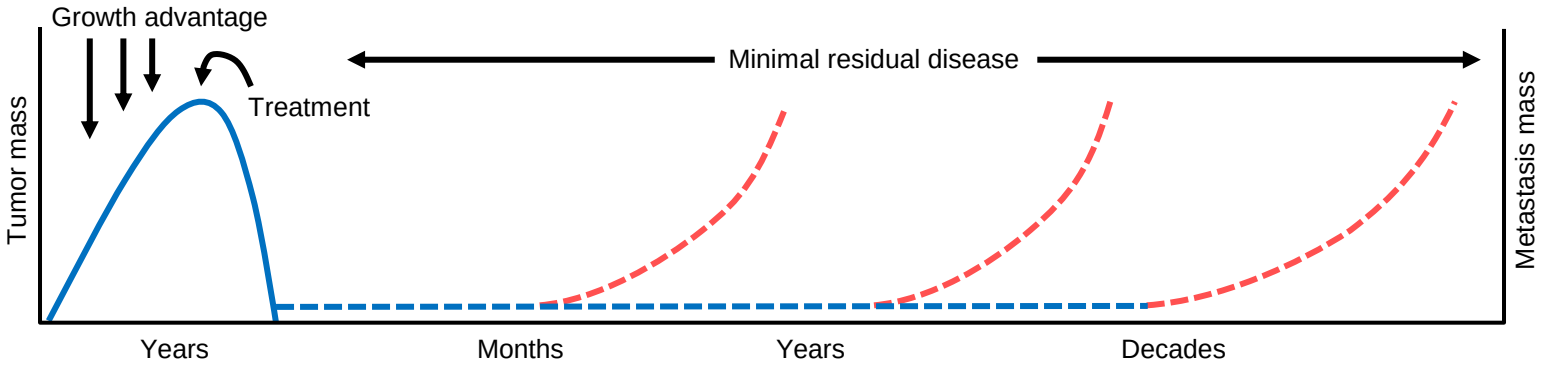
VEGF, vascular endothelial growth factor; EGFR, epidermal growth factor receptor; HGF, hepatocyte growth factor.
Hanahan D, et al. *Cell.* 2011;144:646-674.

Tumor Effects with Available Results of Tumor Genomic Alterations



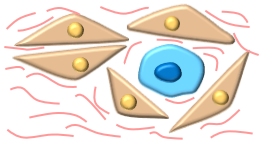
Shimizu T, et al. *Clin Cancer Res.* 2012;18:2316-2325.

Genetic/Epigenetic Changes

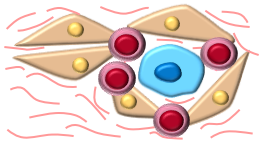


Cellular Dormancy

Quiescent solitary tumor cell
Microenvironment-dependent

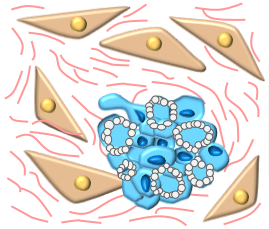


Evasion of the immune system by quiescent tumor cells



Angiogenic Dormancy

Dormant micrometastasis



Pro-angiogenic factors

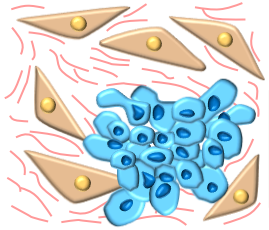
Ras → VEGF
Ras ⊣ TSP
Low O_2

Anti-angiogenic factors

p38 ⊣ VEGF
p38 → TSP
p53 → TSP

Angiogenic switch
Exogenous angiogenic "spike"

Growing micrometastasis



Pro-angiogenic factors

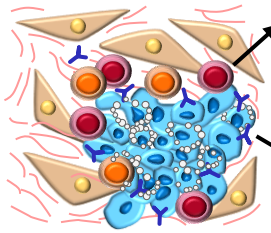
Ras → VEGF
Ras ⊣ TSP
Low O_2

Anti-angiogenic factors

~~p38~~ ~~p53~~

Immunosurveillance

Dormant micrometastasis

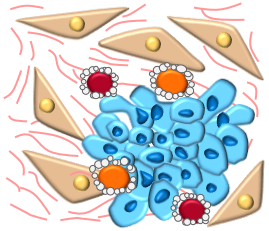


Immunity coordinated by CD8* T-cells and memory T cells

Humoral response

Cellular escape mechanisms
Immunosuppression?

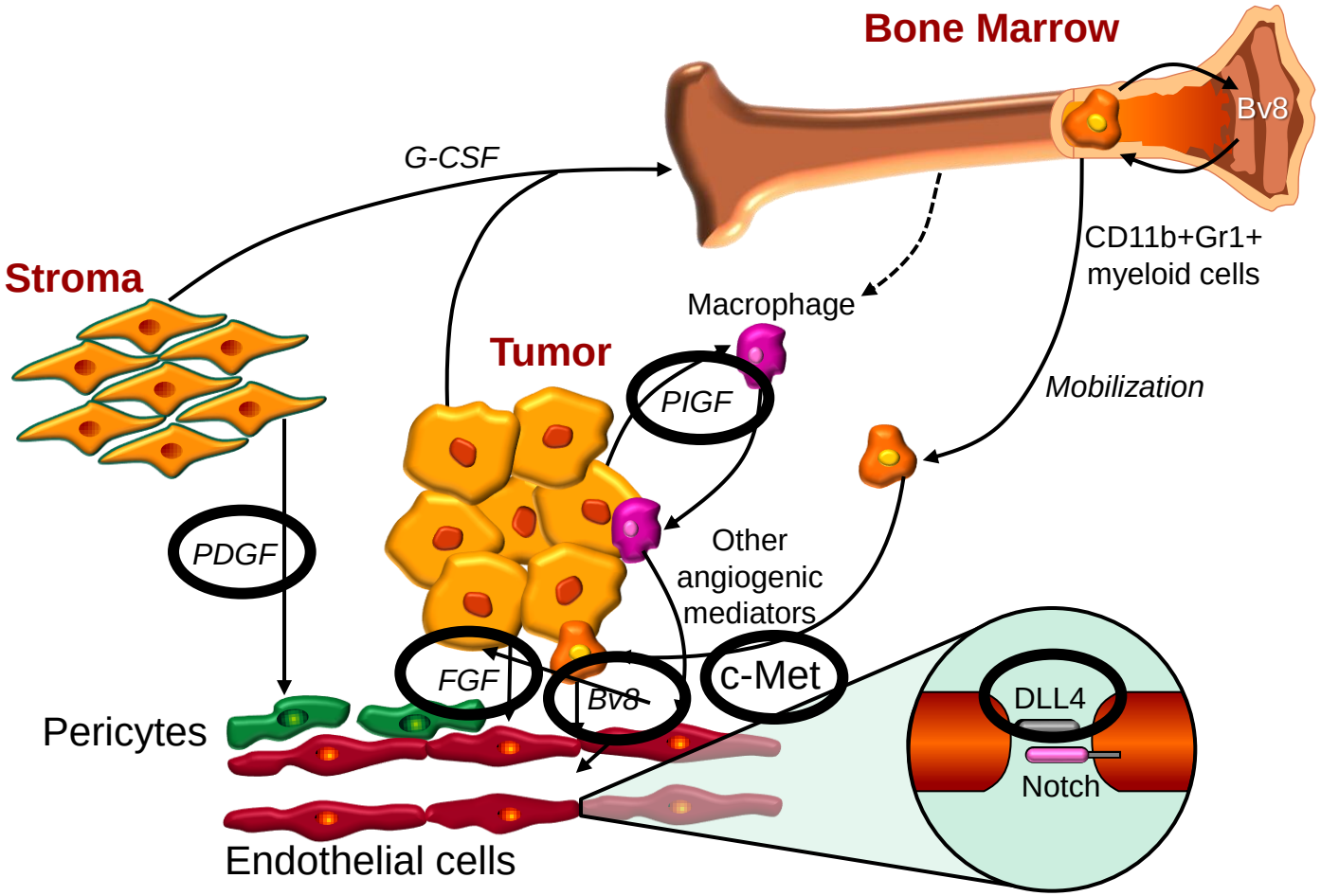
Growing micrometastasis



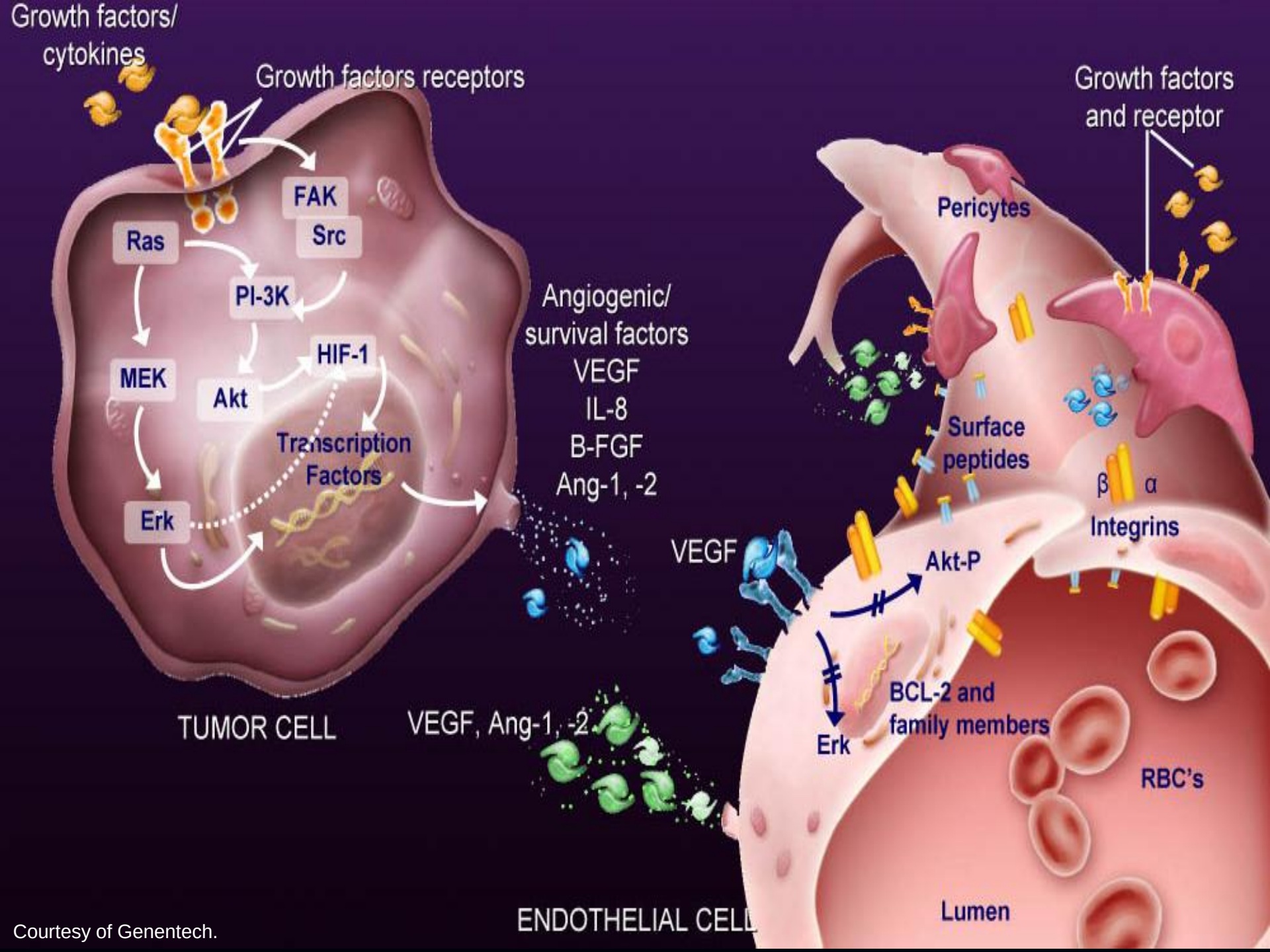
Evasion of the immune system causes tumor mass expansion

Adapted from: Aguirre-Ghiso J. *Nat Rev Cancer*. 2007;7:834-846.

Most Resistance Manuscripts and Reviews Focus on Redundant Angiogenic Pathways

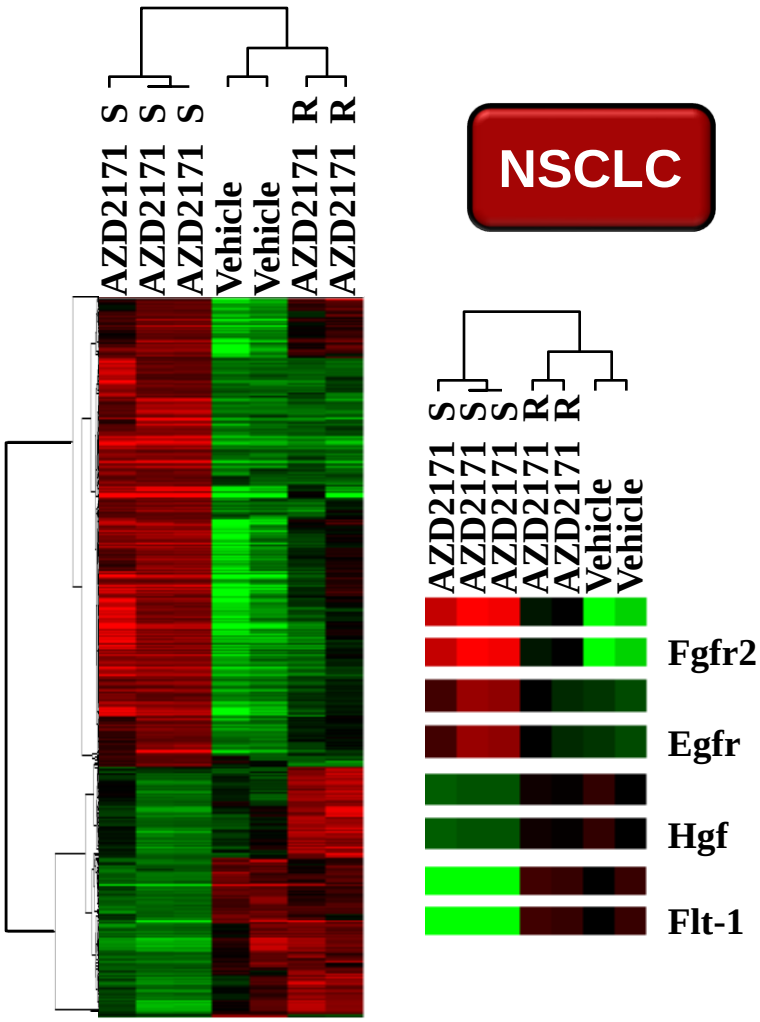


Ellis L, et al. *Clin Cancer Res*. 2008;14:6371-6375.



Courtesy of Genentech.

Stromal VEGFR1 (Flt-1) and VEGFR TKI Resistance

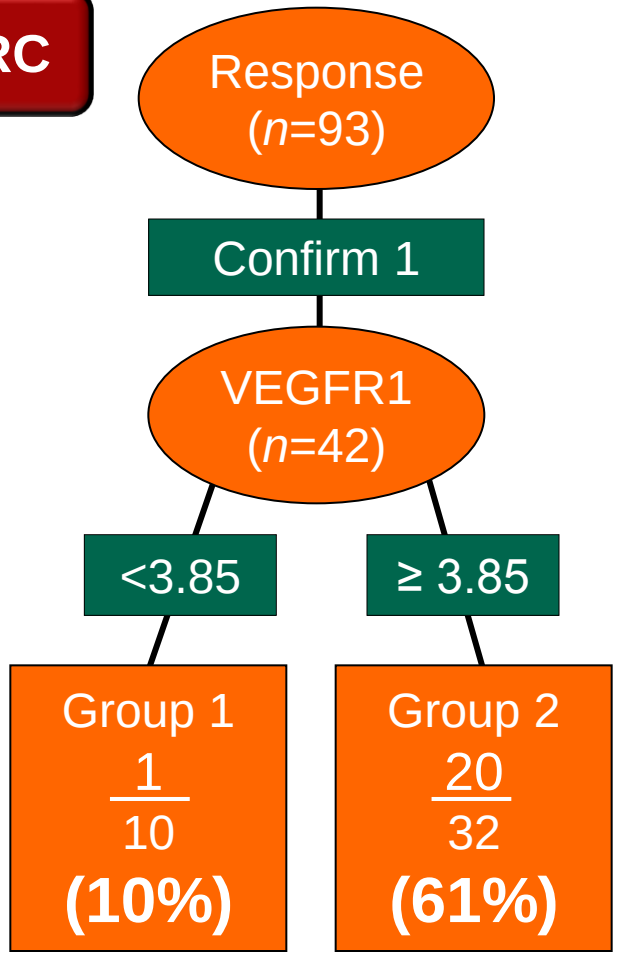


(*p* <0.005)

Cascone et al. In preparation.
Lenz, ASCO 2011.

VEGFR1 (Flt-1) mRNA and VEGFR TKI Resistance

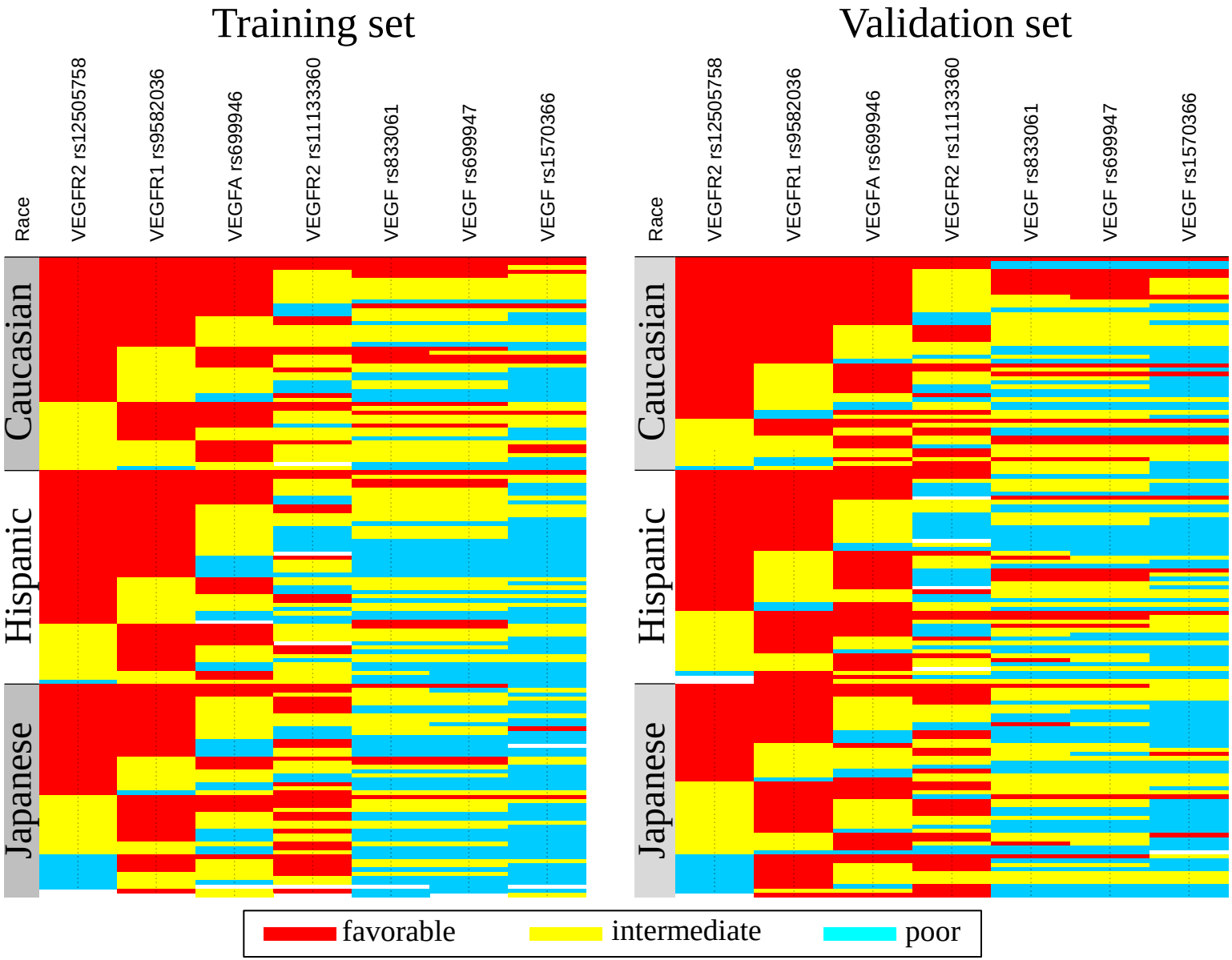
NSCLC **mCRC**



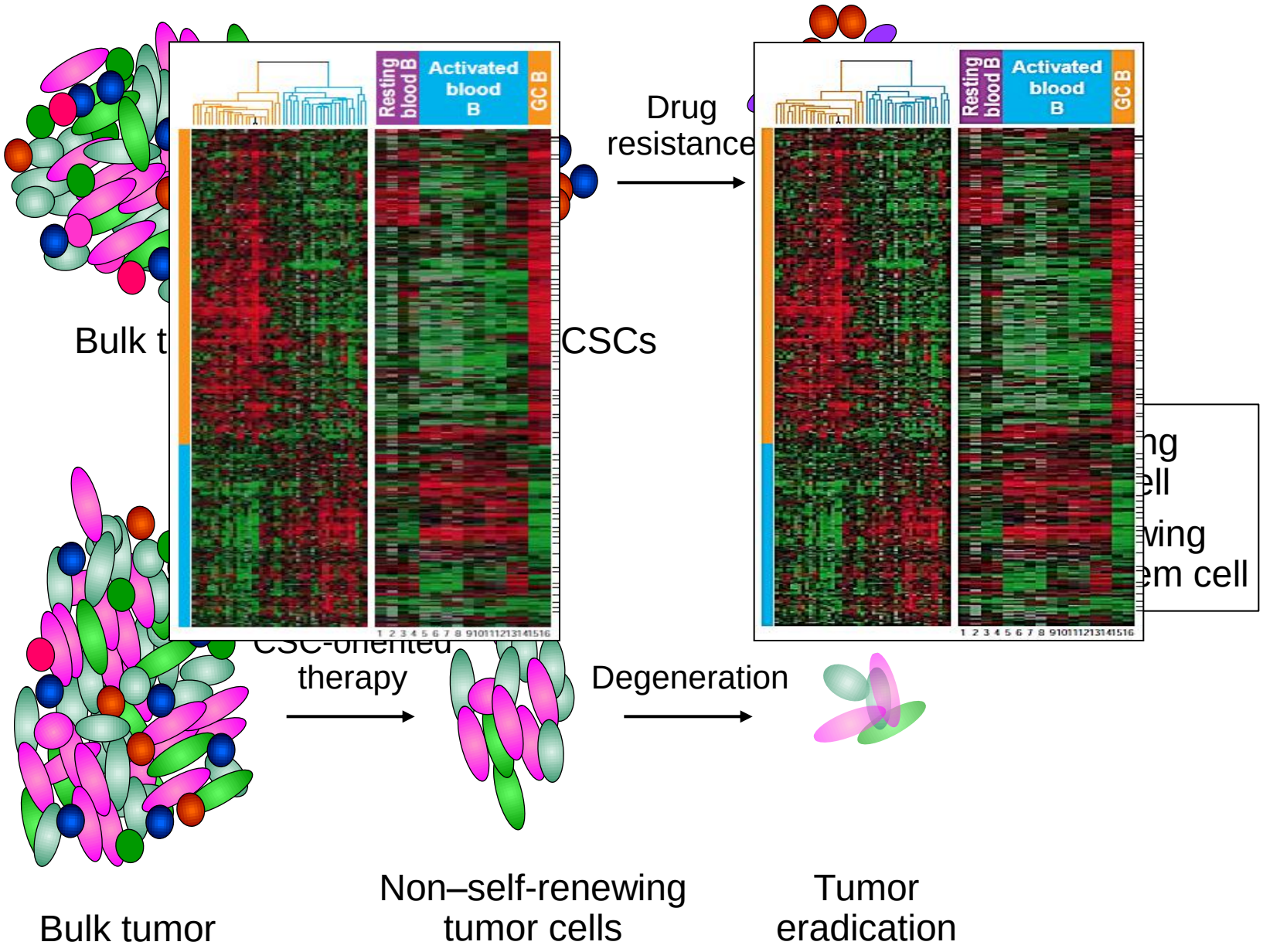
Unsupervised clustering analysis in control and AZD2171 sensitive and resistant H1975 tumors

Courtesy of Heinz-Josef Lenz, MD.

Heatmaps in 7 Favorable Polymorphisms in Bevacizumab

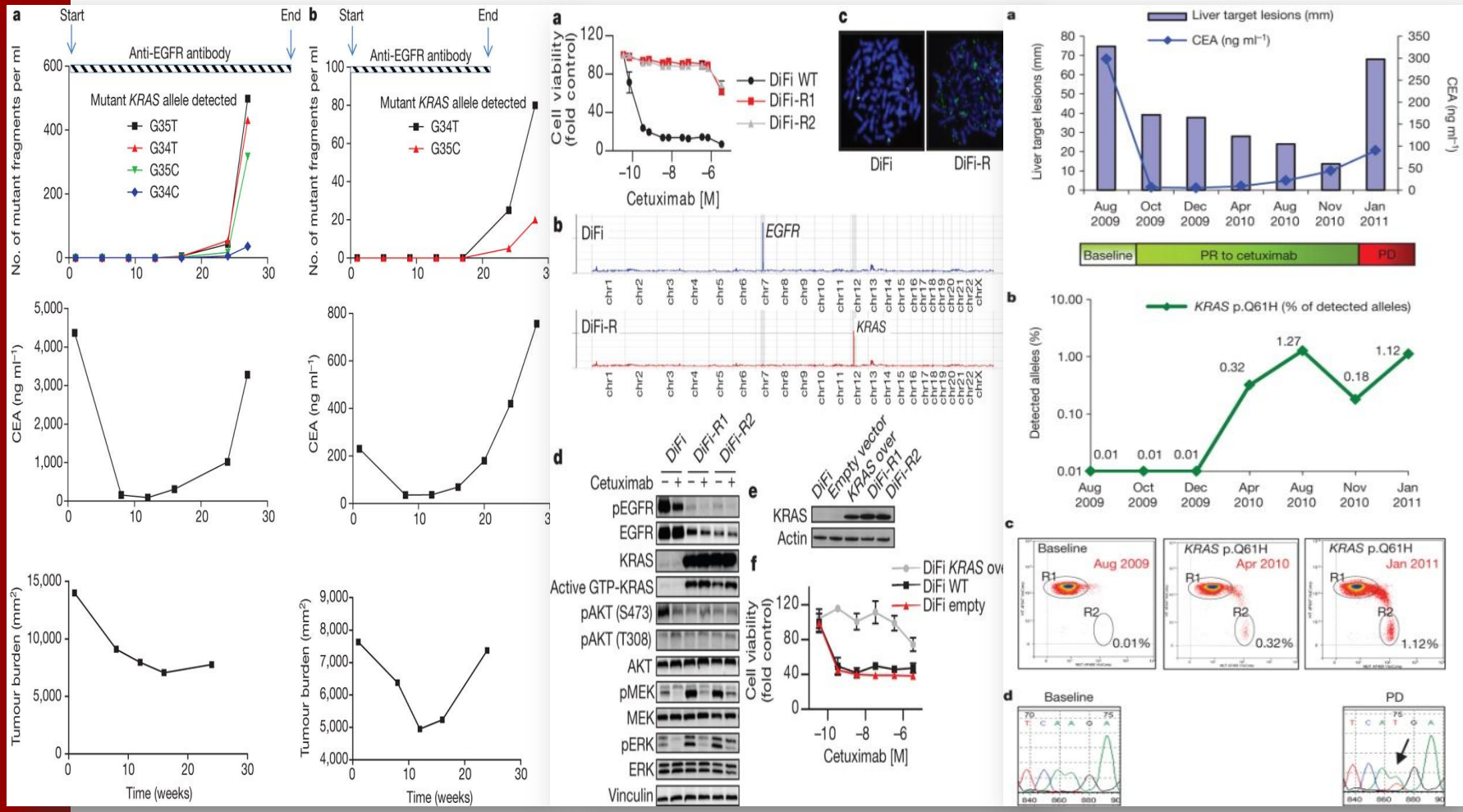


Wakatsuki et al ASCO 2012. Abstract 4026 .



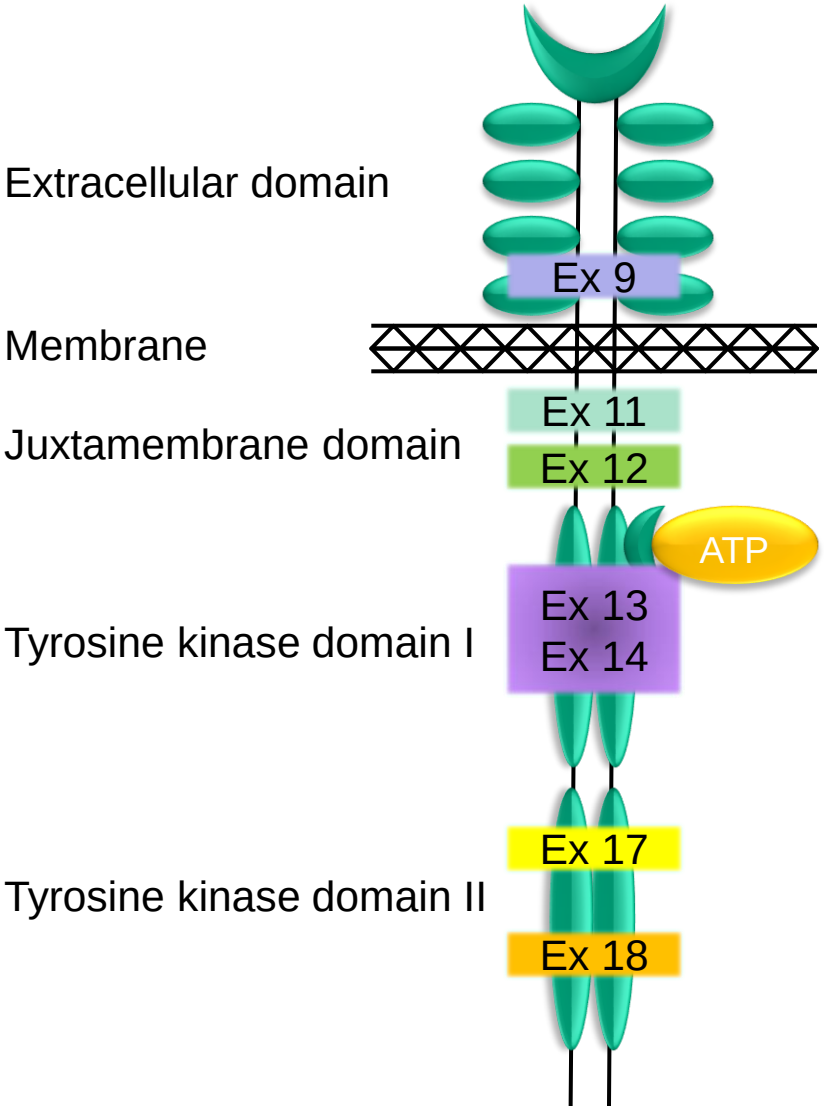
Courtesy of Heinz-Josef Lenz, MD.

Emergence of Circulating (New) Mutant *KRAS* and Kras Amplification as Mechanisms of Resistance to EGFR Inhibitors



1. Diaz L. et al. *Nature*. 2012;486(7404):537-40; 2.Misale S, et al. *Nature*. 2012;486(7404):532-536.

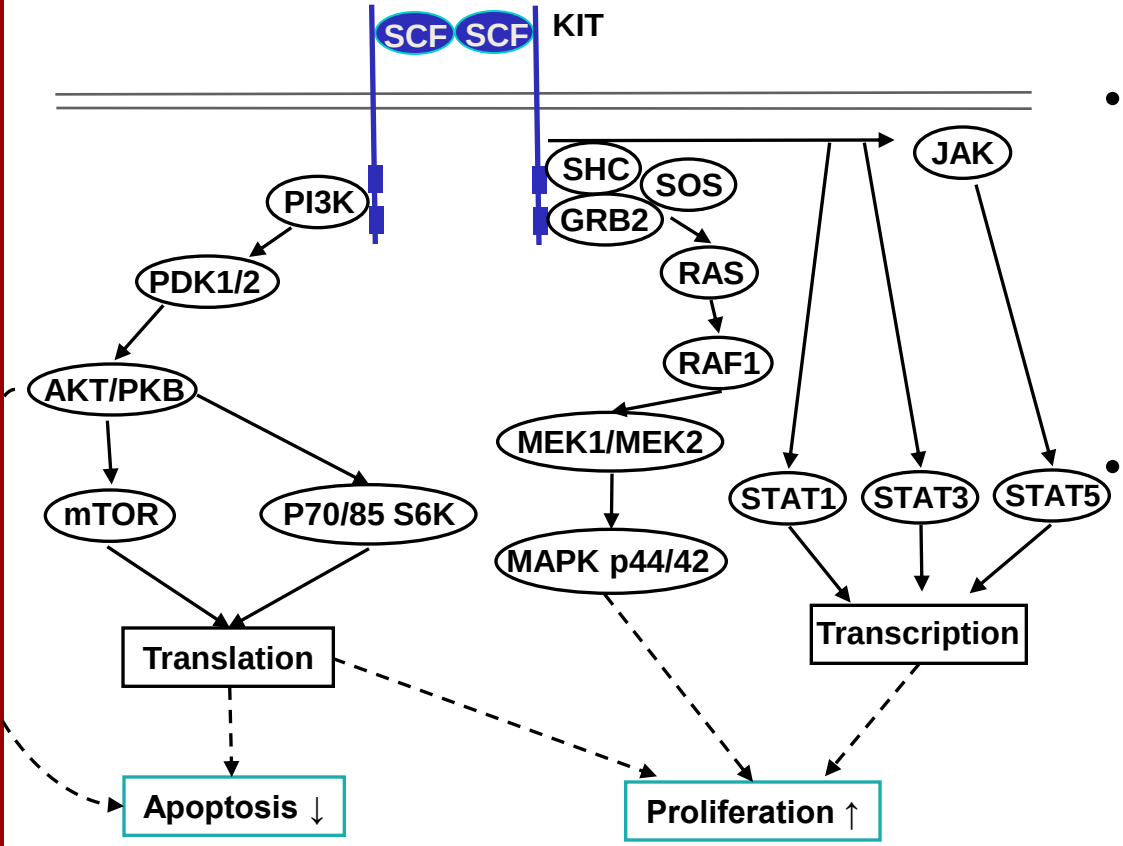
Oncogenetic Activation in the Pathogenesis of GIST



Gene	Exon	Prevalence
KIT	9	18%
	11	67%
	13	2%
	17	2%
PDGFRA	12	1%
	18	4%

1. Zhao X, et al. *J Gastrointest Oncol.* 2012;3(3):189-208; 2. Demetri GD, et al. *J Natl Compr Canc Netw*. 2010;8:S1-S41; 3. Heinrich M, et al. *J Clin Oncol*. 2003;21:4342-4349.

Constitutive Activation of KIT and PDGFR Promotes Tumor Growth

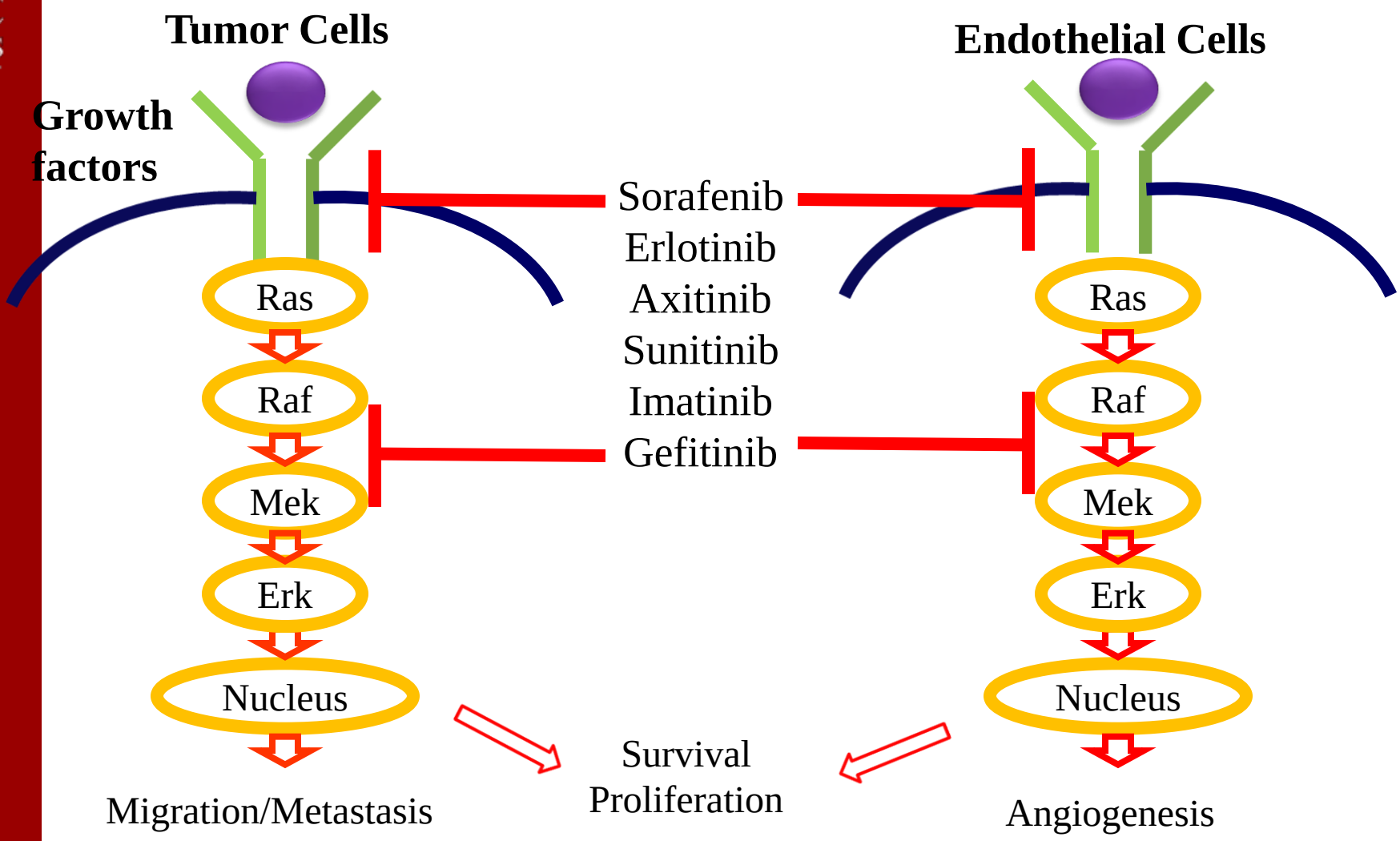


- Mutations of KIT and PDGFRA RTKs increase cell proliferation while decreasing apoptosis
- Downstream signaling pathways of mutant KIT or PDGFRA are thought to be similar, although specific gene expression differs

PDGFRA, platelet-derived growth factor receptor-α; PI3K, phosphoinositide 3-kinase; RTK, receptor tyrosine kinase; SCF, stem cell factor.

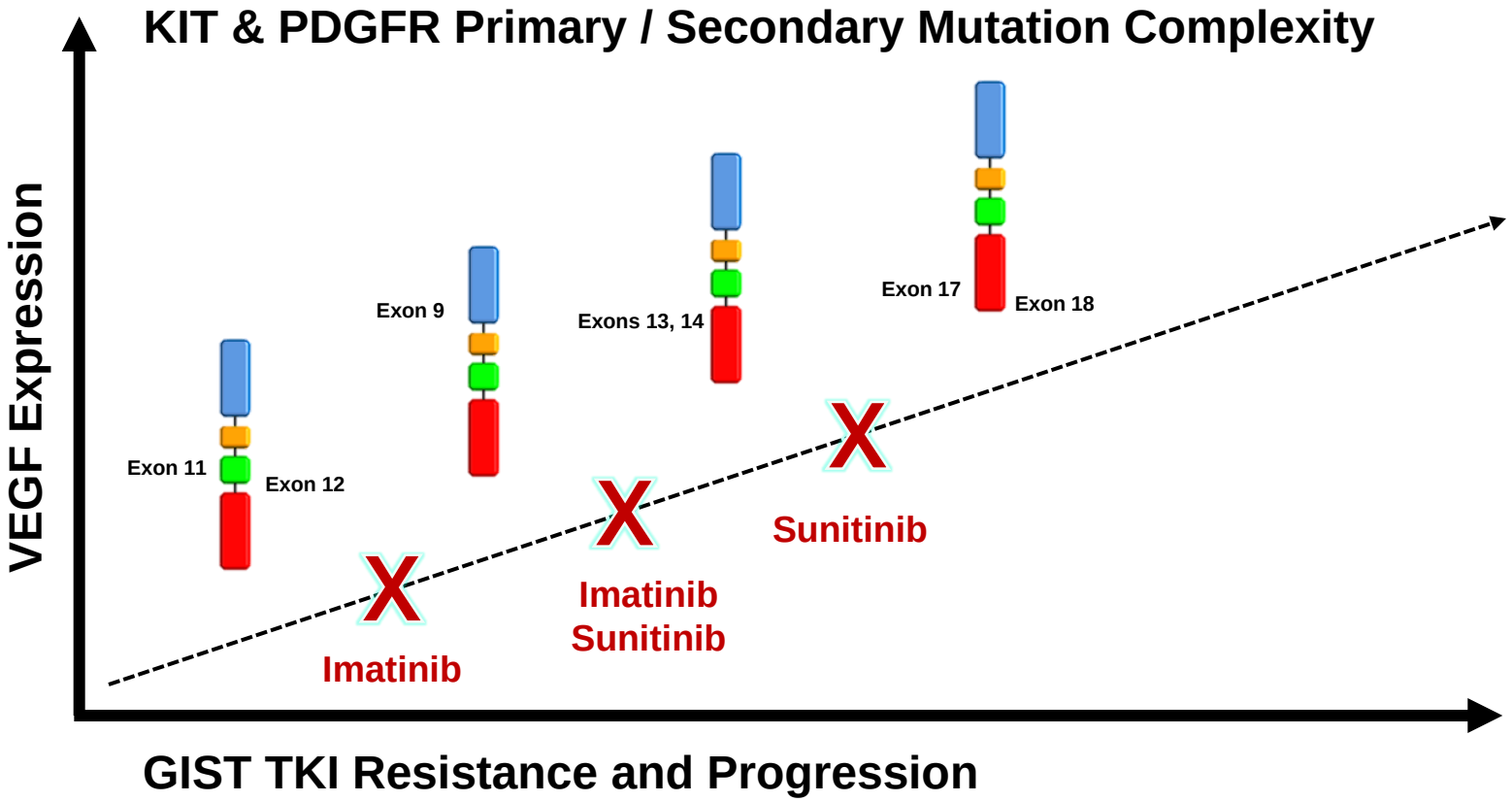
GIST Support International website. www.gistsupport.org/about-gist/mutation-analysis-kit-and-pdgfra.php. Accessed September 11, 2012.

Benefits of Multikinase Inhibitors as Therapeutic Agents



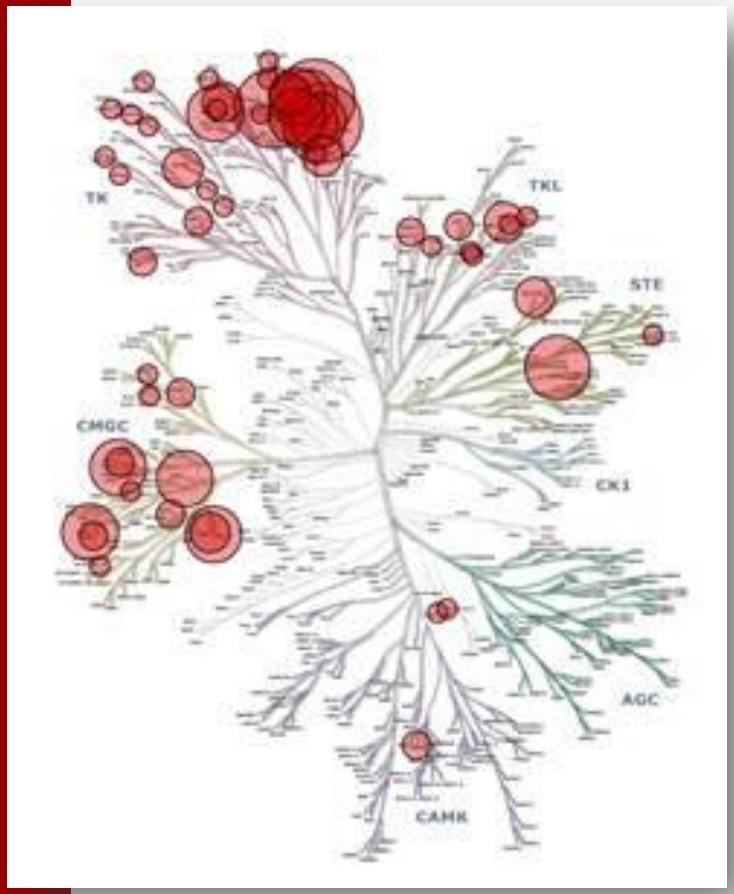
1. Wilhelm S, et al. *Cancer Res.* 2004;64;7099-7109; 2. Carlomagno F, et al. *J Natl Cancer Inst.* 2006;98:326-334; 3. Heath VL, et al. *Nat Rev Clin Oncol.* 2009;6(7):395-404.

Therapeutic Disruption of Oncogene Addiction



1. Imamura M, et al. *Mod Pathol*. 2007;20:529-537; 2. Demetri GD. *Semin Oncol*. 2011;38 (Suppl 1):S10-S19.

Regorafenib (BAY 73-4506) Is a Structurally Distinct Oral Inhibitor of Multiple Kinases



Percent control

- 0%
- 0.1%
- 0.1%-1%
- 1%-5%
- 5%-10%
- 10%-35%

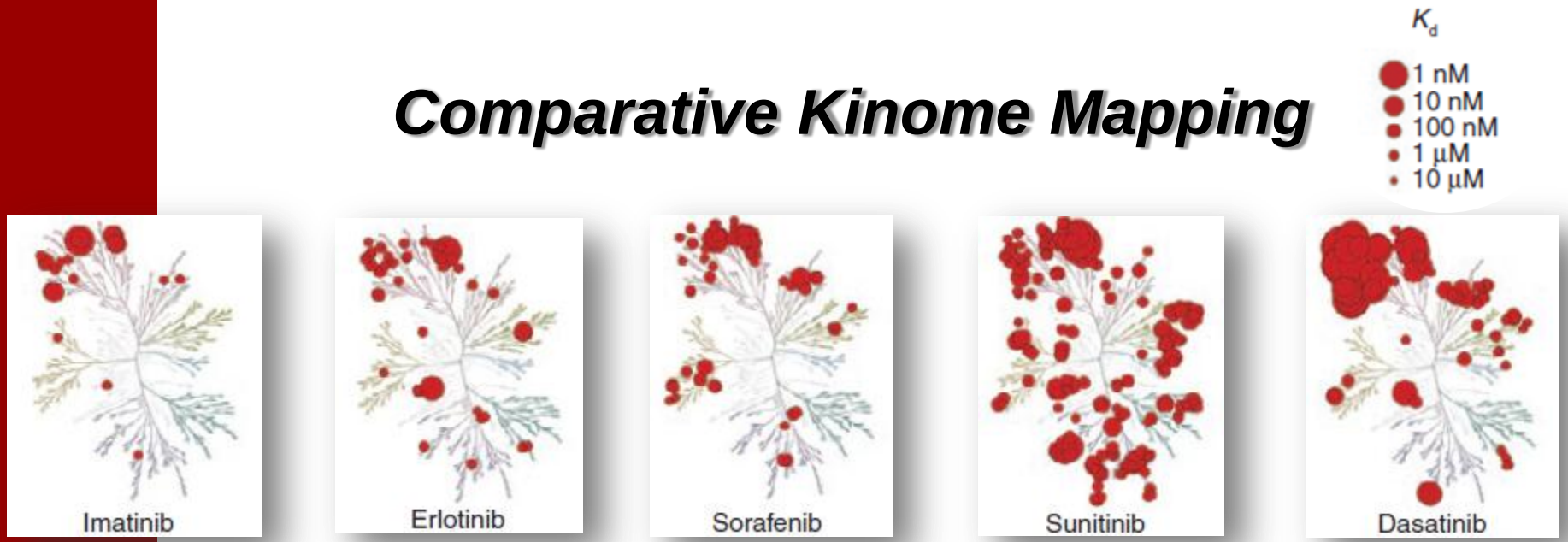
Biochemical Activity

	IC_{50} (nmol/l)
KIT	7
VEGFR-1	13
Murine VEGFR-2	4
PDGFR-β	22
RET	1.5
B-RAF	28
FGFR1	202

Wilhelm SM, et al. *Int J Cancer.* 2011;129:245-255.

Biologic Specificity and Potency of Diverse Multikinase Inhibitors

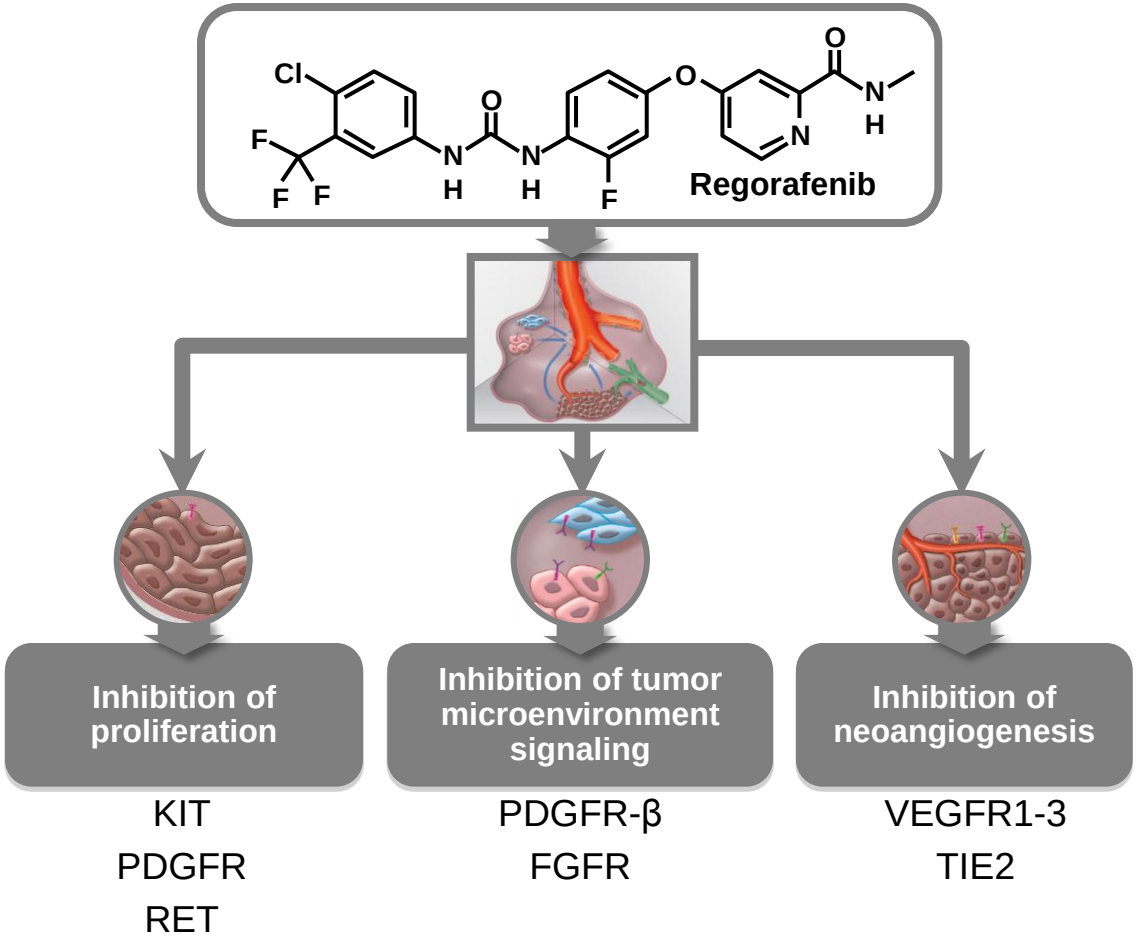
Comparative Kinome Mapping



Promiscuity and affinity drives tolerability and efficacy

Karaman MW, et al. *Nat Biotechnol.* 2008;26(1):127-132.

Regorafenib (BAY 73-4506), an Oral Multikinase Inhibitor Targeting Multiple Tumor Pathways[1-3]



1. Wilhelm SM, et al. *Int J Cancer.* 2011;129(1):245-255; 2. Mross K, et al. *Clin Cancer Res.* 2012;18(9):2658-2667; 3. Strumberg D, et al. *Expert Opin Investig Drugs.* 2012;21(6):879-889.

Summary

- Mutations identified in an individual cancer, whether driver or passenger, can be used as a specific biomarker to guide patient management[1]
- Selective co-targeting of multiple hallmark capabilities in mechanism-guided combinations will result in more effective and durable therapies for cancer[2]
- Signaling pathways controlled by tyrosine kinases offer unique opportunities for pharmacological intervention[3-5]
- Regorafenib is potentially a new approach in the management of patients with mCRC and refractory GIST [6-7]

1. Sjoblom T, et al. *Science.* 2006;314:268-274; 2. Hanahan D, et al. *Cell.* 2011;144:646-674; 3. Wilhelm S, et al. *Cancer Res.* 2004;64:7099-7109; 4. Carlomagno F, et al. *J Natl Cancer Inst.* 2006;98:326-334; 5. Heath VL, et al. *Nat Rev Clin Oncol.* 2009;6(7):395-404; 6. Van Cutsem E, et al. Oral abstract presented at ASCO 2012. *J Clin Oncol*. 2012;30: (suppl). Abstract 3502; 7. Demetri G, et al. Oral abstract presented at ASCO 2012. *J Clin Oncol*. 2012;30:(suppl). Abstract LBA10008.