THE MOLECULAR DIVERSITY OF "WILD-TYPE" GIST

Maria Debiec-Rychter, M.D., Ph.D.
Department of Human Genetics
KU Leuven, Belgium

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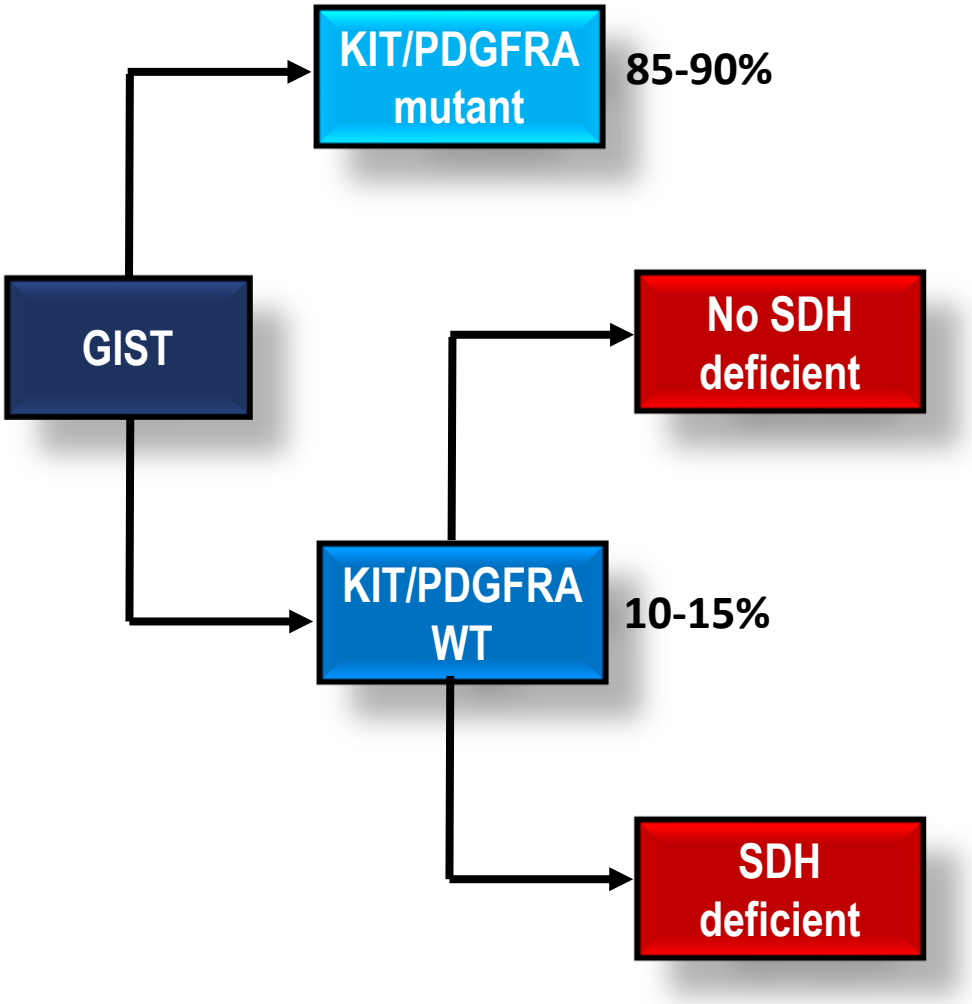
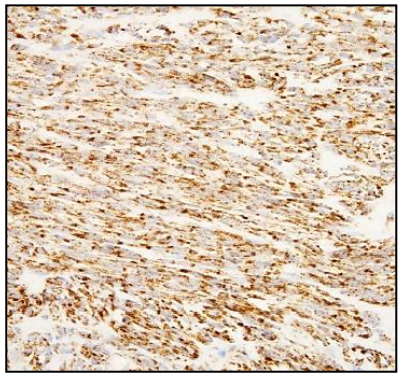
DISCLOSURE SLIDE

No conflict of interest to declear

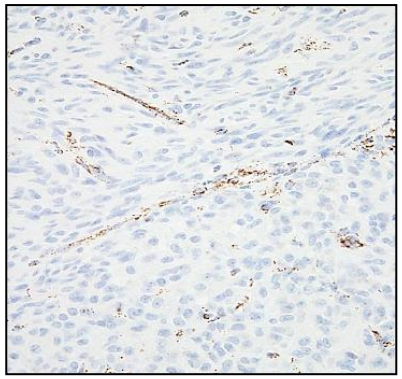
MOLECULAR HETEROGENEITY OF GIST





SDHB (+)

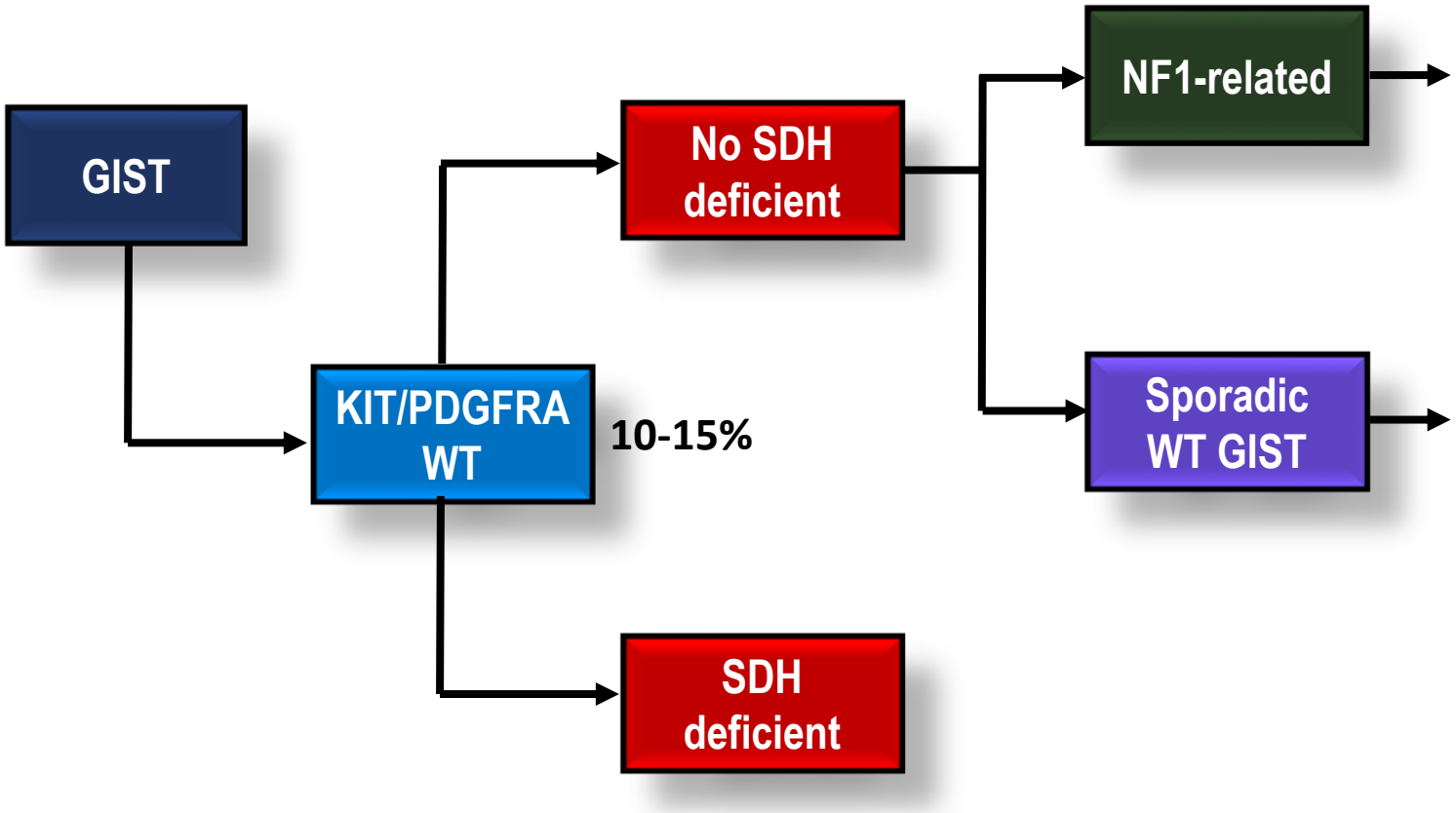
SDHB-immunostaining



SDHB (-)

Boikos&Stratakis, *Endocrine* 2014; 47:401-408
Nannini et al. *BMC Cancer* 2014; 14:685

SDHB-IMMUNOPOSITIVE WT GIST



Miettinen&Lasota, *Int J Biochem Cell Biol*. 2014
Pantaleo et al. *Cancer Med*. 2015; 4:101-103

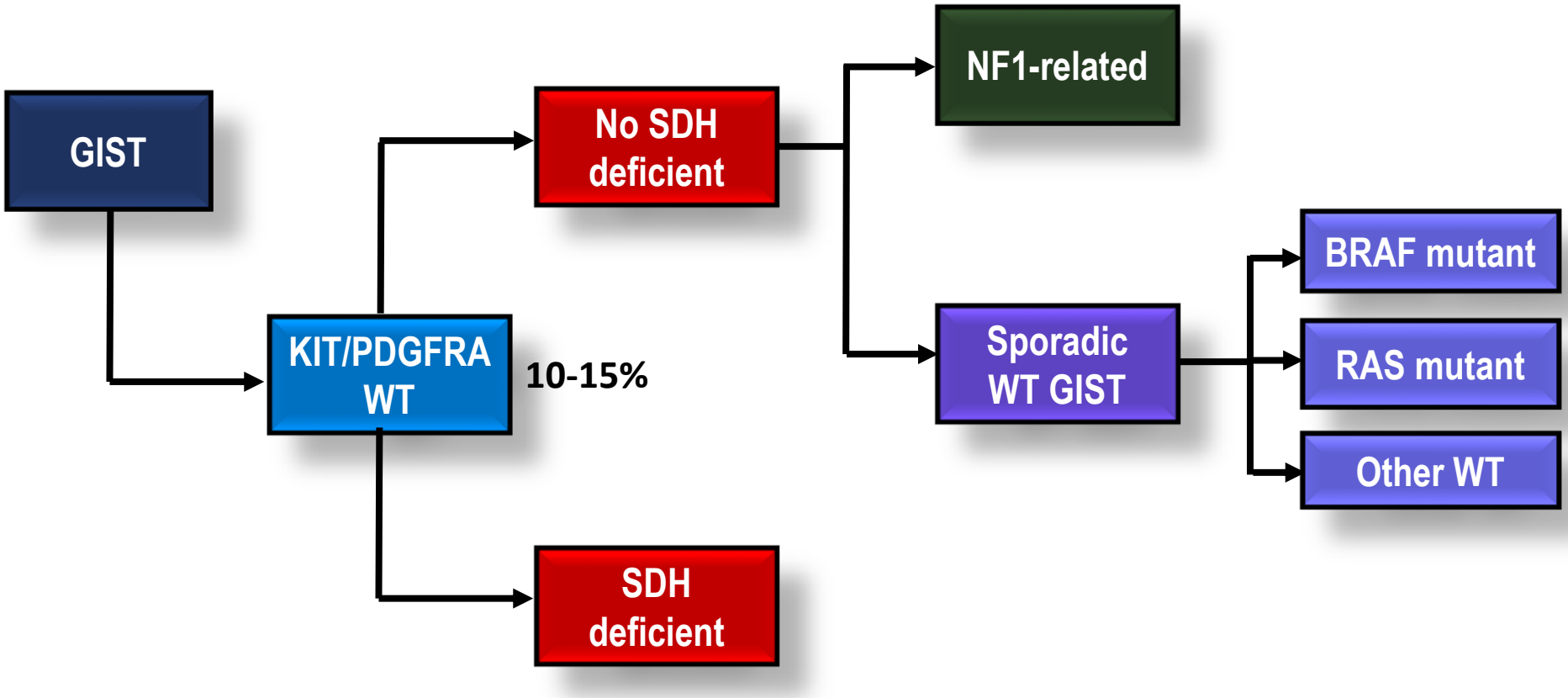
NF-1 ASSOCIATED GIST

- Neurofibromatosis type 1
  - Cuased by germ-line *NF1* mutation (frequency 1/3000)
  - Autosomal dominant inheritance pattern
  - Familial tumor syndrome (benign neurofibromas, MNPST, gliomas, GISTs, juvenilne monocytic leukemia)
- NF-1 GIST
  - 200-fold increased risk of GIST
  - >70% located in the duodenum or small bowel
  - Can be multi-focal
  - ~90% without activating *KIT*/*PDGFRA* mutations
  - Activation of the MAPK pathway

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

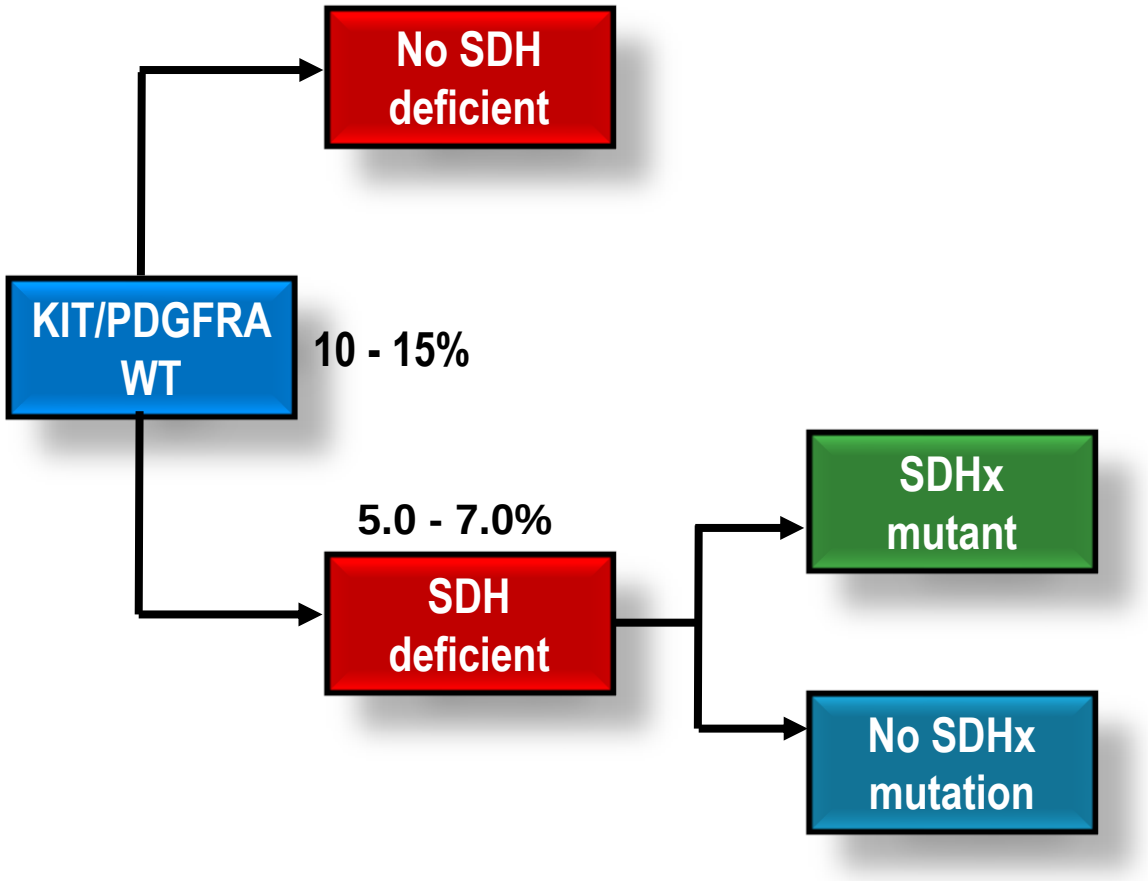
Maertens et al. *Hum Mol Genet*. 2006; 15:1015-23
Wang et al. *J Cancer* 2011; 2:90-93

SDHB-IMMUNOPOSITIVE WT GIST



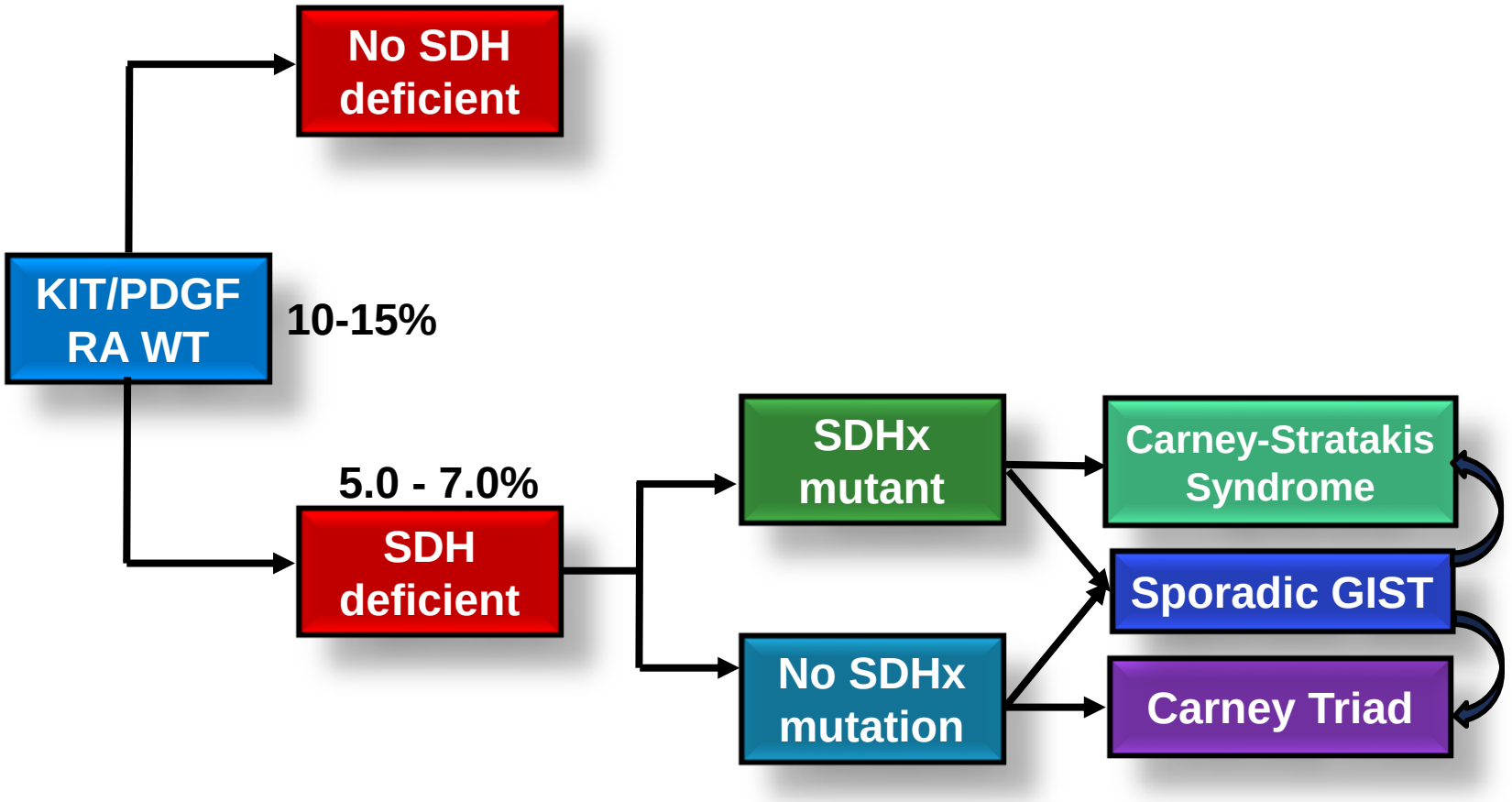
Martens et al. *Human Mol Genet* 2006; 15:1015
Miettinen&Lasota, *Int J Biochem Cell Biol*. 2014
Pantaleo et al. *Cancer Med*. 2015; 4:101-

SDHB-IMMUNONEGATIVE GIST



Pantaleo et al. *Eur J Hum Genet*. 2014; 22:32-39
Boikos&Stratakis, *Endocrine* 2014; 47:401-408
Miettinen&Lasota, *Int J Biochem Cell Biol*. 2014

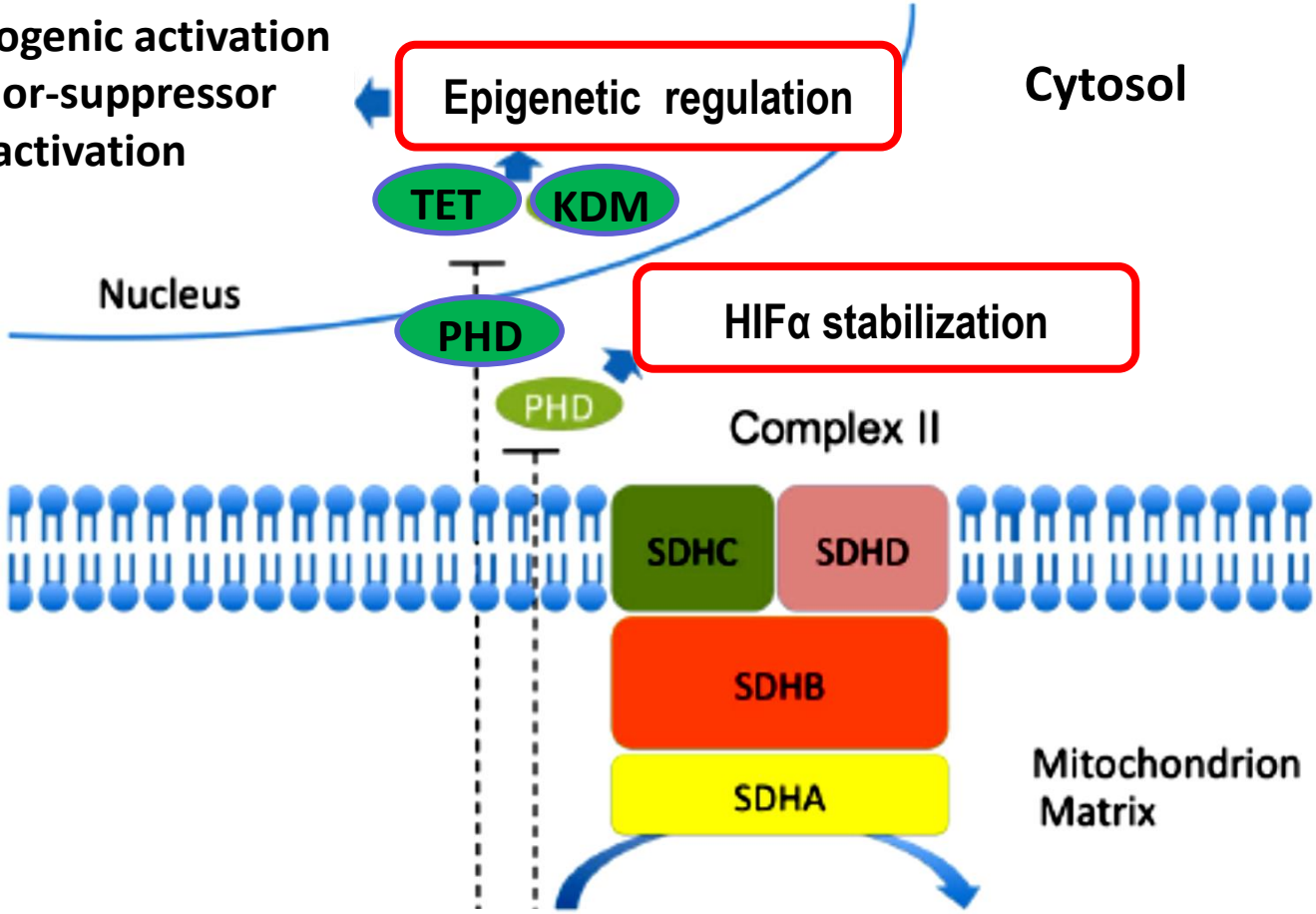
SDHB-IMMUNONEGATIVE GIST



Killian et al. *Science Transl Med*. 2014; 6:268
Haller et al. *Endocr Relat Cancer* 2014; 21:567-577

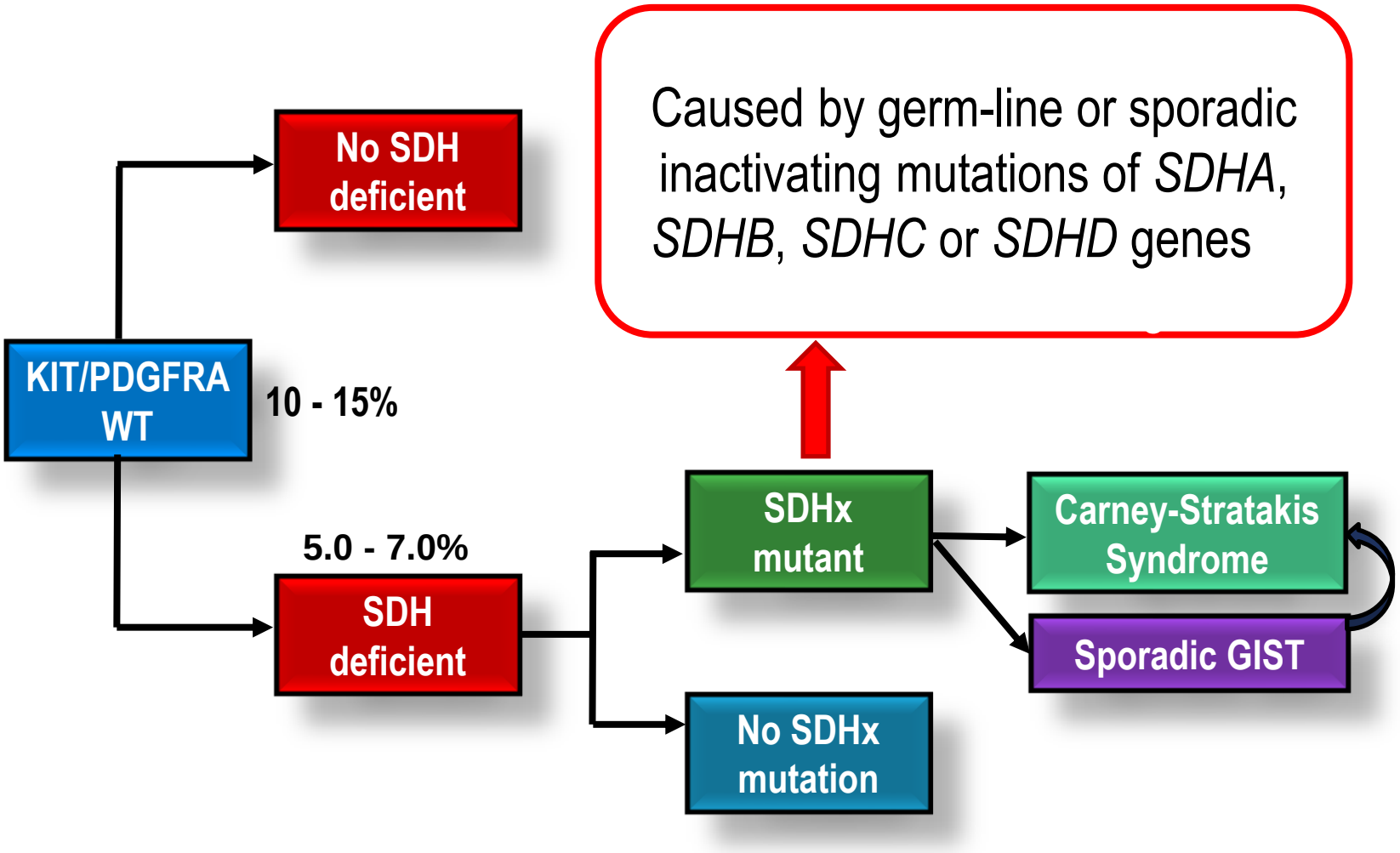
SDH-DEFICIENT GIST ARE CHARACTERIZED BY SDH-COMPLEX INACTIVATION

- **Oncogenic activation**
- **Tumor-suppressor inactivation**



Janeway et al. *PNAS* 2011; 108:314-318
Pantaleo et al. *Eur J Hum Genet*. 2014; 22:32-39
Miettinen&Lasota, *Int J Biochem Cell Biol*. 2014

SDHB-IMMUNONEGATIVE GIST



Pantaleo et al. *Eur J Hum Genet*. 2014; 22:32-39
Boikos&Stratakis, *Endocrine* 2014; 47:401-408
Miettinen&Lasota, *Int J Biochem Cell Biol*. 2014

CARNEY-STRATAKIS SYNDROME (CARNEY DYAD)

- Hereditary condition, autosomal dominant inheritance pattern, incomplete penetrace
- Caused by germ-line inactivating mutations of *SDHB* (10%), *SDHC* (80%) or *SDHD* (10%) genes

  (the same mutations are found in paraganglioma hereditary syndrome)
- Mutations lead to loss of expression of the protein
- Multifocal, gastric GISTs, SDHB-immunonegative
- Imatinib treatment might be less effective than in sporadic *KIT*/*PDGFRA*-mutant GISTs

Pasini et al. *Eur J Hum Genet*. 2008; 16:79-88
Janeway et al. *PNAS* 2011; 108:314-318
Pantaleo et al. *Eur J Hum Genet*. 2014; 22:32-39

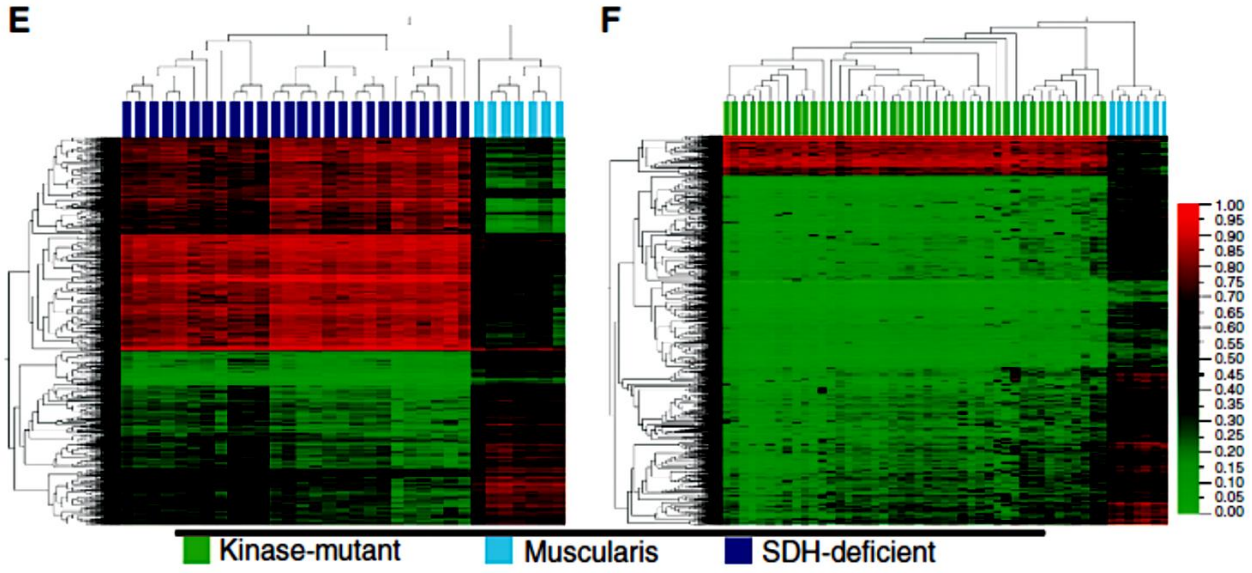
DIVERGENCE BETWEEN THE DNA METHYLATION PROFILES OF SDH-DEFICIENT GIST *VS*. KIT-MUTATED GIST

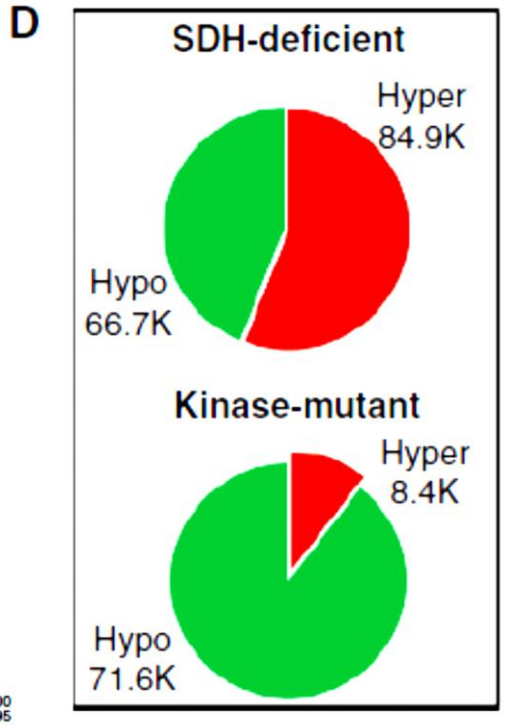
648 | CANCER DISCOVERY JUNE 2013

RESEARCH BRIEF

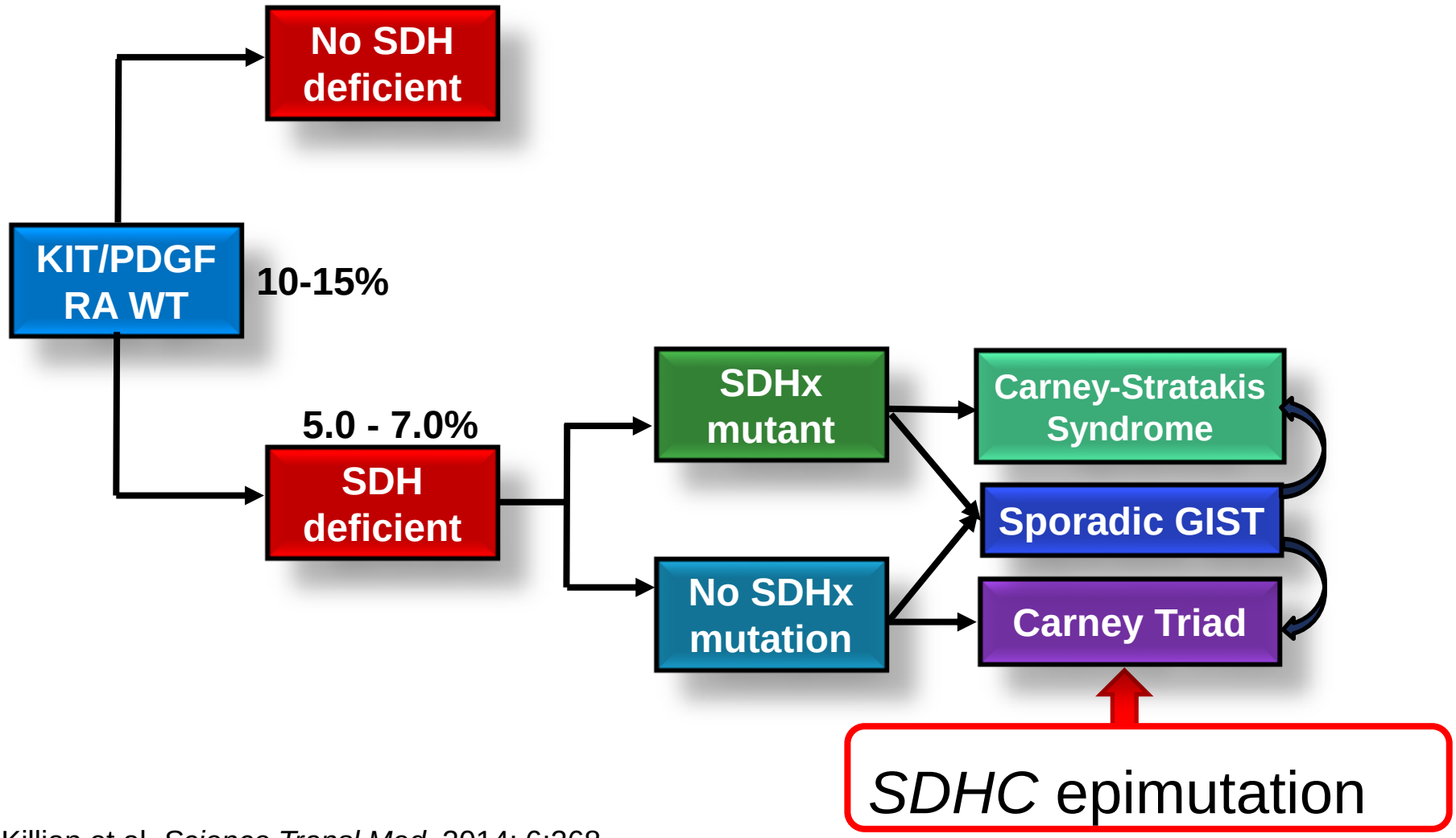
Succinate Dehydrogenase Mutation Underlies Global Epigenomic Divergence in Gastrointestinal Stromal Tumor

J. Keith Killian[1], Su Young Kim[1], Markku Miettinen[1], Carly Smith[1], Maria Merino[1], Maria Tsokos[1], Martha Quezado[1], William I. Smith Jr[2], Mona S. Jahromi[4], Paraskevi Xekouki[3], Eva Szarek[3], Robert L. Walker[1], Jerzy Lasota[1], Mark Raffeld[1], Brandy Klotzle[5], Zengfeng Wang[1], Laura Jones[1], Yuelin Zhu[1], Yonghong Wang[1], Joshua J. Waterfall[1], Maureen J. O'Sullivan[7], Marina Bibikova[5], Karel Pacak[3],





SDHB-IMMUNONEGATIVE GIST



Killian et al. *Science Transl Med*. 2014; 6:268
Haller et al. *Endocr Relat Cancer* 2014; 21:567-577

CARNEY TRIAD

Non-familial association of different tumor types

- Multifocal, gastric, epithelioid type of **GIST**, frequently CD117-immunonegative
- **Pulmonary chondromas** (usually multiple)
- **Paragangliomas**
- Less frequently: Pheochromocytomas / Adrenal adenomas, Esophageal leiomyoma

Only 20% all three components

Female predilection, young age at diagnosis

Lymph node involvement

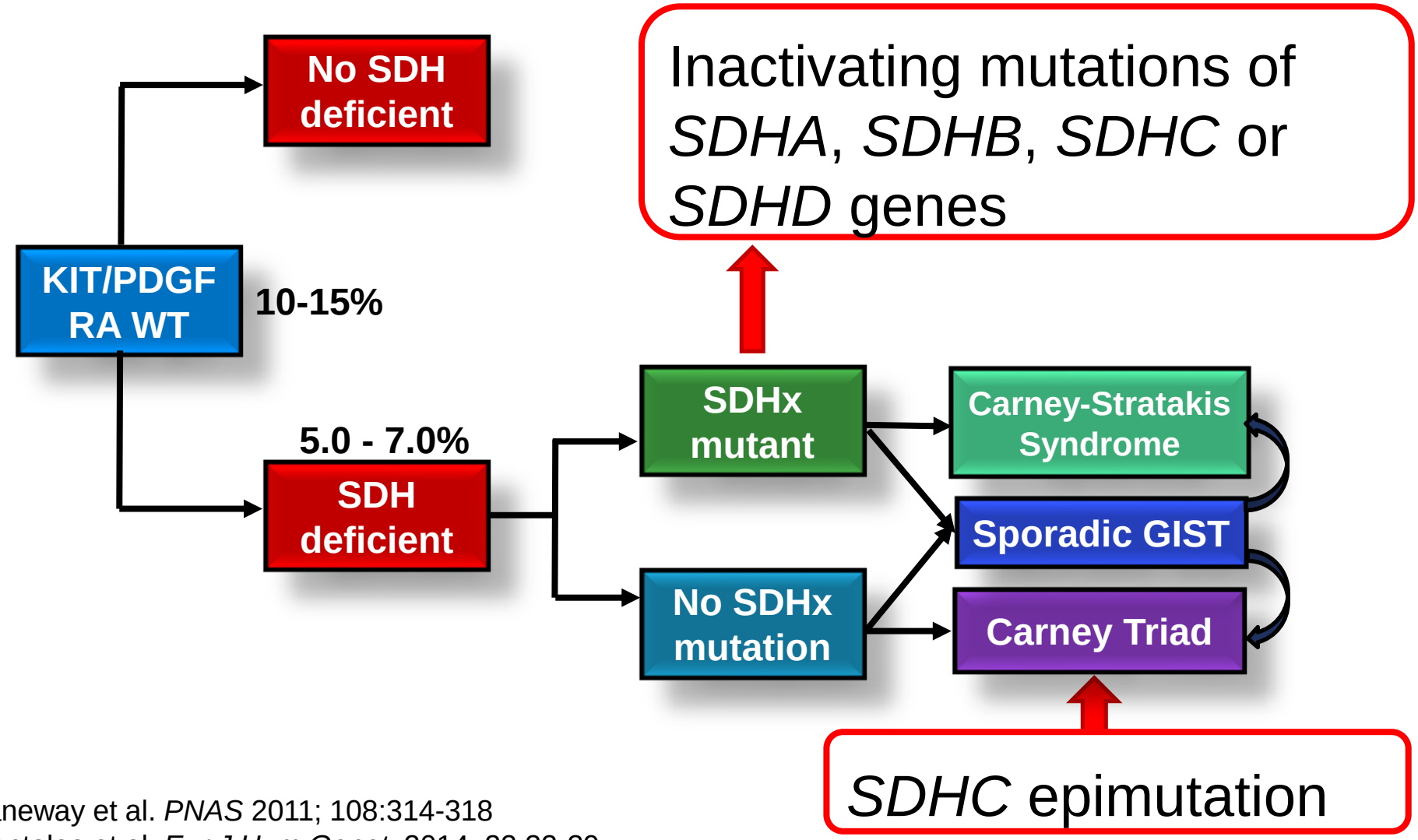
Caused by primary/de novo **SDHC epimutation**

- GIST by IHC: SDHB (-), SDHA (+)

Imatinib less effective than for KIT/PDGRA-mutant GIST

Kim et al. Science Transl Med. 2014, 268ra177
Zhang et al. Am J Surg Pathol. 2010; 34:53-64
Matyakhina et al. J Clin Endocrinol Matab. 2007; 92:2938-43

SDHB-IMMUNONEGATIVE GIST



Janeway et al. *PNAS* 2011; 108:314-318
Pantaleo et al. *Eur J Hum Genet*. 2014; 22:32-39
Miettinen&Lasota, *Int J Biochem Cell Biol*. 2014

NON-SYNDROMIC SDH-DEFICIENT GIST

- Typically occur in children and young adults (85%), female predominance
- Multinodular or multiple, exclusively gastric tumors, common lymphovascular invasion, may remain clinicall stable after metastatic spread
- 50% have *SDH* gene mutation, often germ-line
  - Most commonly *SDHA* (30%) – SDHA-immunonegative, occur at an older age
  - *SDHB*, *SDHC*, *SDHD* (together 20%)
- Hypermethylation of the *SDHC* promoter is an alternative mechanism
- Characterized by the extensive genomic methylation pattern
- Overexpress IGF1R – possible target for the therapy

Nannini et al. *J Med Genet*. 2013; 50:653-661.
Miettinen&Lasota, *Int J Biochem Cell Biol*. 2014; doi:10.1016

CHARACTERIZATION OF *KIT*/*PDGFRA*-WT GIST

RAS-P MUTANTS		SDH DEFICIENT		QUADRUPLE WT
NF-1	RAS-BRAF	SDH mutation	No SDH mutation	No RAS-P / No SDH mutations
SDHB+	SDHB+	SDHB-	SDHB-	SDHB+
IGF1R-	IGF1R-	IGFR+	IGFR+	IGF1R-
Young adults/ Adults	Adults	Pediatric/ Young adults	Pediatric/ Young adults	Any age?
Equal sex	Equal sex	Prevalence of female	Prevalence of female?	Equal sex
Multifocal	Single	Often multifocal	Multifocal?	Single?
Sm.intestine	Gastric/ Sm.intestine	Gastric	Gastric?	Any site?
		Lymph nodes involvement		

Janeway et al *PNAS* 2011; 108:314-318
Nannini et al. *J Med Genet*. 2013; 50:653-661
Kim et al. Science Transl Med. 2014, 268ra177

KIT/PDGFRA "WILD-TYPE" GIST

- The molecular background and underlying mechanisms of this subtype of GIST are heterogenous
- Once a germline SDHx mutation is found in a patient with SDH-deficient GIST, it is very important to screen other members of the family for the same mutation
- WT GIST are less sensitive to tyrosine kinase inhibition
- Optimization of medical management, including clinical test of novel therapies is needed


KU LEUVEN
Thank You
maria.debiec-rychter@
med.kuleuven.be