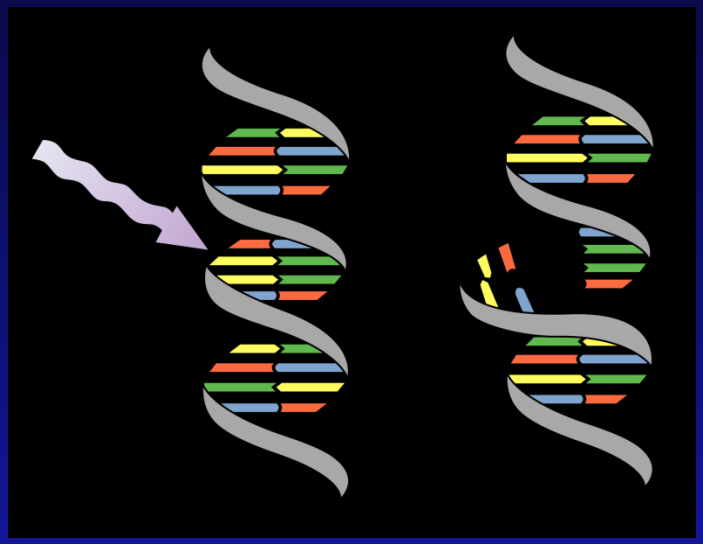
Mutations in Erdheim Chester Disease

Mark Heaney MD PhD

Columbia University Medical Center

What are mutations?

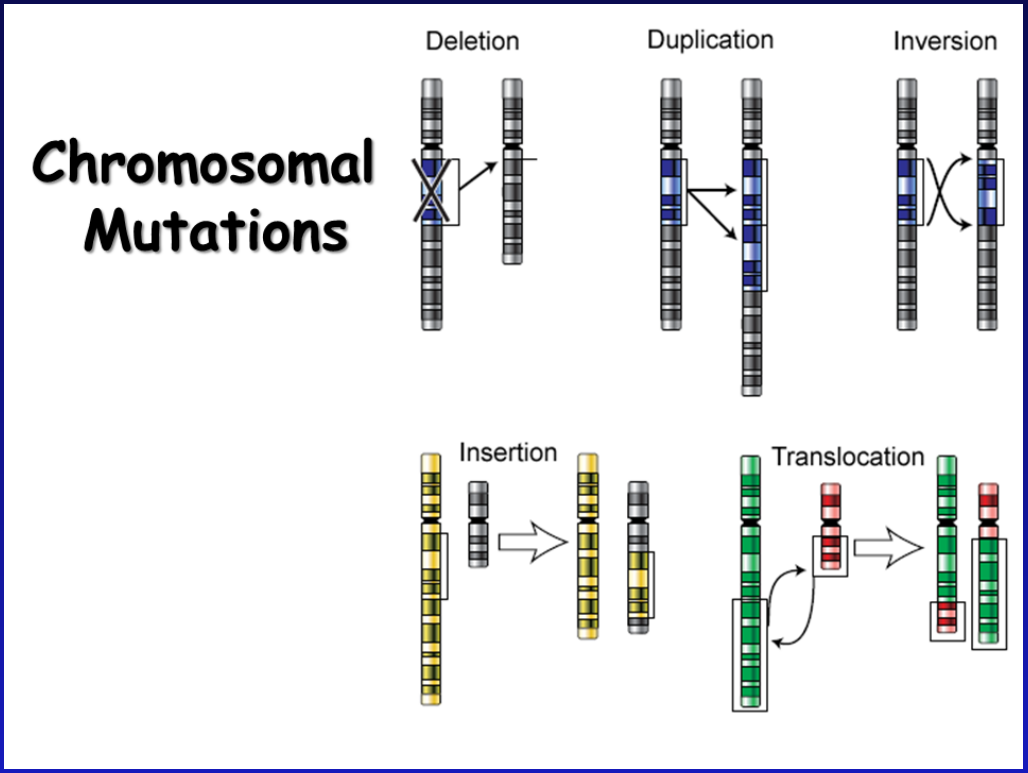
- Mutations are changes in the DNA code



- The DNA code is the template for the proteins that make up the cell

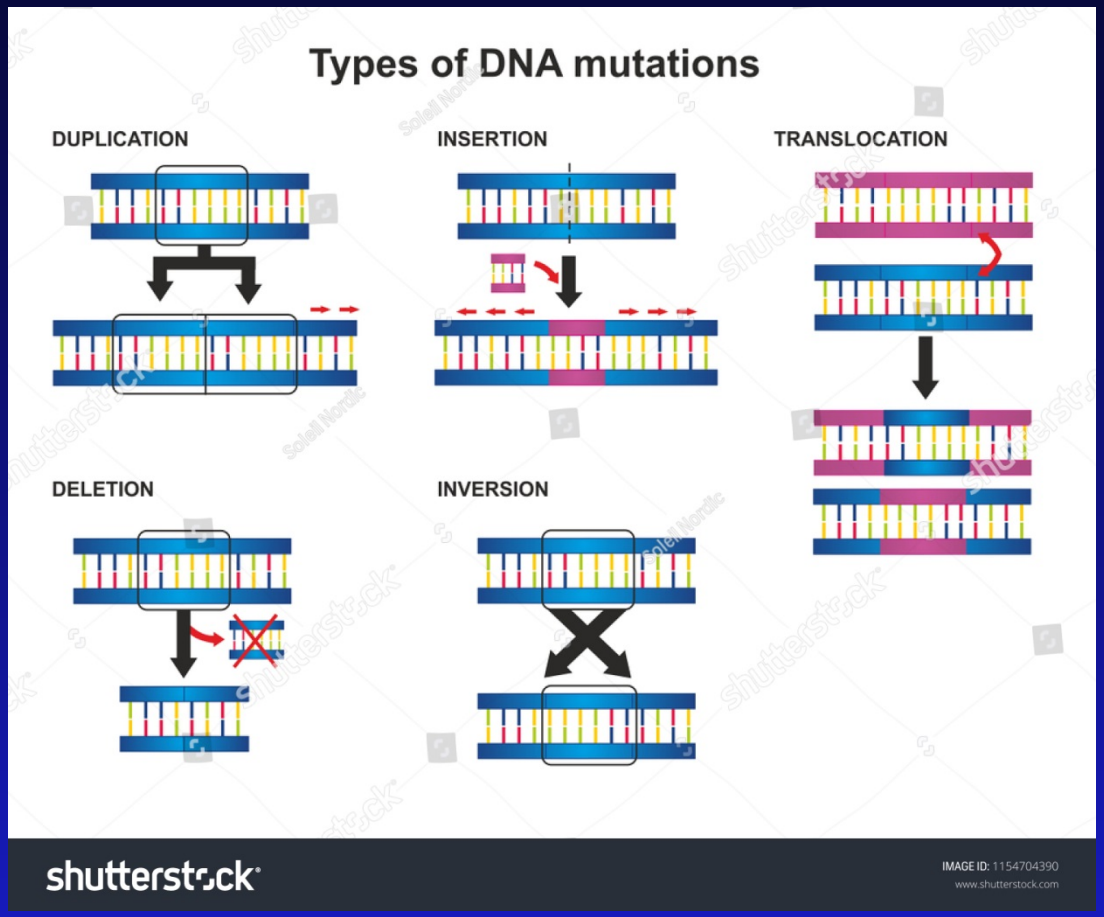
Different kinds of mutations

Some mutations are big--chromosomal mutations



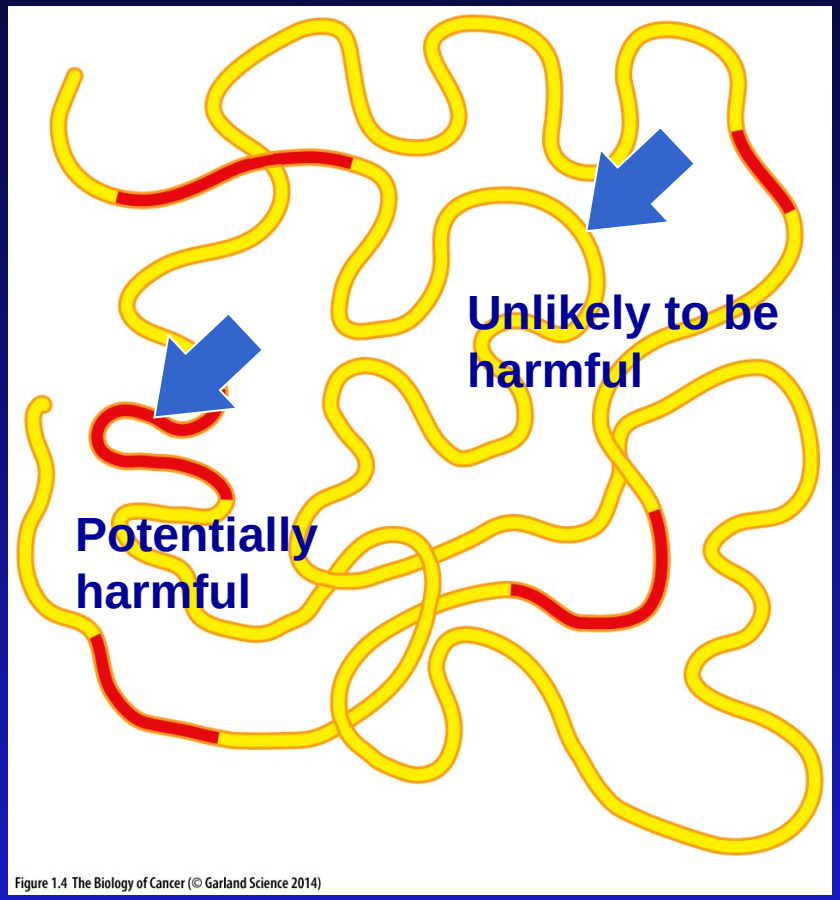
Different kinds of mutations

Some mutations are small



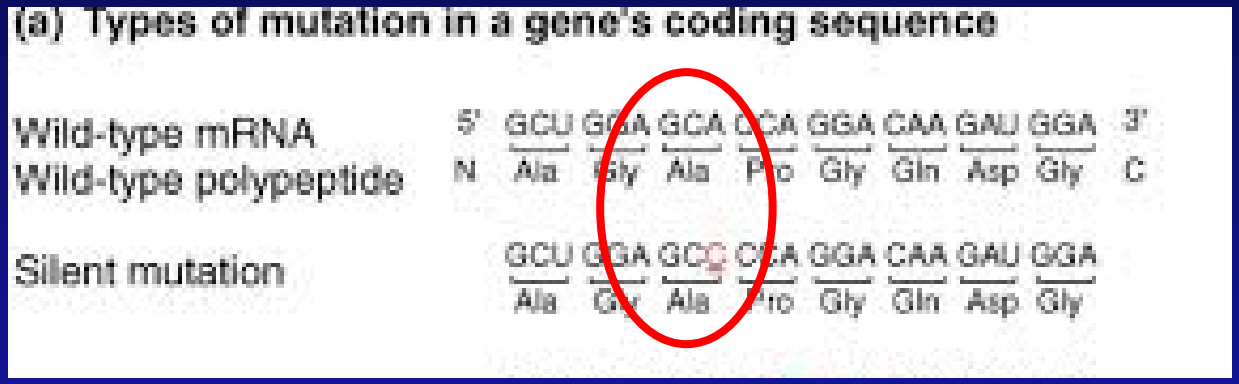
Not all mutations are harmful

Only 2% of human DNA encodes proteins



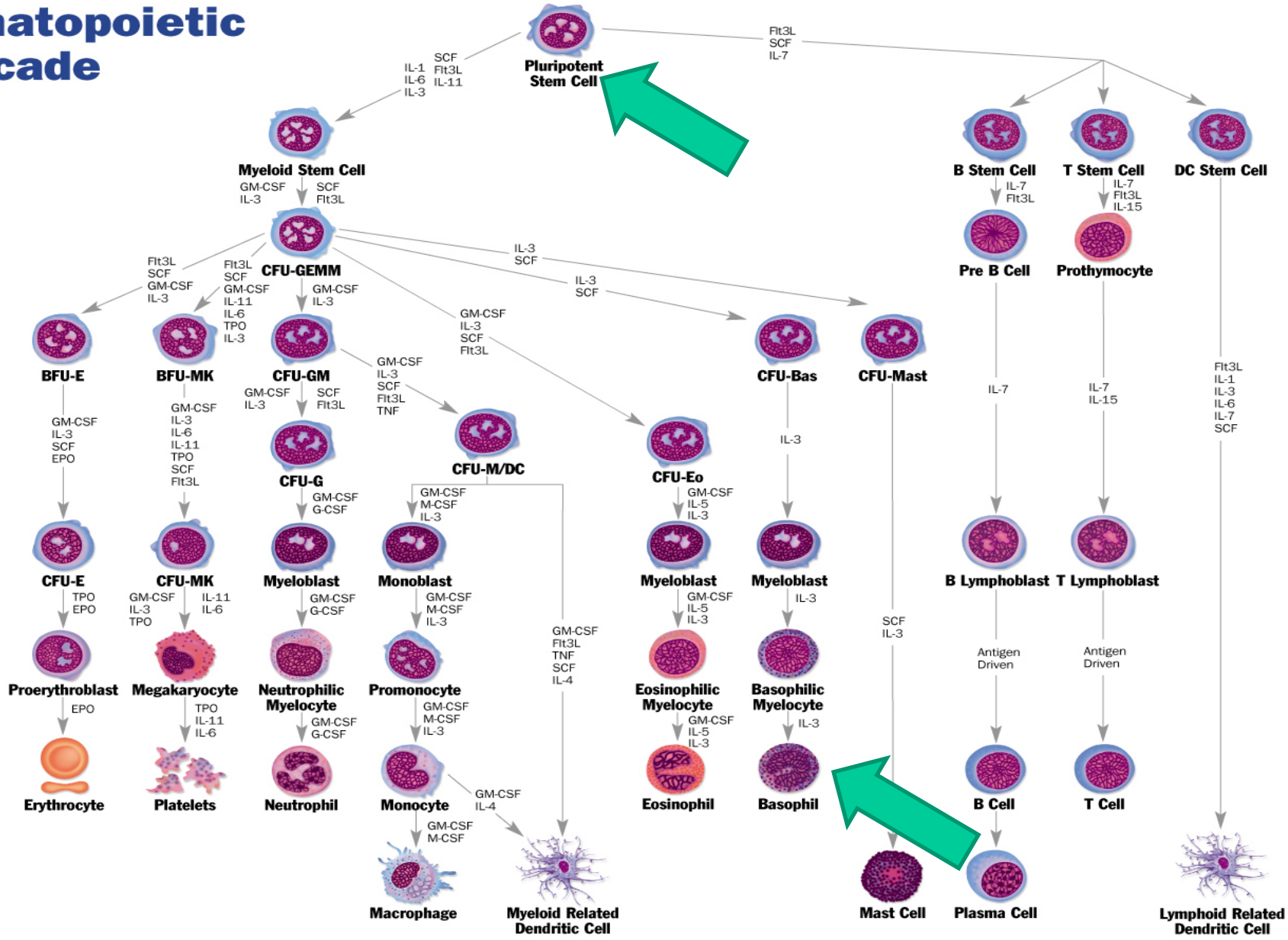
Not all mutations are harmful

"Silent" mutations

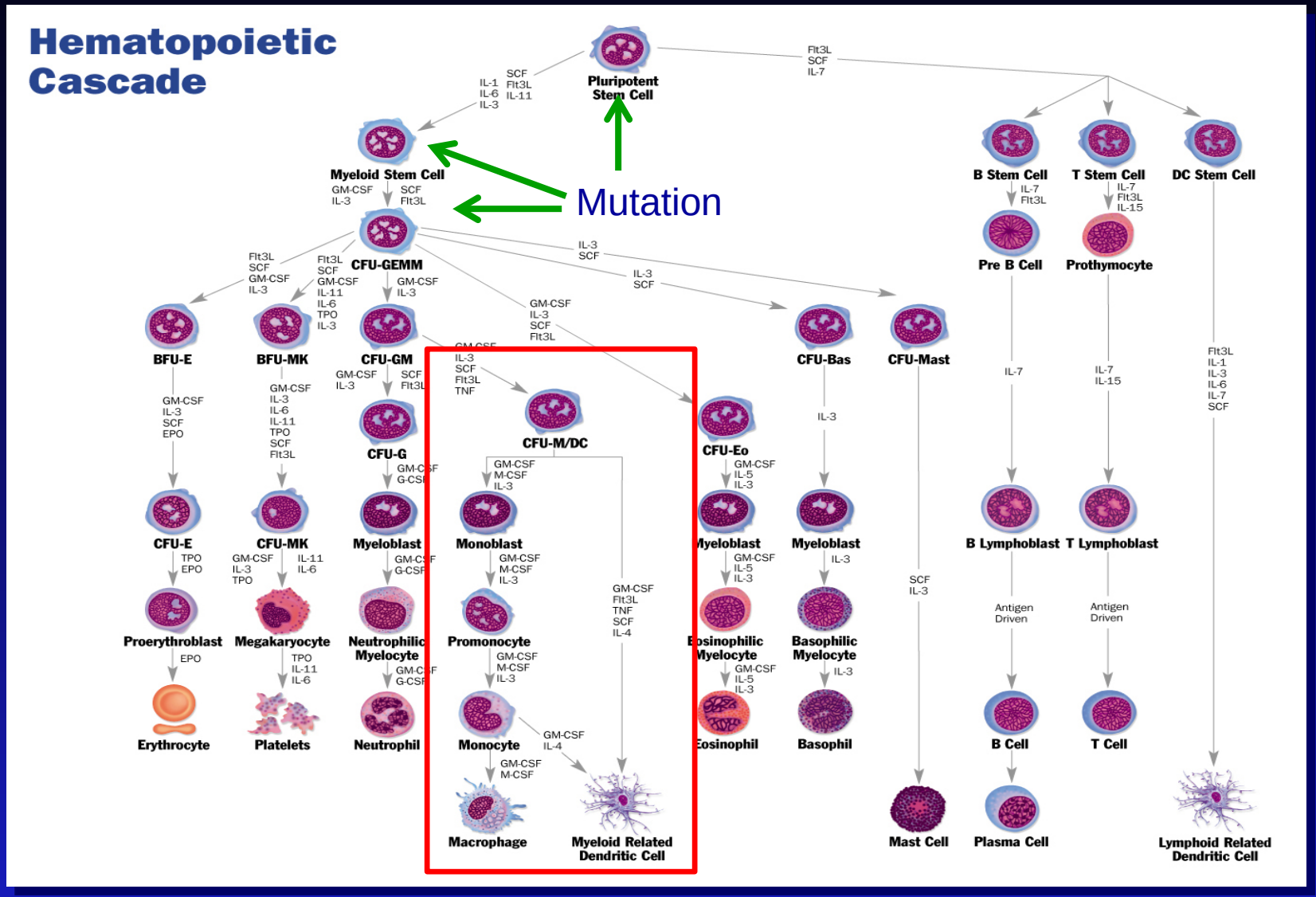


Factors that Affect Mutations

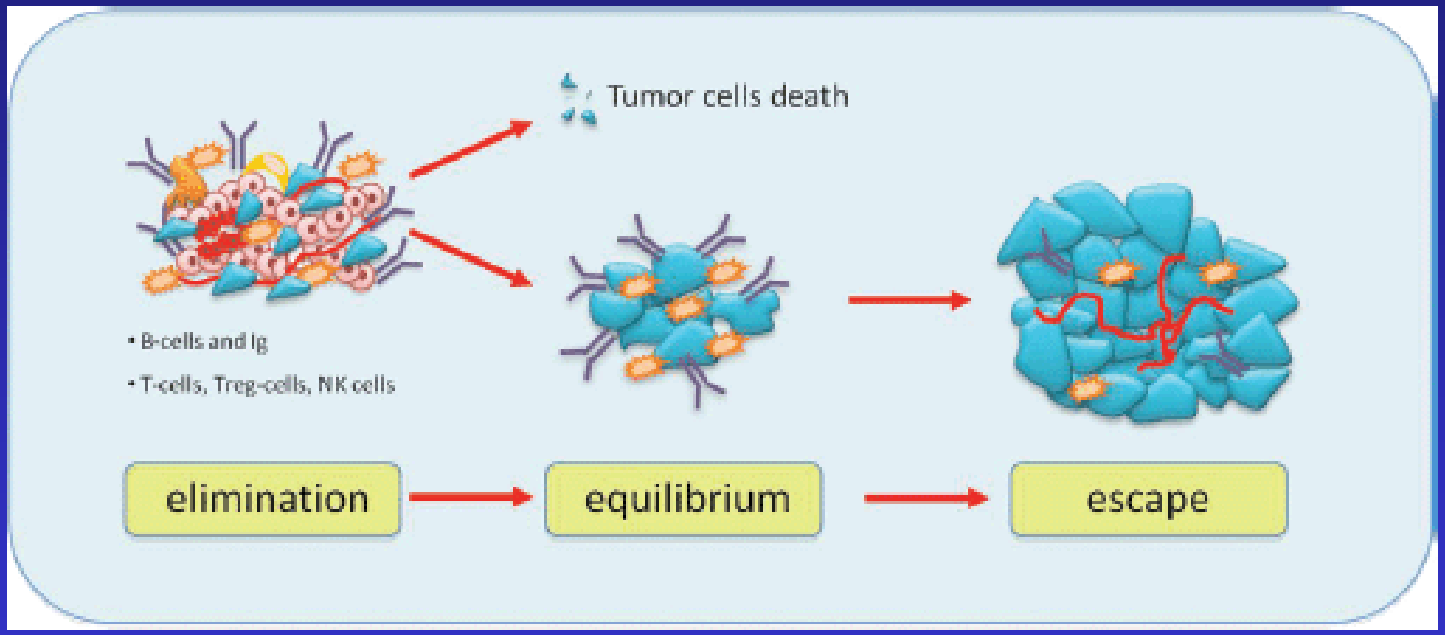
Hematopoietic Cascade



What goes wrong in ECD?



The immune system protects against cancer: Immune surveillance



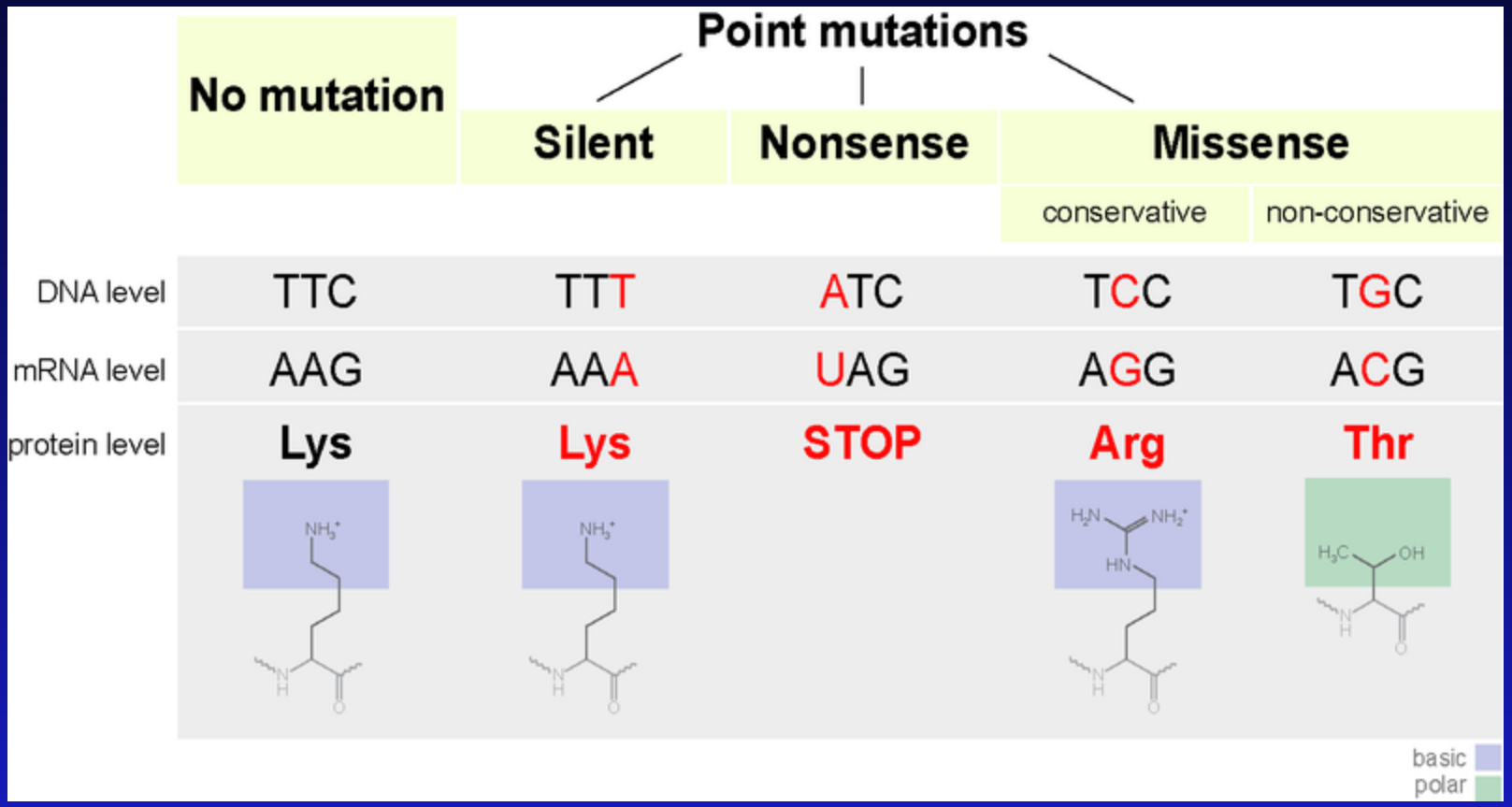
Environmental Carcinogens

Table 2.7 Known or suspected causes of human cancers

Specific carcinogenic agents implicated in the causation of certain cancers[c]	
Cancer	**Exposure**
Scrotal carcinomas	chimney smoke condensates
Liver angiosarcoma	vinyl chloride
Acute leukemias	benzene
Nasal adenocarcinoma	hardwood dust
Osteosarcoma	radium
Skin carcinoma	arsenic
Mesothelioma	asbestos
Vaginal carcinoma	diethylstilbestrol
Oral carcinoma	snuff
ER+ breast cancer[d]	hormone replacement therapy (E + P)[e]

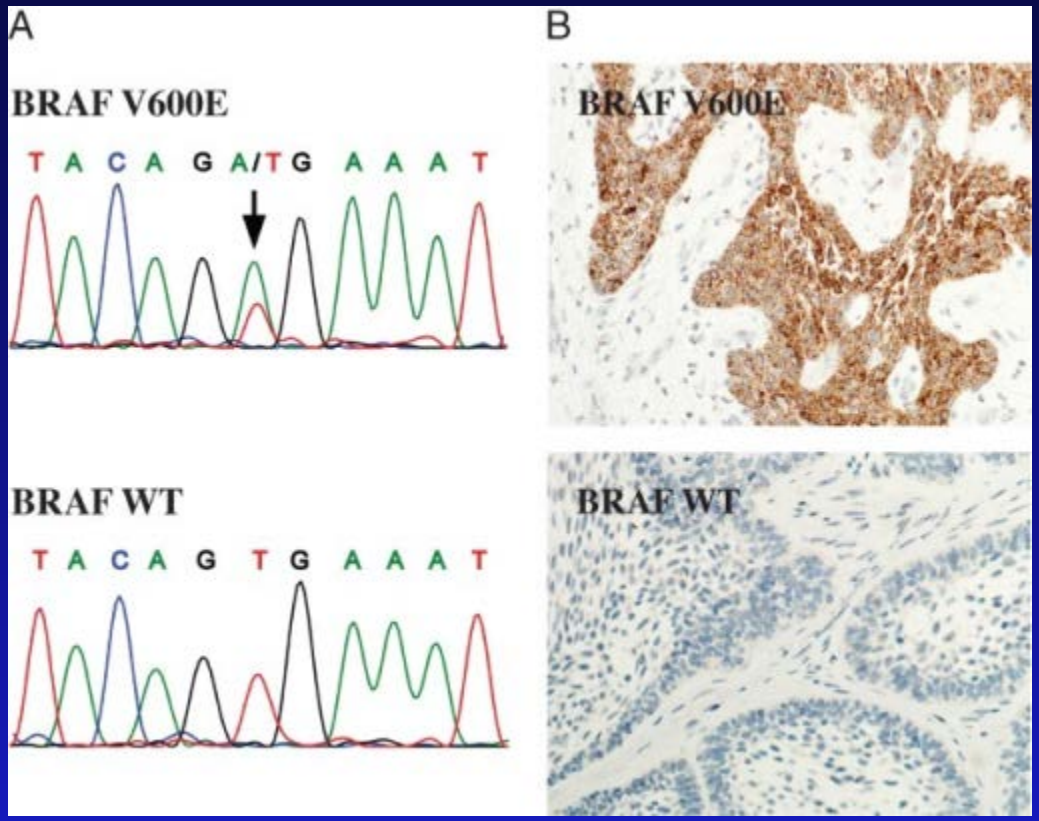
[a]Adapted from American Cancer Society. Cancer Facts & Figures 1990. Atlanta: American Cancer Society, Inc.
[b]A large number of cancers are thought to be provoked by a diet high in calories (see Sidebar 9.10) acting in combination with many of these lifestyle factors.
[c]Adapted from S. Wilson, L. Jones, C. Coussens and K. Hanna, eds., Cancer and the Environment: Gene–Environment Interaction. Washington, DC: National Academy Press, 2002.
[d]ER+, estrogen receptor–positive.
[e]E + P, therapy containing both estrogen and progesterone.

Most mutations in ECD are “missense point” mutations



The Most Common Mutation in ECD is BRAF V600E

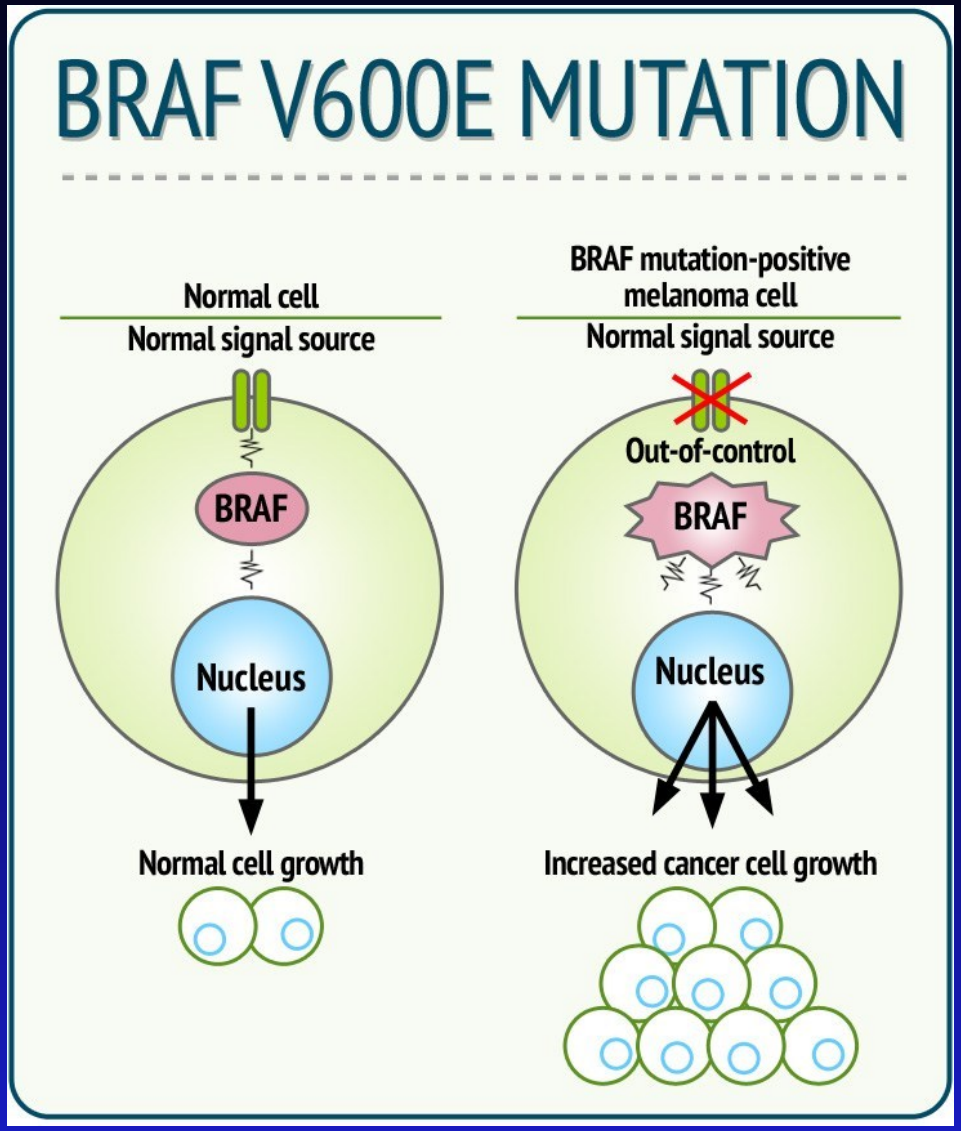
Substitution of the amino acid glutamic acid for valine at position 600



BRAF V600E Mutations

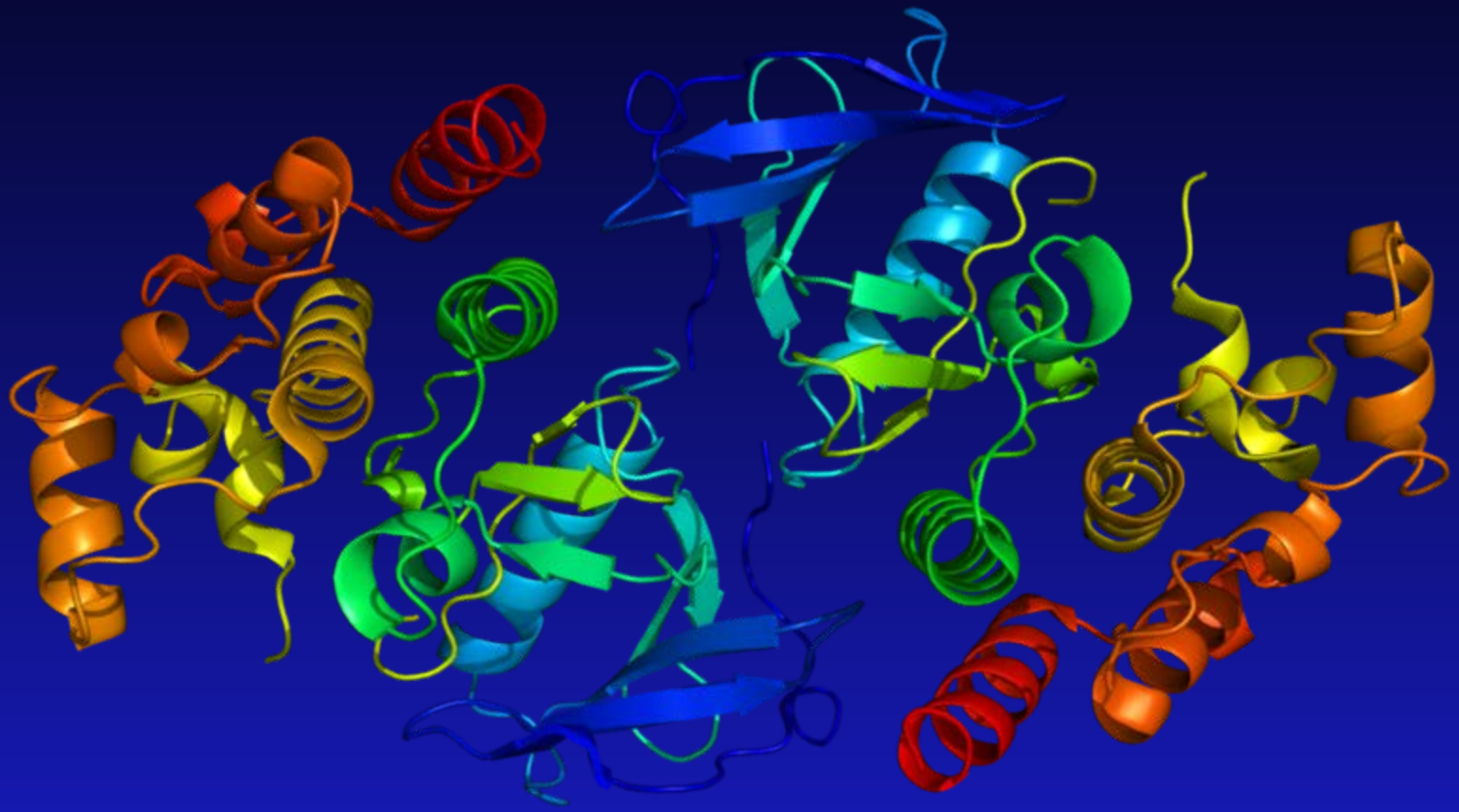
- Melanoma
- Colorectal cancer
- Lung cancer
- Thyroid cancer
- Hairy Cell Leukemia
- Langerhans cell histiocytosis
- Erdheim-Chester Disease

BRAF V600E Mutation



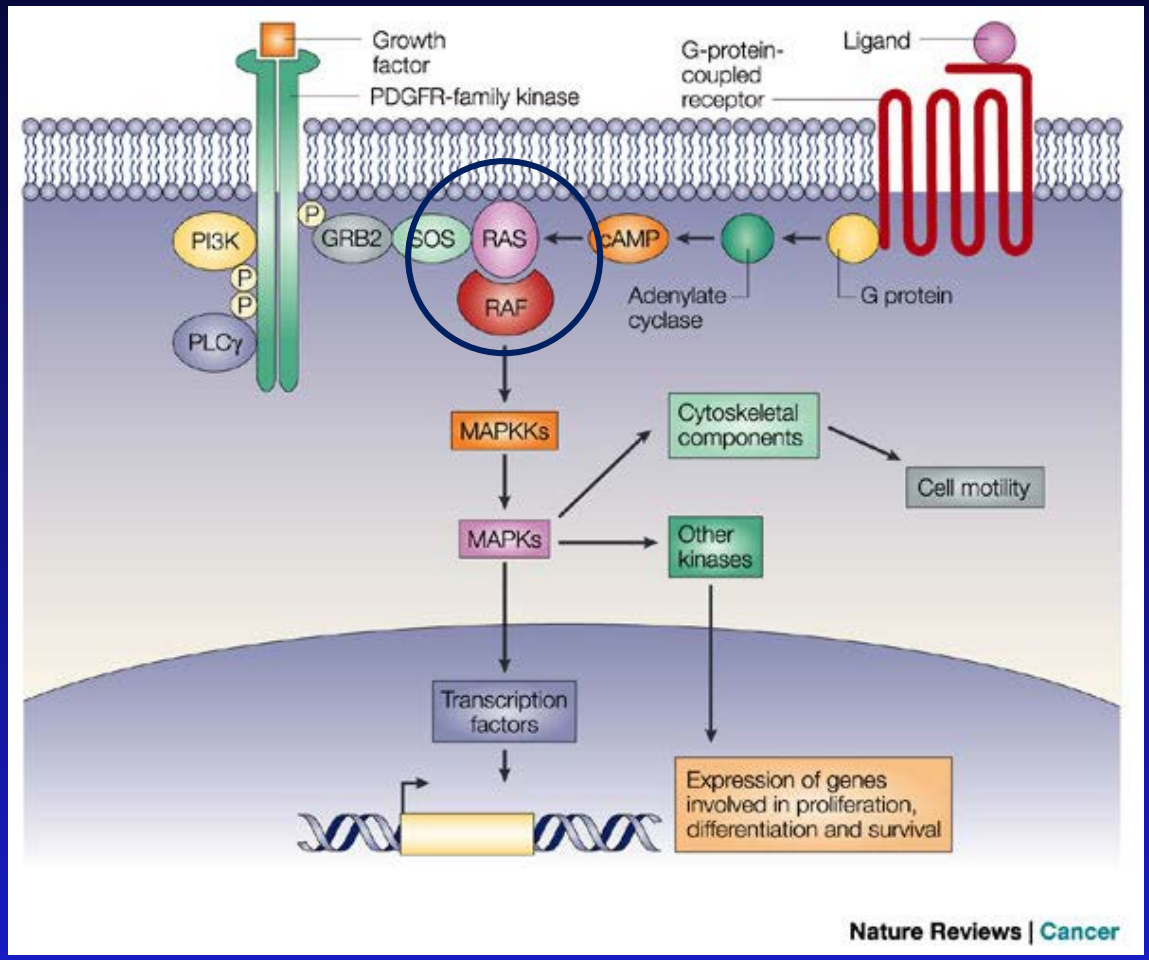
BRAF is a kinase

Kinases transfer phosphate groups from one protein to another

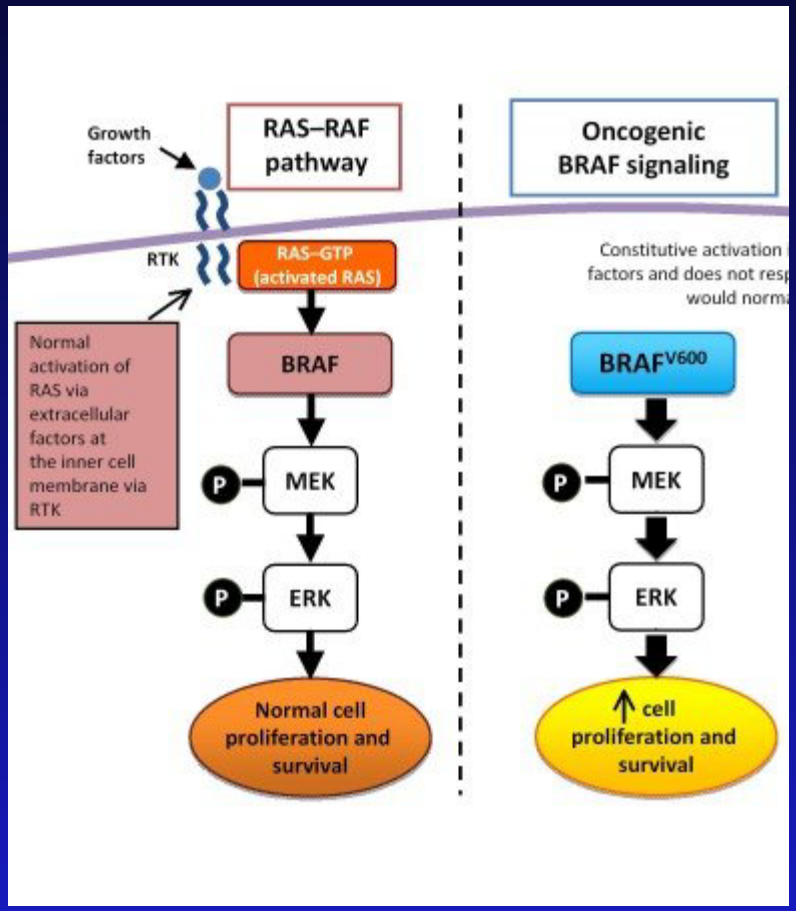


BRAF is a kinase

Kinases transfer phosphate groups from one protein to another as a signal for the cell to grow



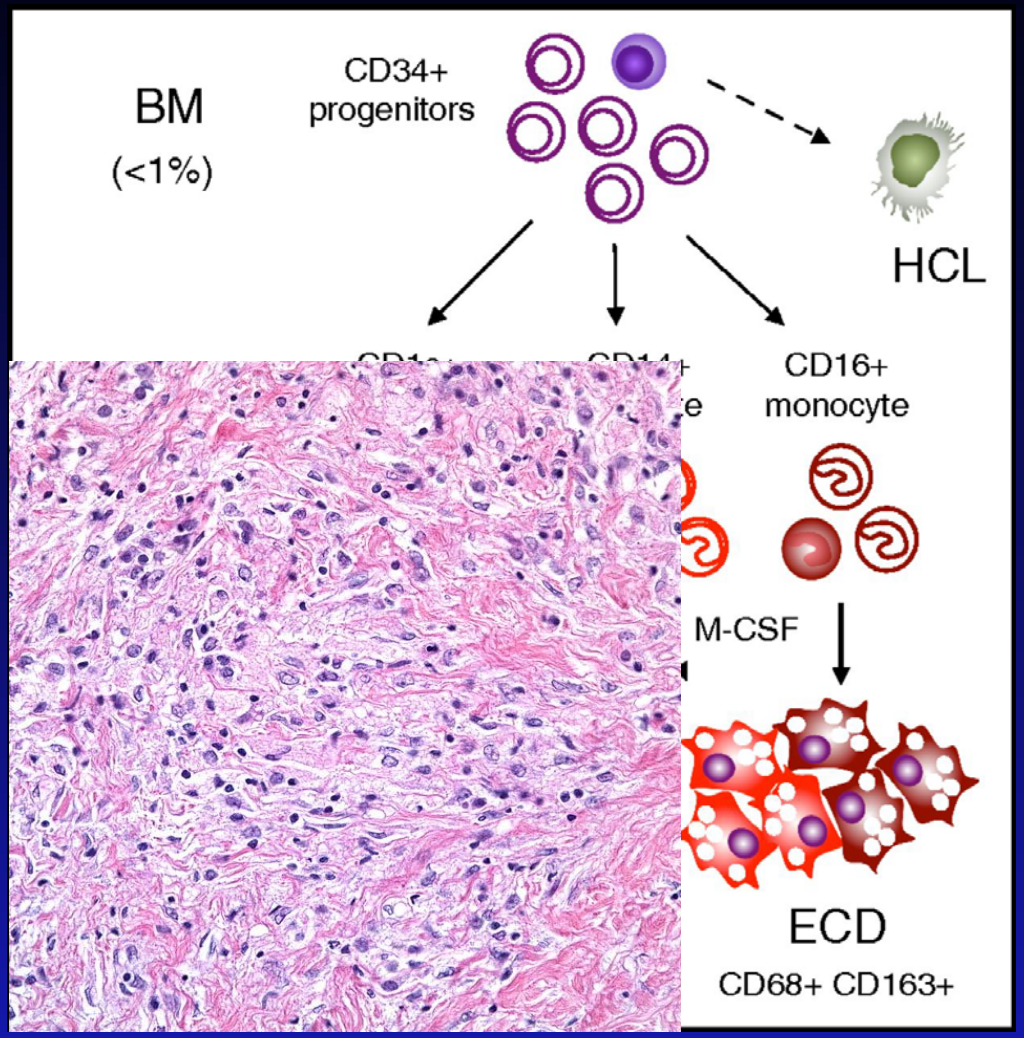
BRAF V600E Mutation Causes the Kinase to be Activated All the Time



ECD Biology

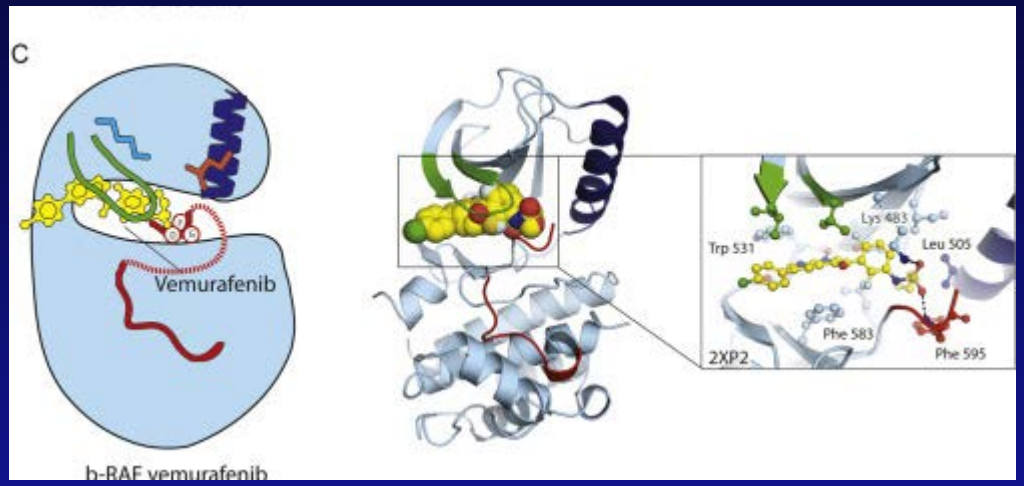
The mutation causes the histiocytes to grow without the normal controls.

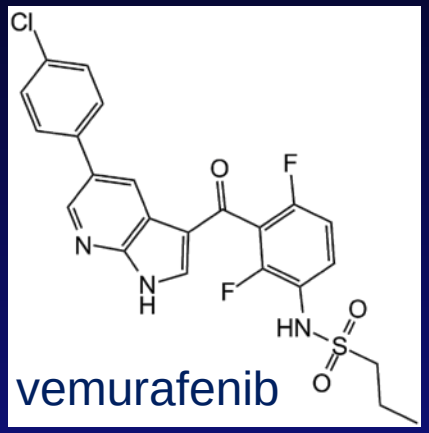
The mutated histiocytes retain some normal characteristics and attract other immune cells

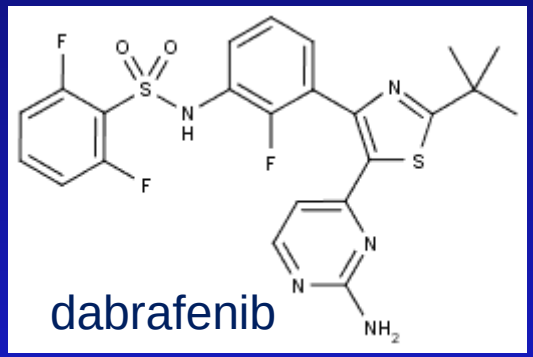


Paul Milne et al. Blood 2017;130:167-175

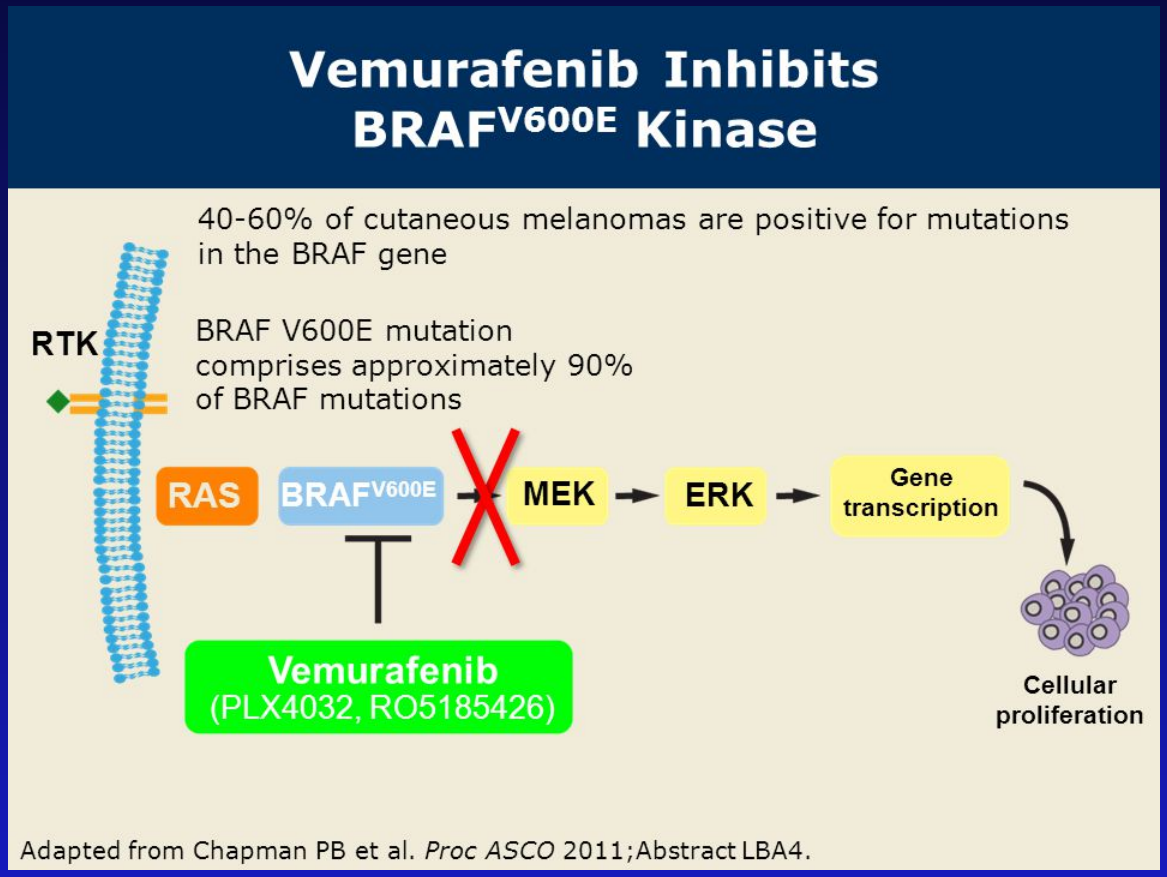
BRAF Inhibition with Vemurafenib and Dabrafenib



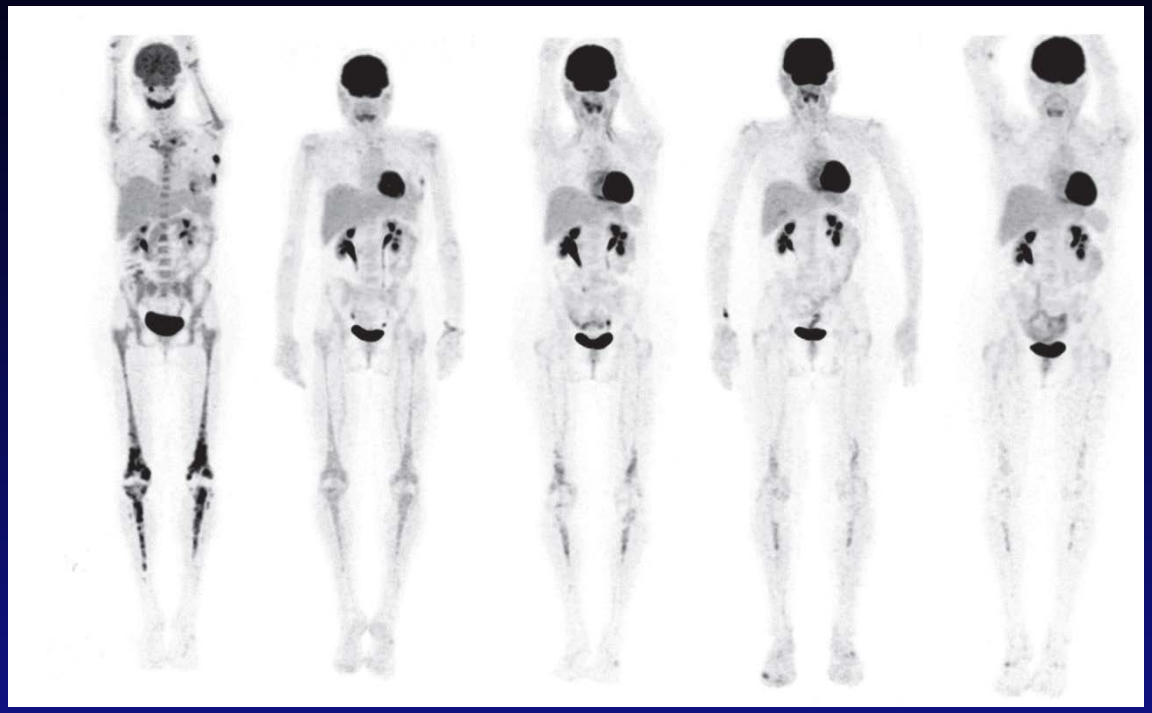




BRAF Inhibitors Block the Kinase Activity and Downstream Signaling



ECD-Vemurafenib

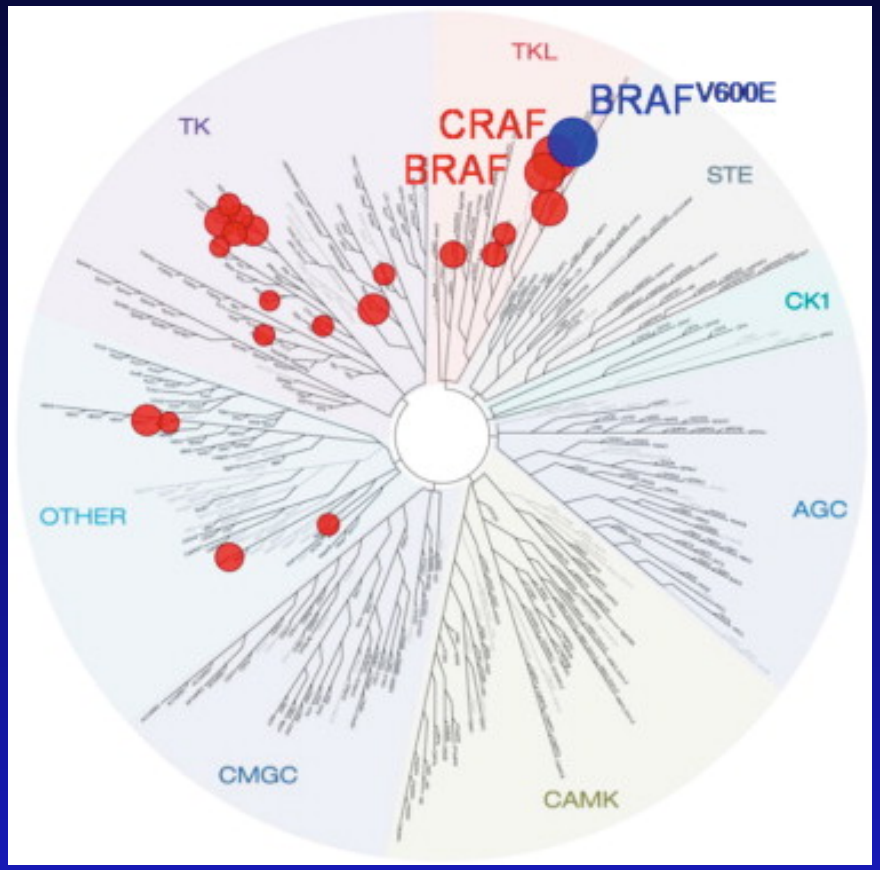


8 patients with interferon-refractory ECD

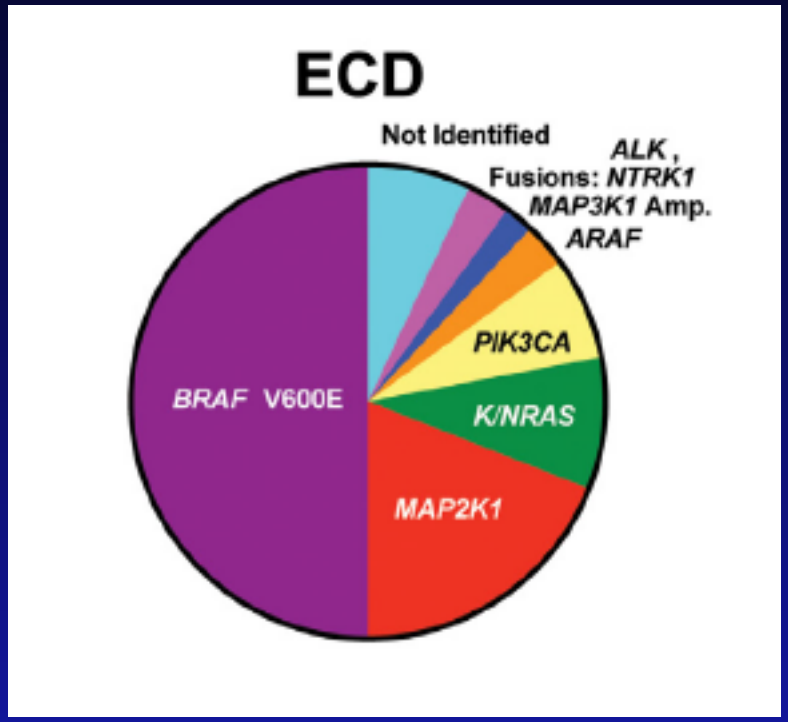
- 100% response by 6 months
- Durable up to 16 months

Haroche et al J Clin Oncol 33:411, 2015

Side Effects May Be Related to “Off Target” Inhibition of Other Kinases



ECD Mutations

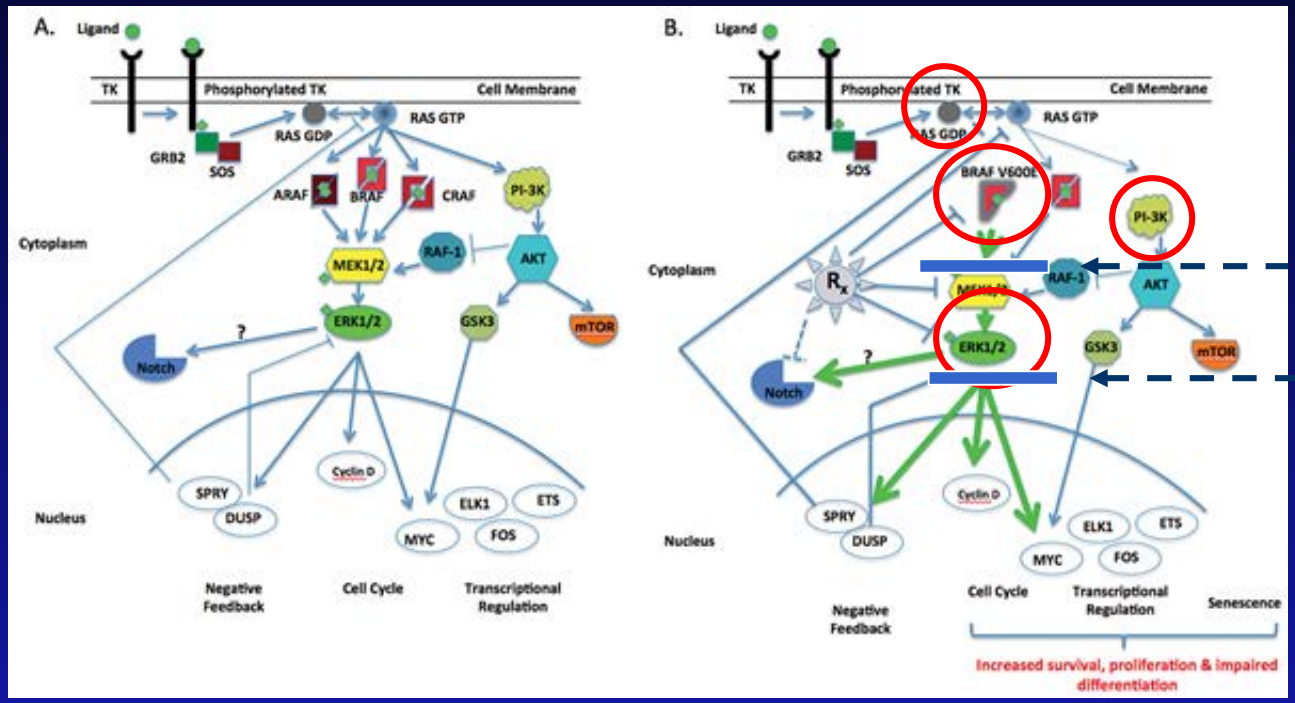


BRAF
K/NRAS
MAP2K
ARAF
MAP3K

PIK3CA

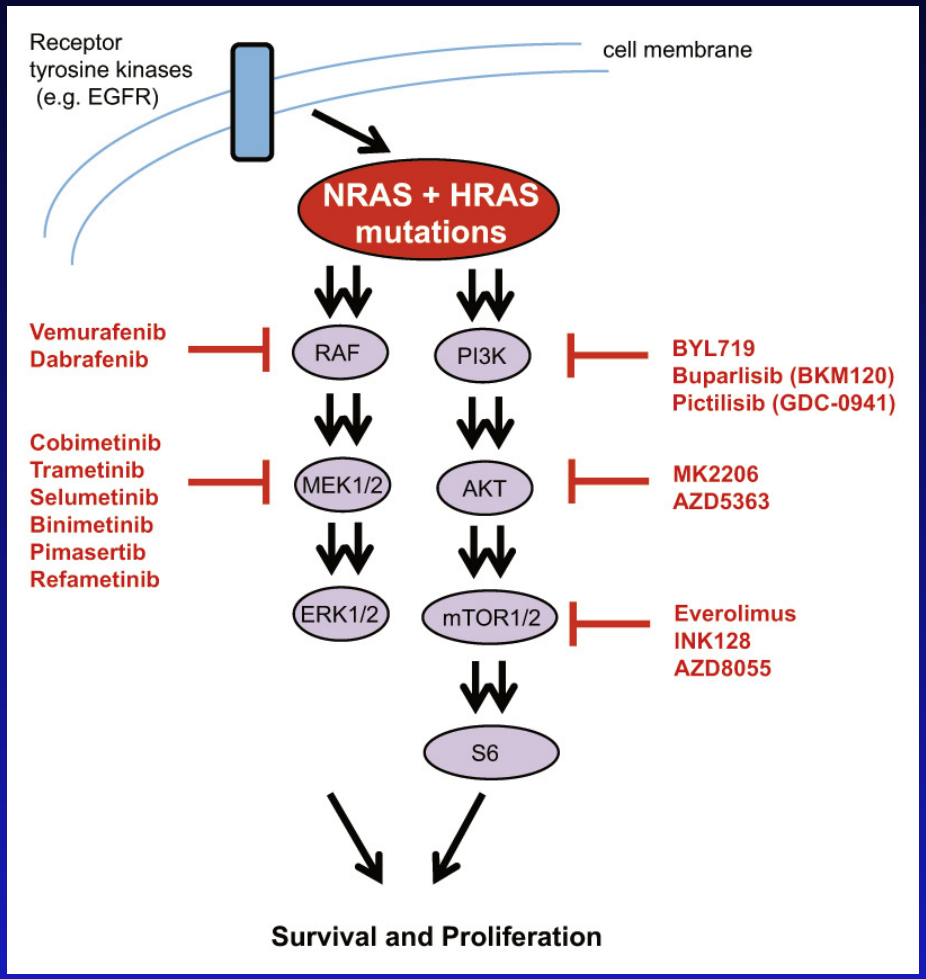
Durham BH, Semin Cell Dev Biol 86:62, 2019

ECD Mutations

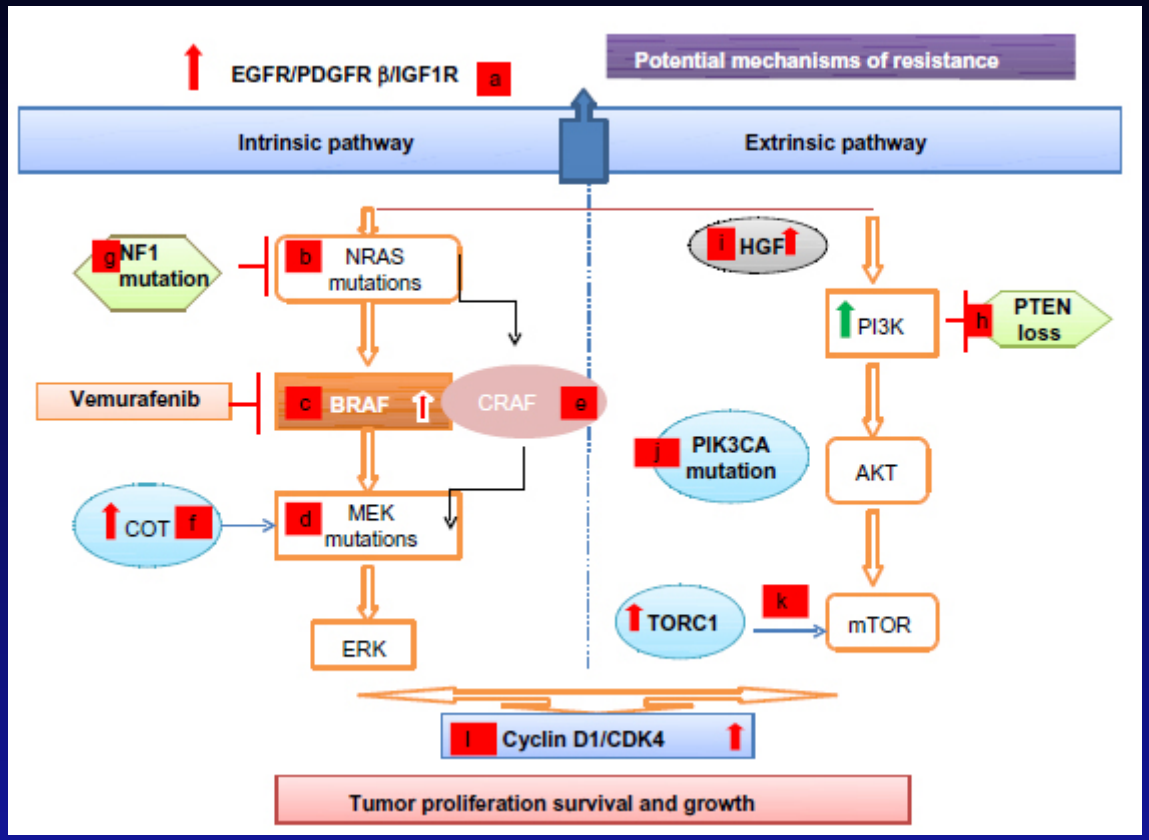


Vemurafenib
Dabrafenib
Cobimetinib
Trametinib

ECD Treatments and Potential Treatments

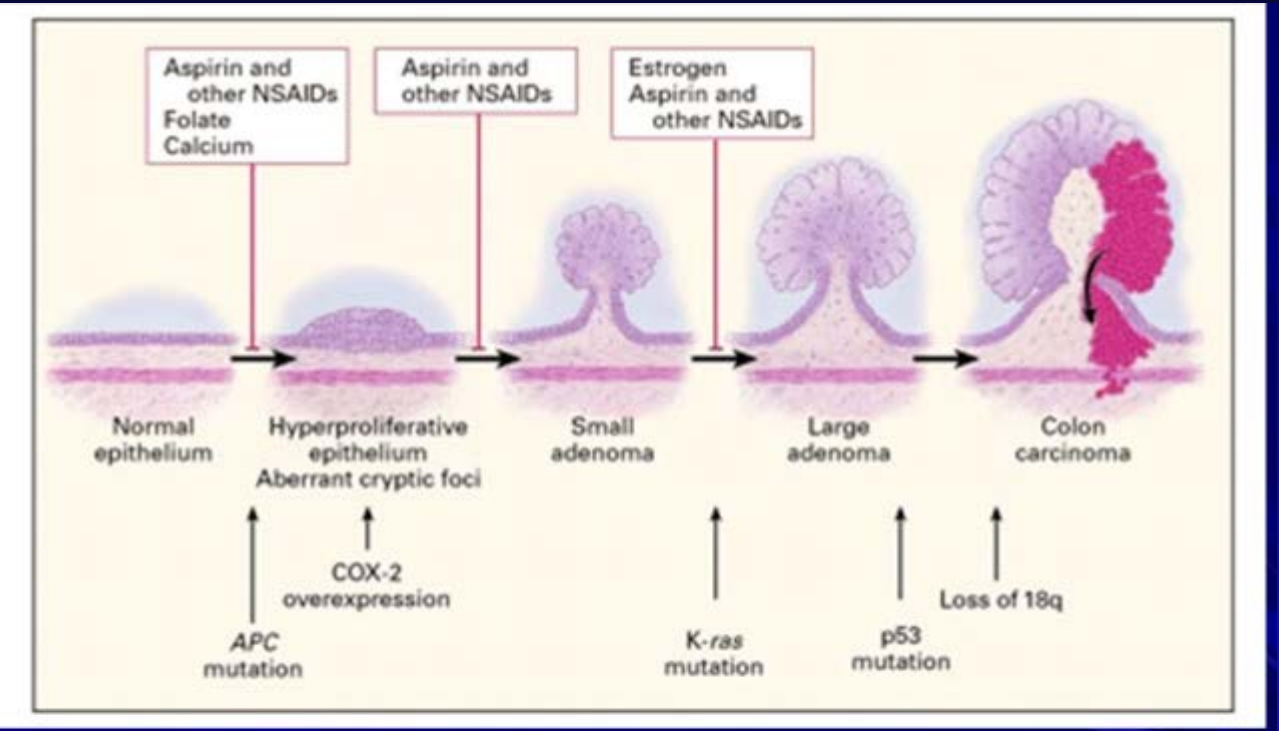


Resistance



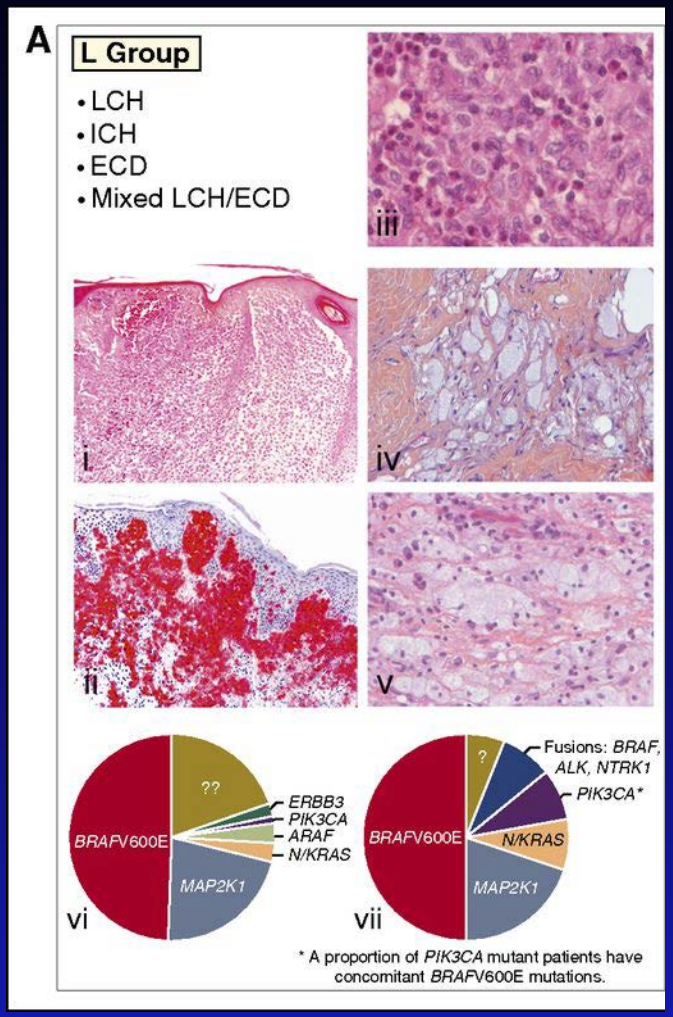
Fortunately ECD has a lower mutation rate and chance of developing resistance than other cancers

Vogelstein model: Cancers Develop by Acquiring Successive Mutations



Colon cancers result from a series of pathologic changes that transform normal epithelium into invasive carcinoma. Specific genetic events, shown by vertical arrows, accompany this multistep process.

ECD Classification

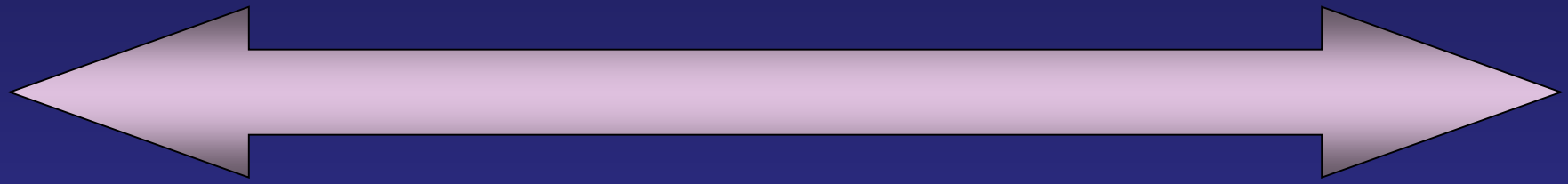


Jean-François Emile et al. Blood 2016;127:2672-2681

- Association between ECD and Langerhans cell histiocytosis
  - Patients with both rare histiocytoses
  - LCH usually preceded ECD
- ECD also seen in patients with other “monocytic” cancers

Histiocytic Diseases

Less aggressive **More aggressive**



Langerhans' cell histiocytosis

Erdheim-Chester Disease

Chronic Myelomonocytic Leukemia

Histiocytic sarcoma

Acute monoblastic leukemia

Conclusions

- Most patients with ECD have mutations in the Ras-Raf-MapK pathway
- The mutations have facilitated diagnosis
- The mutations may be targeted by existing drugs or drugs in development as treatments