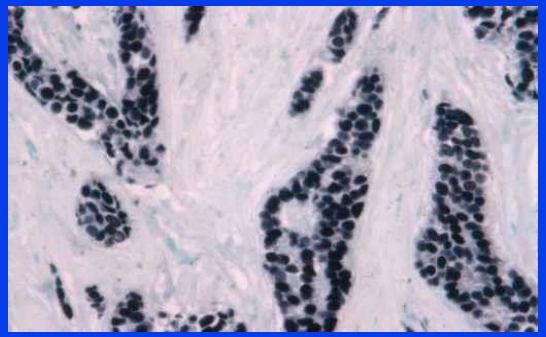
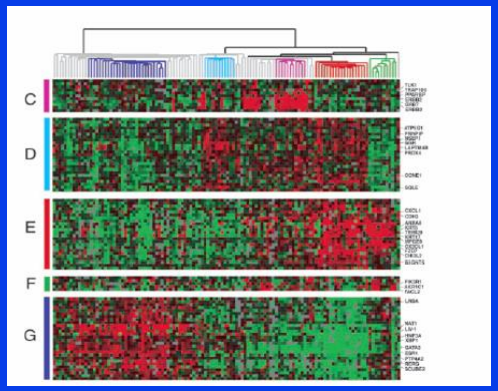
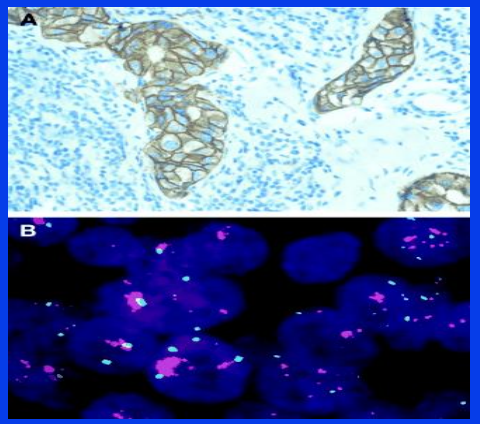
Biologic Basis of Breast Cancer Treatment







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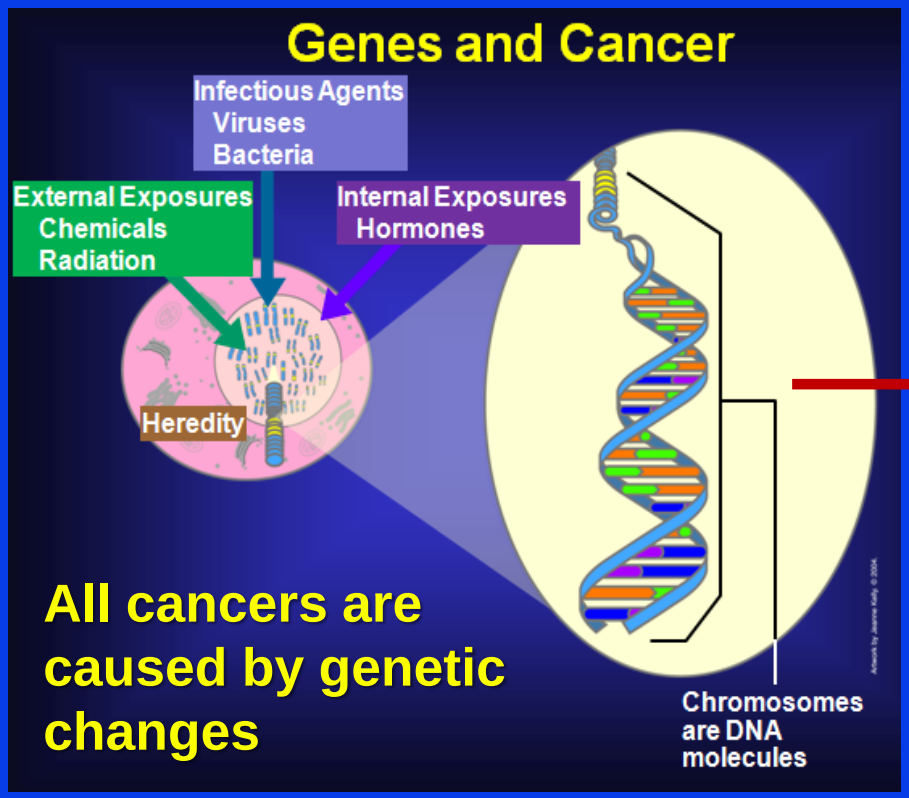
History of Cancer Treatment

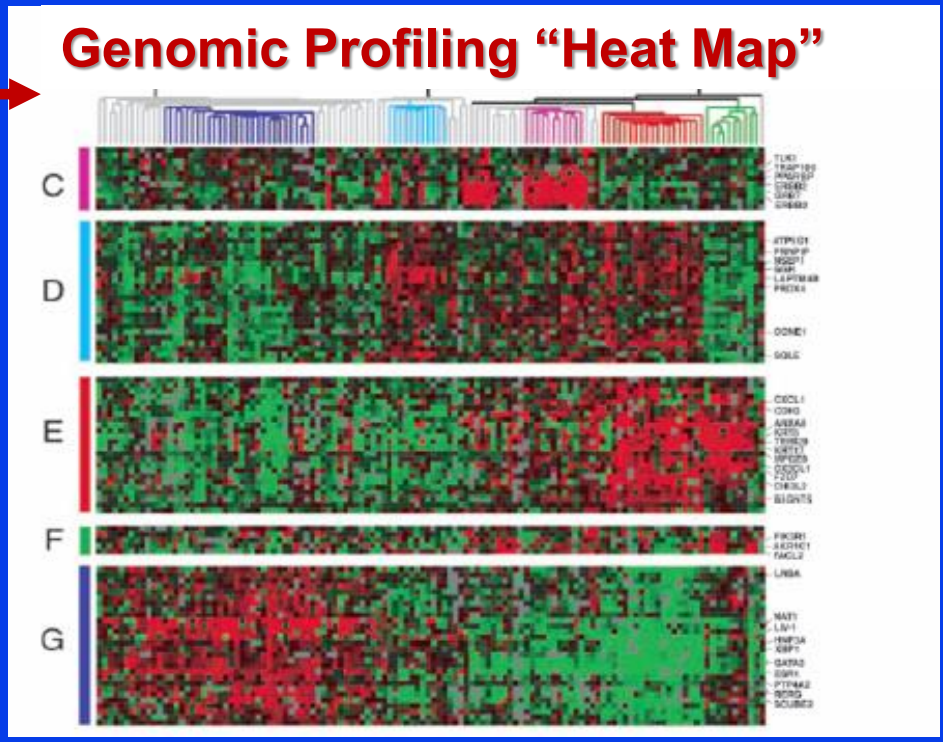
From George Sledge's ASCO 2011 Presidential Address

- 19th century: Loco-regional era
- Late 1940s-50s: Developed non-specific systemic approaches
- Past decade: Targeted therapies exploded
- Just entering a 4th era: Genomics

Genomic Classification: Many Subtypes of Breast Cancer!



Red dots: Genes "turned up" in cancer cells compared to normal cells

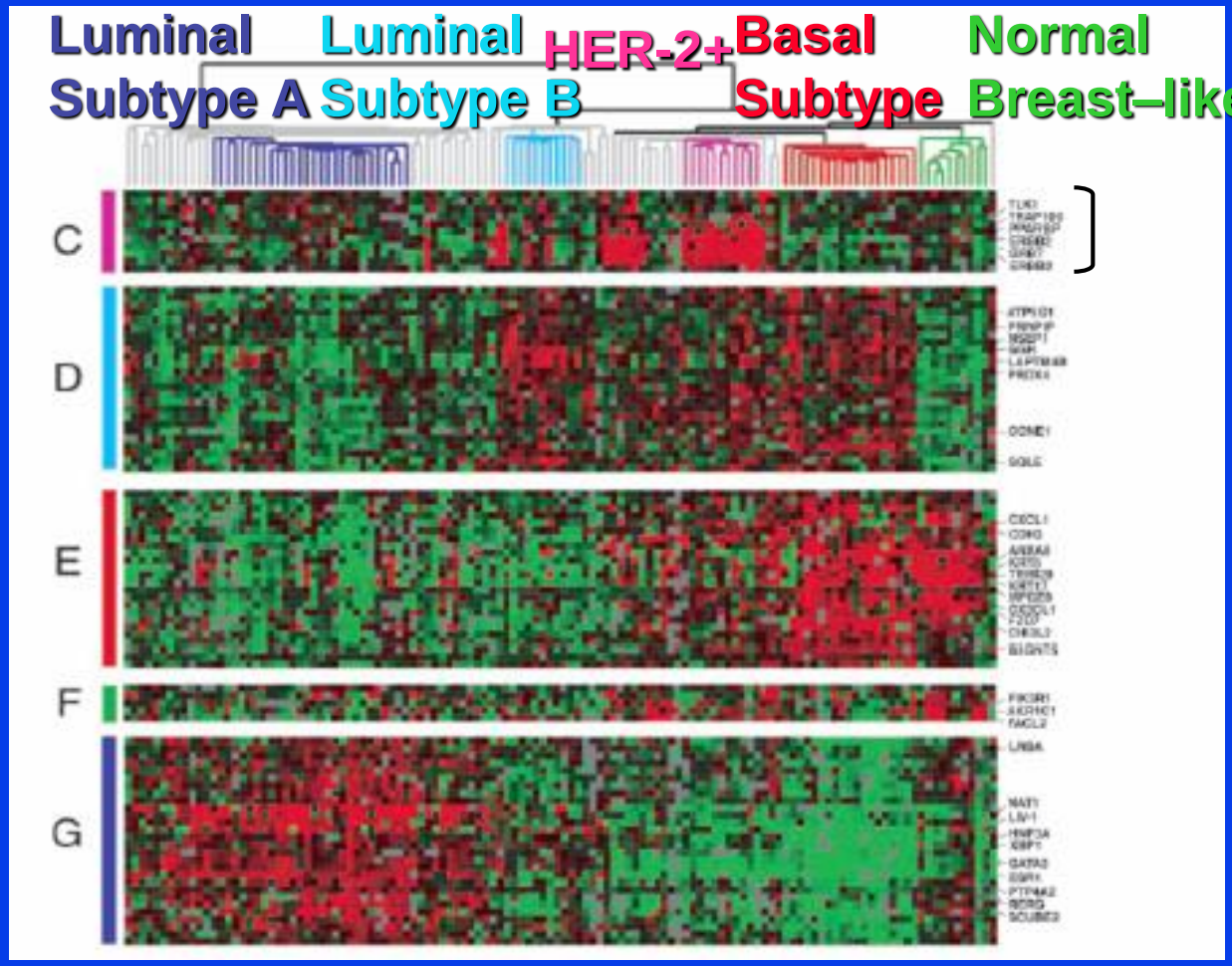


Individual genes

Individual tumors

Genomic Classification: Many Subtypes of Breast Cancer!

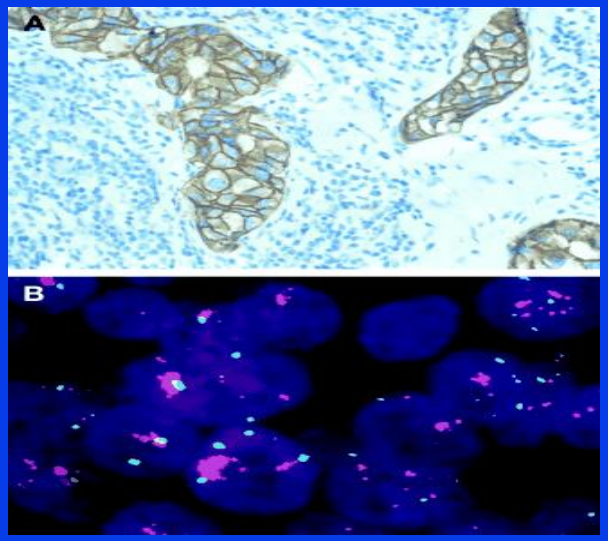
Sorlie et al, Proc Natl Acad Sci 100:8418, 2003



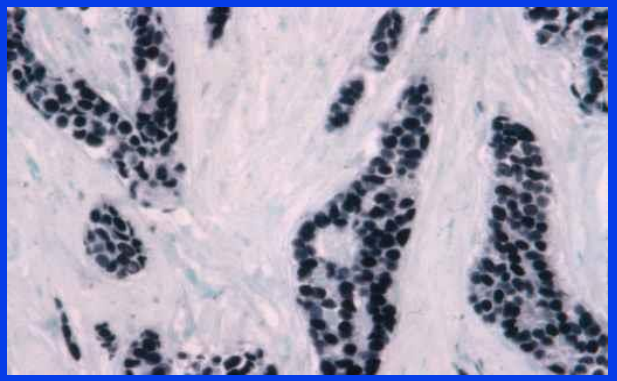
Subtypes vary with respect to:

- Likelihood of recurrence
- Sites of metastases
- Response to treatment
- *Frequency of subtypes varies across populations –additional subtypes likely exist*

Breast Cancer Biology: Not all Breast Cancers are the Same!!



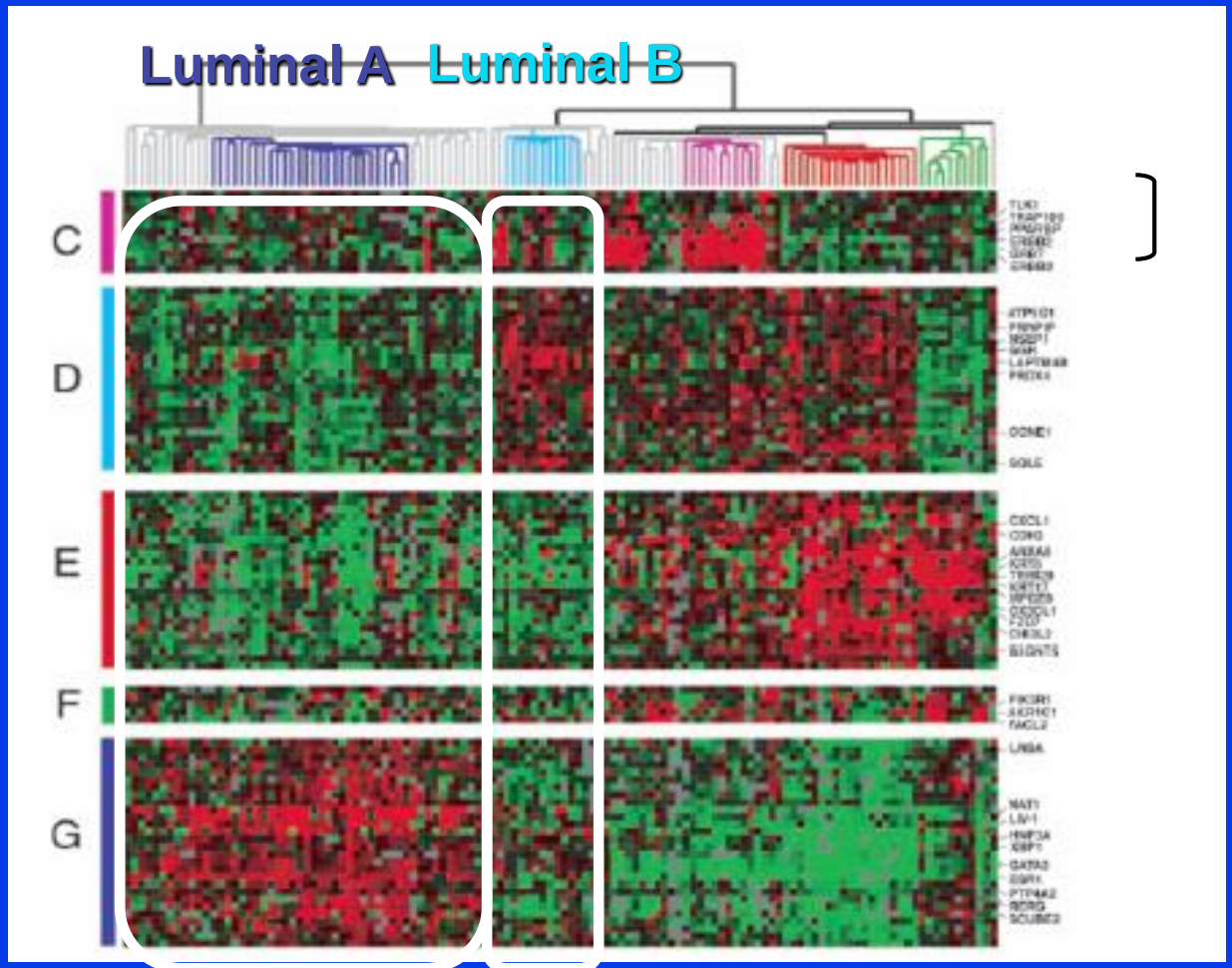
HER-2 +
20-25% of
Breast Cancer



Estrogen
Receptor (ER) +
75% of Breast
Cancer

Tumor ER and HER2 status are CRITICAL in selecting therapy in both early stage and metastatic breast cancer!

Estrogen Receptor Positive Breast Cancer is a Spectrum in Itself: Luminal A and Luminal B Subtypes



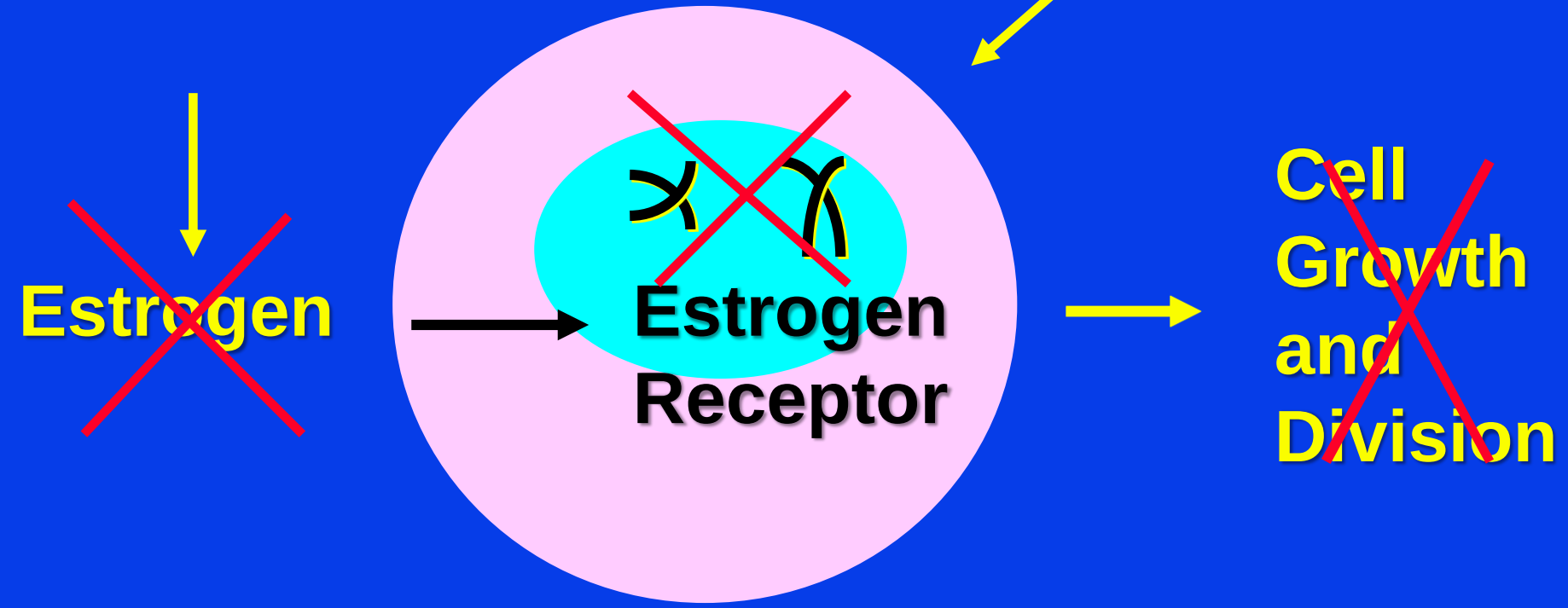
Breast Cancer: Luminal A and B Subtypes

- Express ER, PR, and genes associated with ER activation
- Luminal A (40 percent of all breast cancers)
  - High expression of ER-related genes, low expression of HER2 cluster genes and proliferation-related genes
  - Best prognosis of all breast cancer subtypes
- Luminal B (20 percent)
  - Relatively lower (although still present) expression of ER-related genes, variable expression of HER2 cluster, higher expression of proliferation cluster
  - Worse prognosis than luminal A

Estrogen Receptor as a Target for Therapy

Aromatase inhibitors, ovarian suppression

SERMS, SERDS



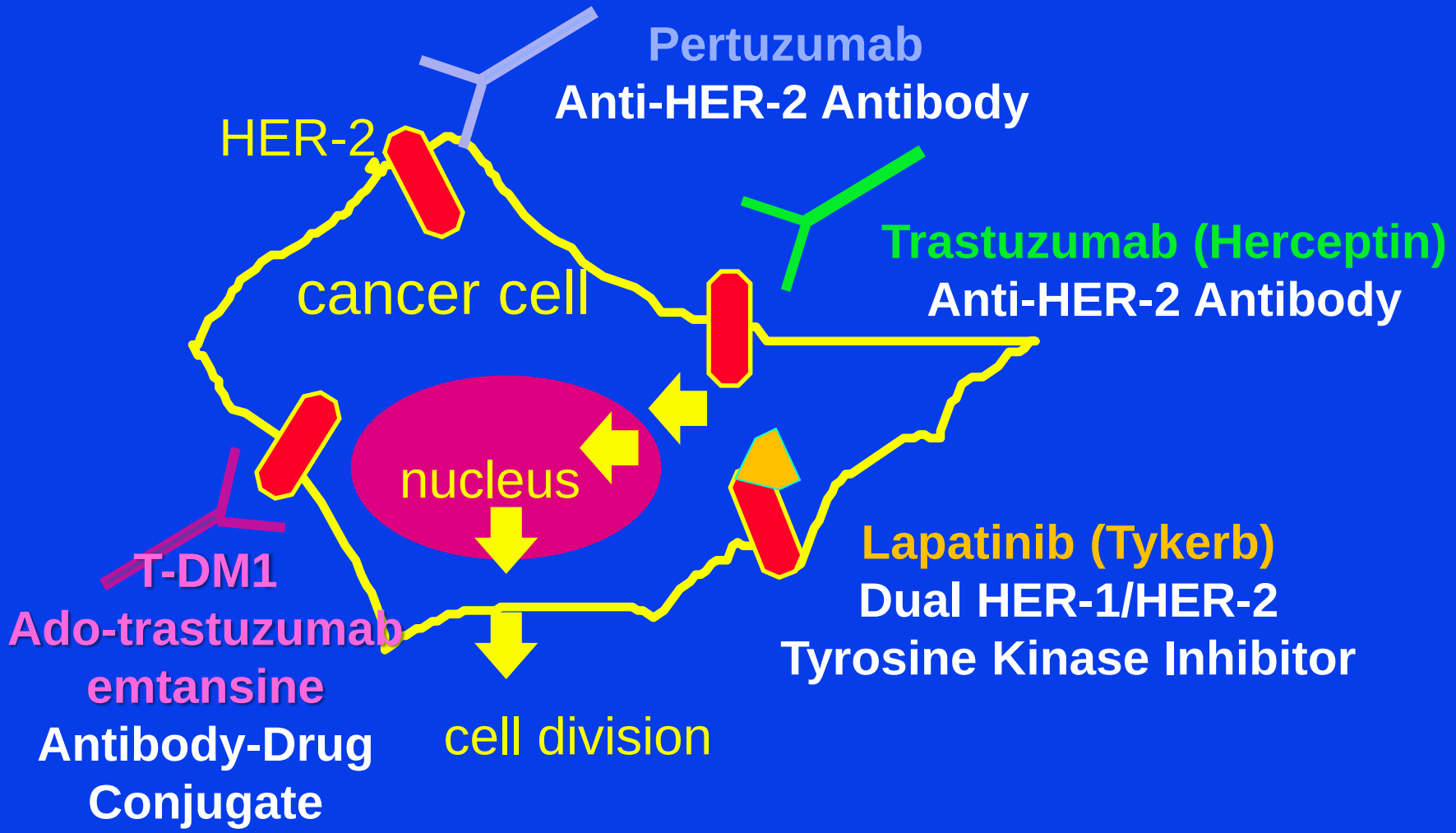
Endocrine therapy is effective only in ER-positive breast cancer

ER/PR staining: CRITICAL IN SELECTING THERAPY!

Breast Cancer: HER-2 Subtype

- 10 to 15 percent of breast cancers
- High expression of HER-2 and proliferation gene clusters, low expression of luminal cluster
  - Typically ER/PR negative, HER-2 positive
  - This subtype comprises only about half of clinically HER-2-positive breast cancer (the rest is luminal B)
- Before HER2-targeted therapy, this subtype carried a poor prognosis.
  - Markedly affected by advances in HER2-directed therapy

HER2 as a Target for Therapy



HER2 therapy effective only in HER2-overexpressing breast cancer

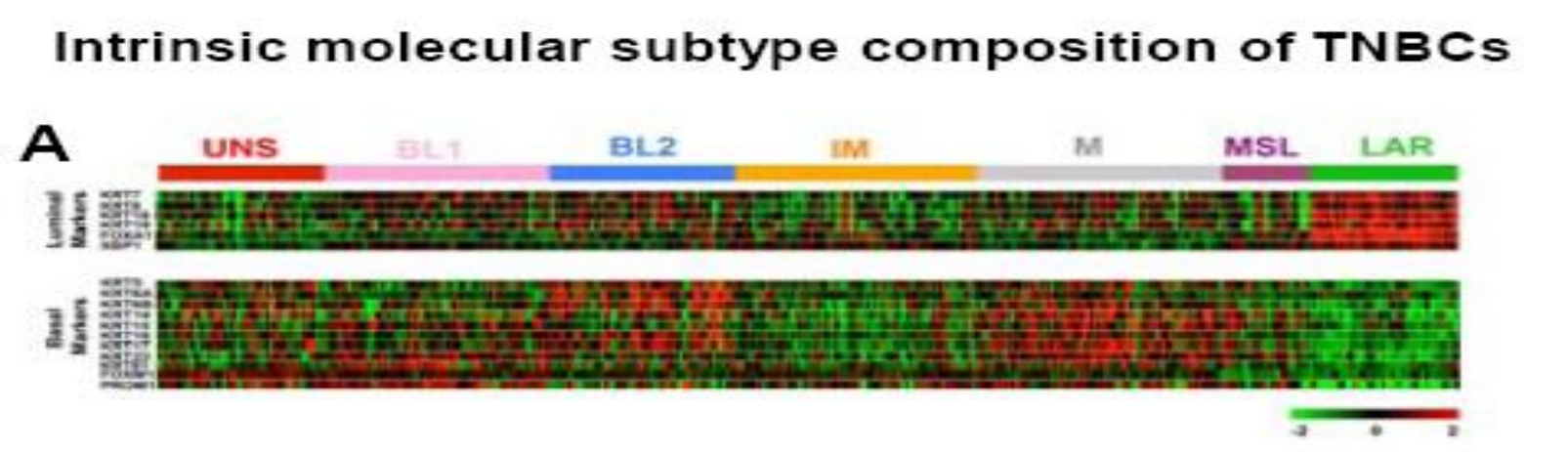
HER2 staining: CRITICAL IN SELECTING THERAPY!

Breast Cancer: Basal Subtype

- 15 to 20 percent of breast cancers
- Low expression of luminal and HER2 gene clusters
  - Typically ER-, PR-, and HER-2-negative ("triple negative")
- High expression of proliferation cluster genes, virtually always high grade, widespread genomic instability
  - High expression of EGFR and unique basal cluster genes (basal epithelial cytokeratins 5, 14, and 17)
- Common in BRCA1 mutation carriers (over 80%)
- Overrepresented in premenopausal and African women
- Poor prognosis
- Sensitive to chemotherapy
- Associated with DNA repair defects - PARP1 commonly increased

Basal/Triple Negative Breast Cancers (TNBC)

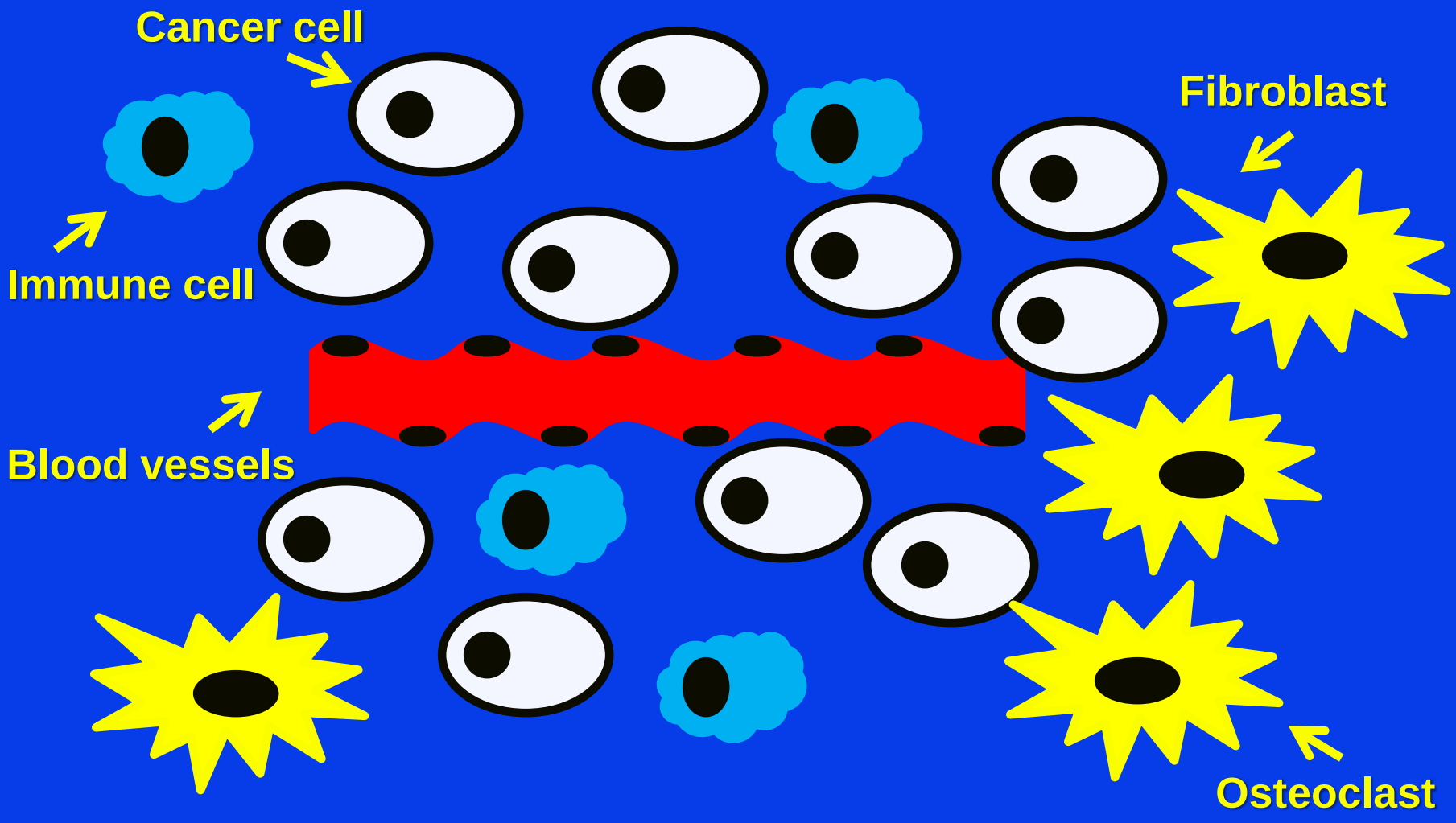
Lehmann BD, et al. J Clin Invest 121:2750-67, 2011



6 subtypes of TNBC identified by gene expression array

Targeting the Cancer Environment

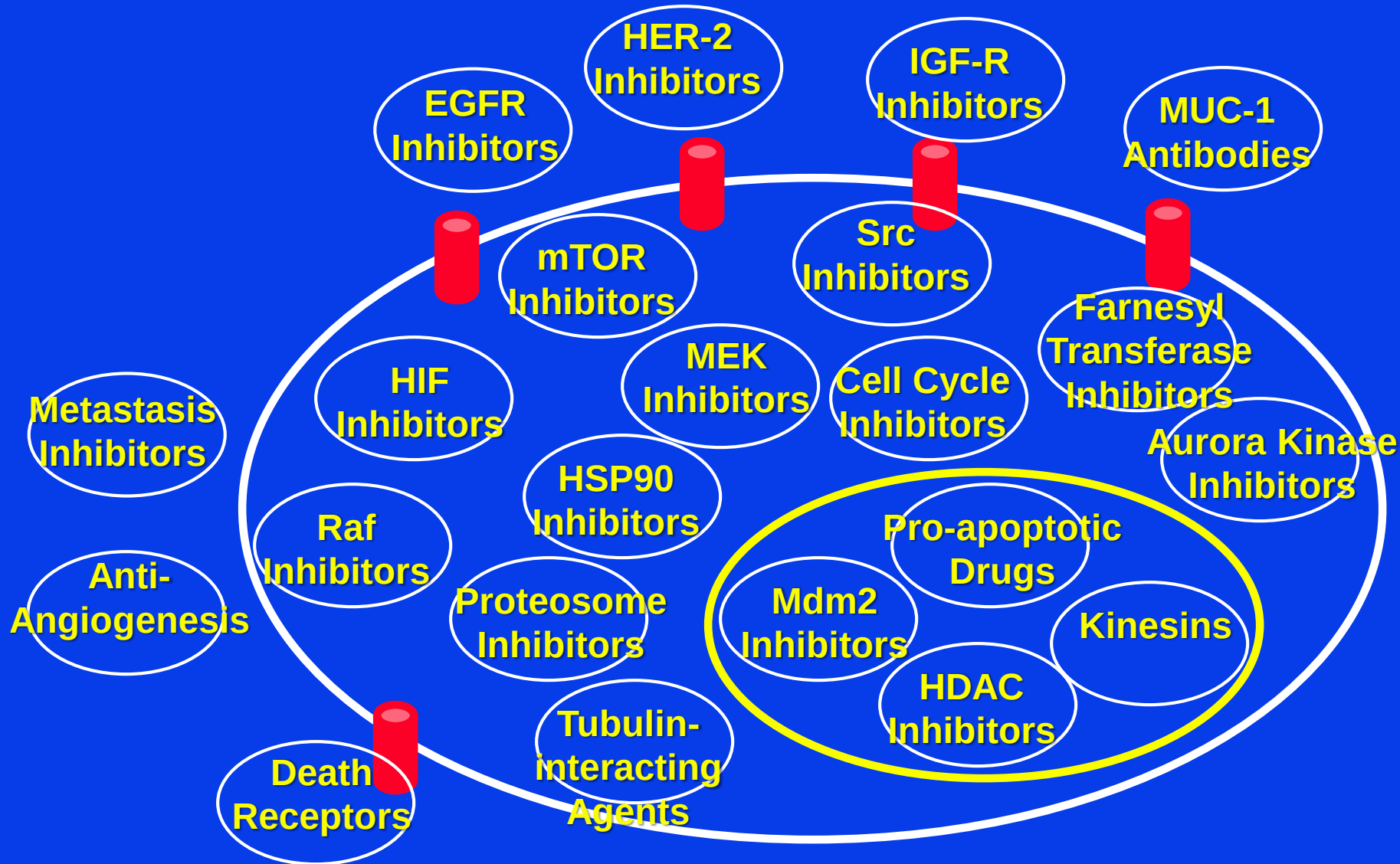
In Addition to Targeting the Cancer Cell, We Can Also Target the Cancer Environment



Biologic Basis of Breast Cancer Treatment: Opportunities and Challenges in Targeting Cancer Therapy

- Identifying the target
  - patient and tumor selection
- Understanding the target
  - role in tumor
  - networks and interactions
  - role in normal tissues
- Monitoring the target
  - does an agent actually target the intended pathway and does it result in clinical benefit?

Merging the Targeted Therapy Era with the Genomic Era of Cancer Treatment: Targets and Drugs



Ongoing NCI MATCH (Molecular Analysis for Therapy Choice) Clinical Trial

http://deainfo.nci.nih.gov/advisory/ncab/164_1213/Conley.pdf

Genomic Profiling of Tumor

↓

Actionable mutation detected → Study Agent 1 → Continue until progression → Progressive disease

↓

Check for additional actionable mutations

↓

Study Agent 2

- **Eligibility:**
  - Metastatic solid tumors and lymphomas that have progressed on ≥ 1 line of therapy
- Access to many drugs in development: currently > 40 drugs pledged

Biologic Basis of Breast Cancer Treatment: The Future

- Cancer care is set to change dramatically in the next 20 years
- Advances in technology and a deeper understanding of cancer biology will transform cancer care
- Continued investments in cancer research required to translate scientific breakthroughs into new treatments