Findings From the Bench: the Future of MBC Care

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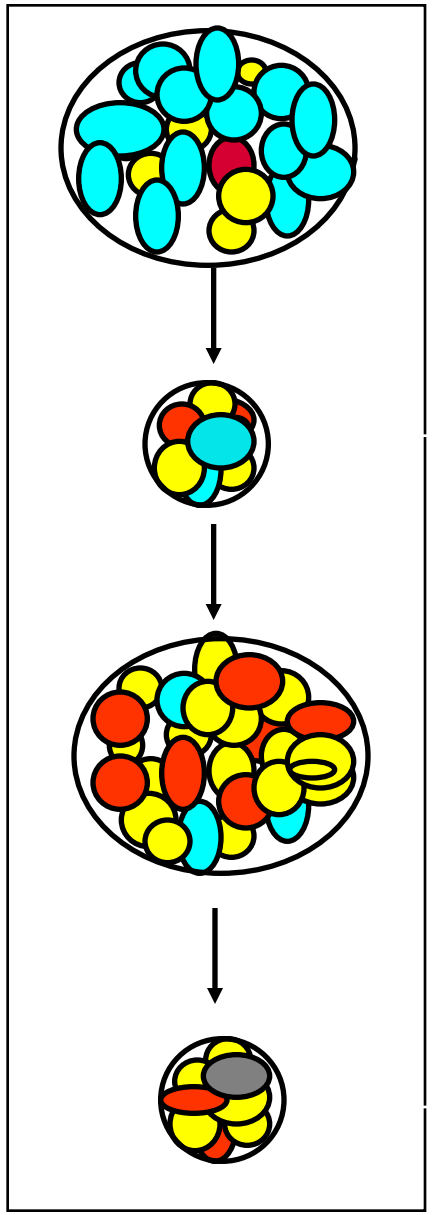
Adjuvant Therapy of Breast Cancer Subtypes

- **ER+/PR+: Hormone therapy (Aromatase Inhibitor (AI) or antiestrogen (Tamoxifen)**
- HER2+/ER- or ER+: HER2 targeted agents
- Triple Negative (ER-/PR-/HER2-): Chemotherapy

Hormone Resistance in ER+ Breast Cancer

AI's
(or Tam)



Primary tumor

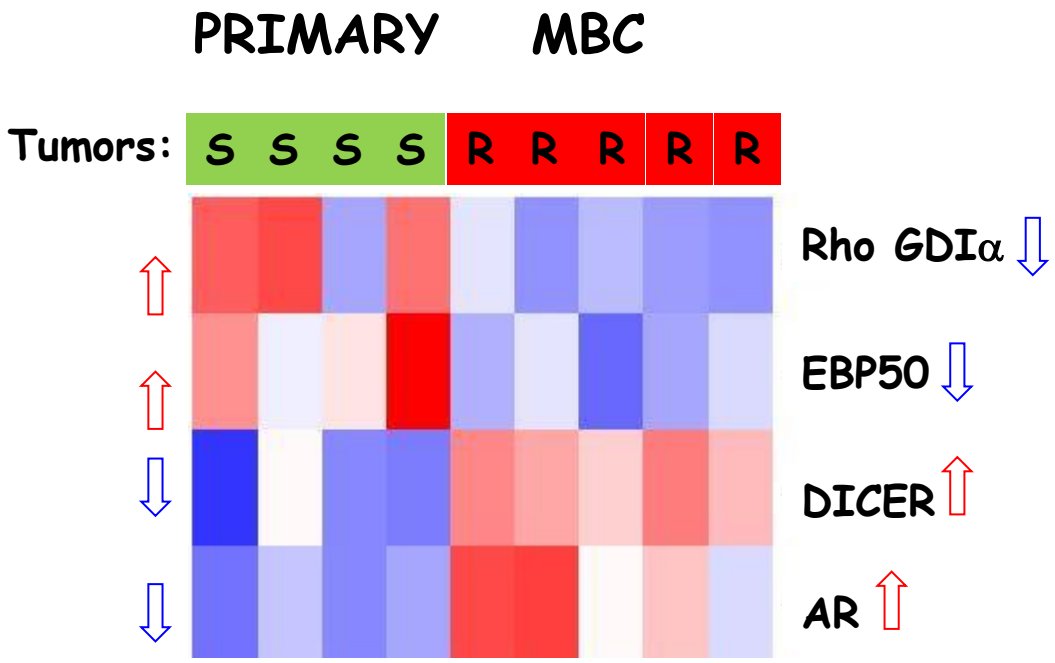
Adjuvant Rx

MBC
Clonal selection of mutations
Acquired hormone resistance

Hormonal Rx.
+
Targeted Agents

MBC
Response

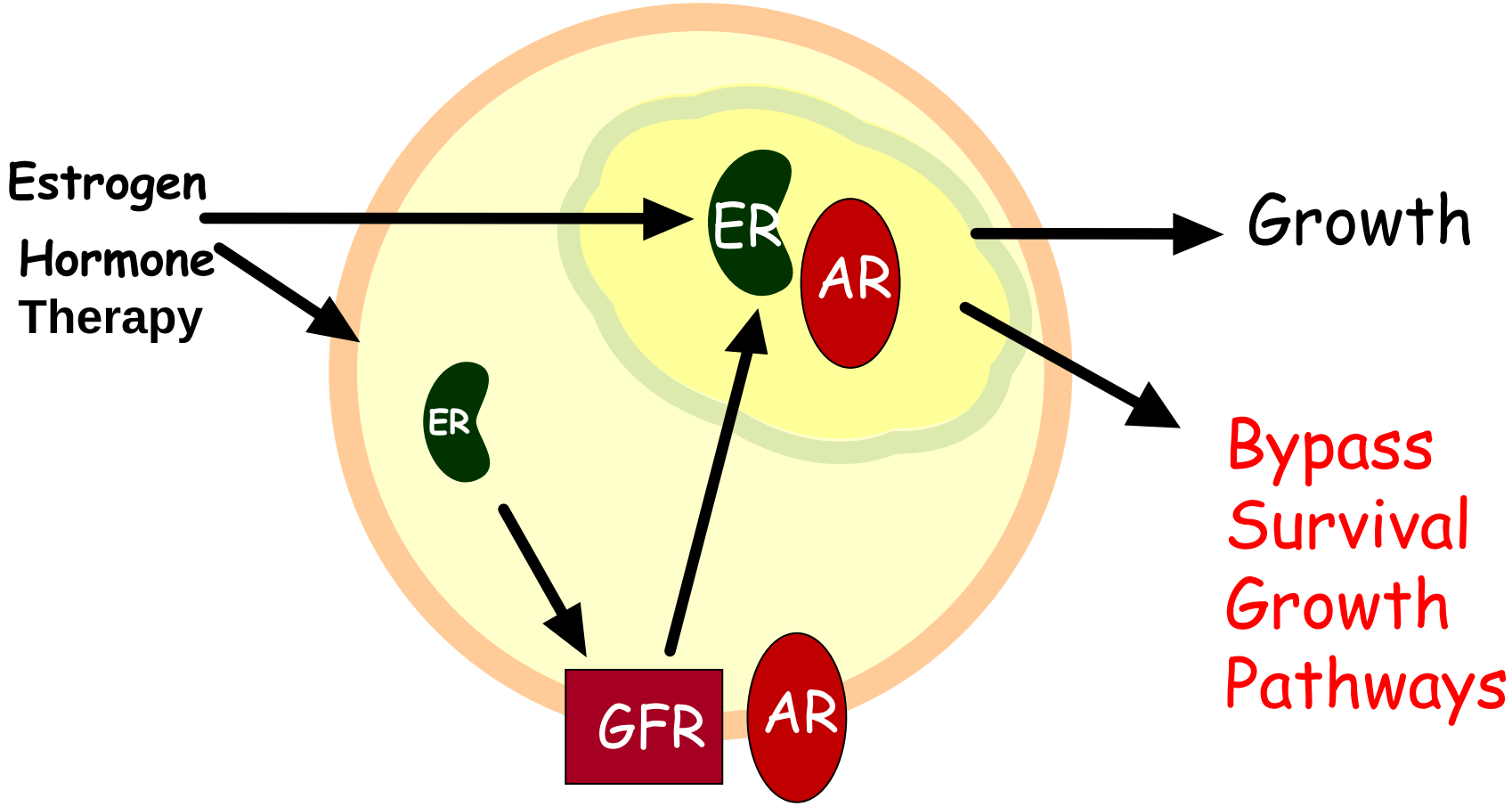
Hormone Resistance in ER+ Breast Cancer



MULTIPLE resistance mechanisms arise in MBC

Therefore need combination targeted therapy or use of novel sequential therapy approaches

Treatment Resistance Reprogramming of Tumors



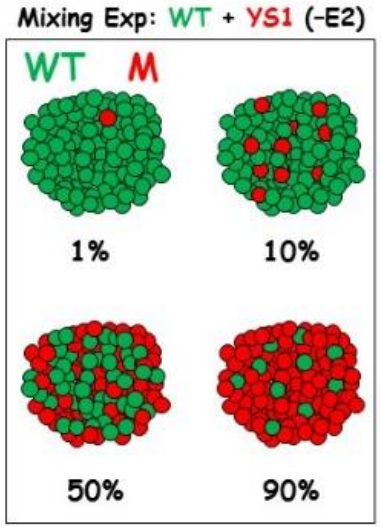
GFR: Growth Factor Receptor (HER2/IGF1R…….)
AR: Androgen Receptor

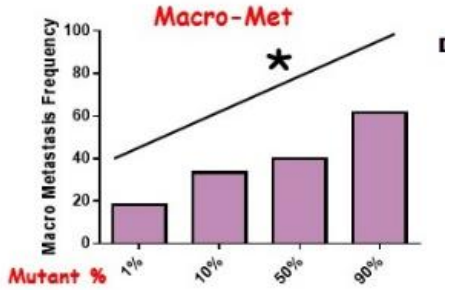
ESR1 Gene Mutations in MBC Confer Resistancet o Hormonal Therapies

- Originally discovered *ESR1* mutations in MBC in 1997
- Now we know 40% of MBC contain *ESR1* gene mutations
- Are acquired during treatment of MBC with AI
  (Clonal selection? Do they drive metastasis?)
- Fulvestrant and targeted therapies (mTOR/CDK4,6)
  are effective in MBC with *ESR1* mutations

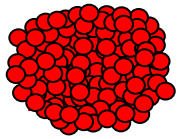
Zhang, Cancer Research, 1997

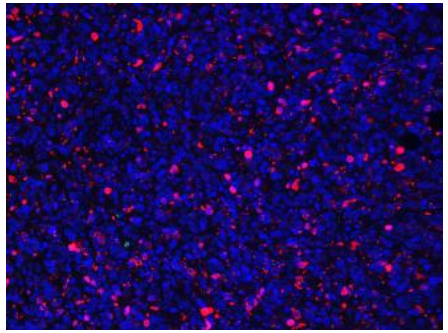
ESR1 Gene Mutations Drive Metastasis





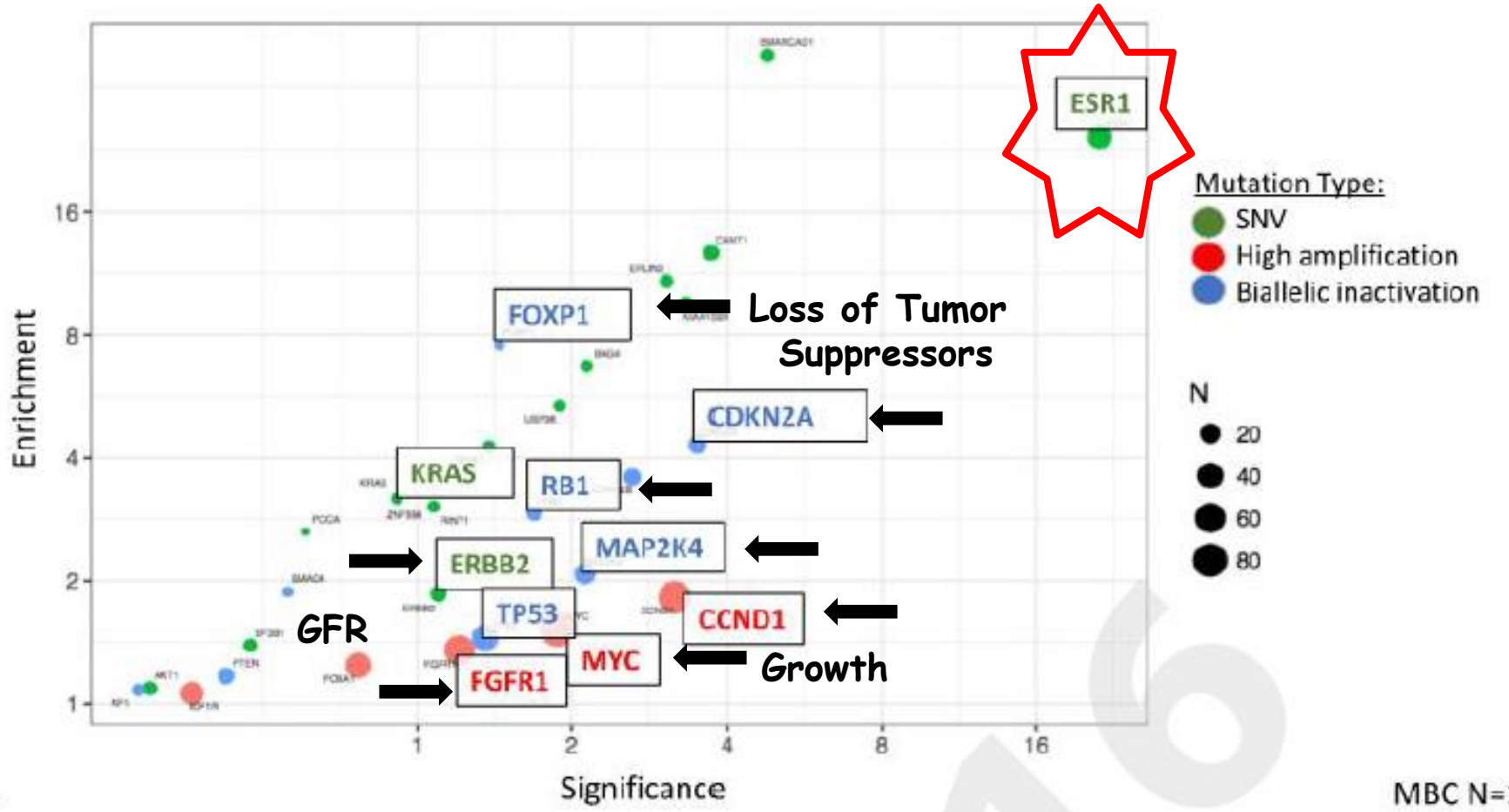
Metastases in all mixing groups were 100% mutant=
Clonal Selection





Fuqua unpublished

Comparison of Acquired Changes in MBC vs. Primary Tumors



Fisher's exact test

MBC N=149
TCGA N=739

How My View of Breast Cancer Has Changed

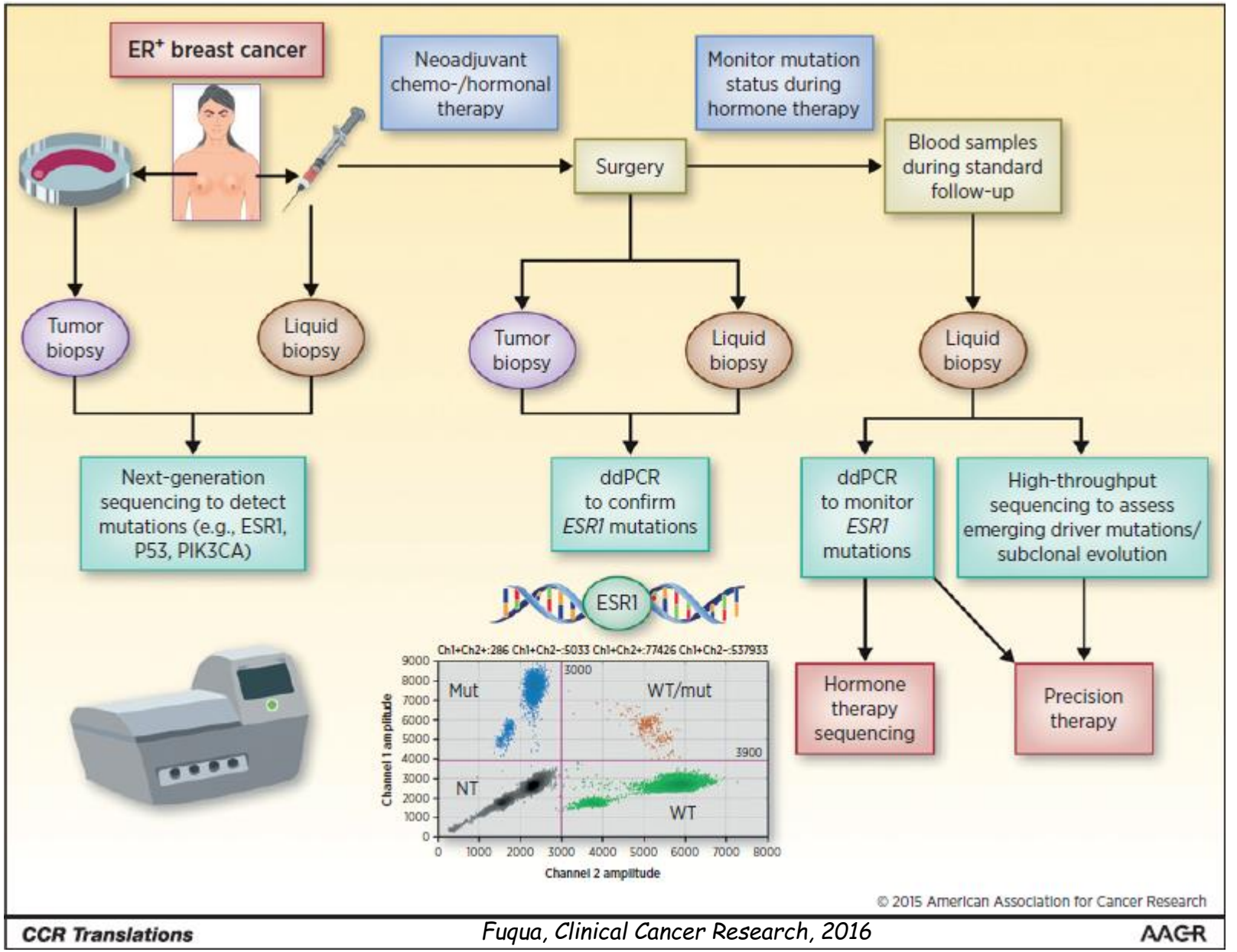
"The Wac-a-Mole Problem"

Resistance to therapy
Tumor progression
Single gene targeted therapy

→

Multiple escape pathways
Many mutations
Metastatic heterogenity

Monitor for *ESR1* Mutations During Long-term Adjuvant Therapy with AIs?



CCR Translations

Fuqua, Clinical Cancer Research, 2016

AACR

Discussion Points for Future of MBC Care:

- *ESR1* mutations are a frequent mechanism of acquired hormone resistance and drive metastasis of MBC
- AI therapy alone in metastatic setting is counter-indicated in *ESR1* mutant+ patients
- Need to sequence for gene alterations in MBC before and during therapy
- Even with our best new targeted therapies, there is a profound need to develop new sequencing strategies and novel agents for personalized therapy of acquired changes in MBC
- Should targeted agents be used earlier during adjuvant therapy to prevent acquisition of gene changes?

This meeting is intended for clinicians, patient advocates, scientists, and other healthcare professionals involved in the research, treatment, or care of patients with metastatic breast cancer