The Challenge and Promise of the Genomic Era

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The Genomic Era
The $1000 Genome is Almost Here
Stupid and Smart Cancers

**Stupid Cancers**
- Single dominant mutation
- Small mutational load
- Monotherapy is effective
- Resistance rare, late, same pathway

**Smart Cancers**
- Multiple mutational drivers
- Large mutational load
- Multi-targeted therapy required
- Resistance common, early
Somatic point mutations: varying rates across cancer (1035 WES)
Breast Cancer: Subtypes Reflect Genomic Complexity

Genome-wide Circos plots of somatic rearrangements

Smart Cancers

- Smart cancers are genomically complex
- Etiology affects complexity
- Complexity affects drug sensitivity
- Complexity $\rightarrow$ tumor heterogeneity
- Complexity evolves
- Darwinian pressures affect complexity
Table 1 | Analysis of the top somatically aberrated genes influencing expression

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Somatic mutation content by case

Oncology as Whack-a-Mole

Rapid emergence of compensatory mechanisms of resistance
Genomic Chaos

• “Smart tumors” = genomic chaos
• This is a quantitative, not just a qualitative, problem
• They are not hard targets just because we haven’t found a single “magic bullet”
• We don’t need a magic bullet, we need a magic shotgun
Developing Targeted Therapies in the Genomic Era: Be Careful What You Ask For
Targeting Rare Mutations in the Genomic Era

• Example: HER2 mutations
  – Occur in <2% of breast cancer
  – IHC and FISH negative
  – Activating
  – Sensitive to RTKi but not trastuzumab
Targeting Rare Mutations in the Genomic Era

• 2% mutation rate, so...
• Screen 500 patients for a 10-patient pilot trial
• Trial now open to accrual
• It’s actually much worse than this
Number Needed to Study: HER2 Mutation

- NNS = \[\frac{1}{\text{(% biomarker-positive) \times \text{assay accuracy} \times \text{fraction trial-eligible} \times \text{fraction giving IC)}}}\]

Example:
HER2 = \[\frac{1}{(0.02 \times 0.9 \times 0.5 \times 0.8)}\]
\[= \sim 138 \text{ patients screened/patient studied}\]
The Mutational Landscape of Breast Cancer

- 100 breast cancers genomes analyzed
- Driver mutations found in at least 40 different cancer genes
- 73 different combinations of driver mutated cancer genes
- 28 cancers had a single driver mutation, but some had as many as 6 driver mutations
- WE HAVE NEVER TARGETED 6 DRIVERS!

Multi-Kinase Activation Requires Multi-Kinase Inhibition

Multiple kinases are activated

Optimal cell kill requires inhibition of multiple kinases

Stommel et al. SCIENCE VOL 318: 287, 2007
Today’s Clinical Trials System is Not Designed for Chaos

- Emphasizes single agents
- Combination trials never biomarker-based
- Biomarker development is secondary
- Regulatory apparatus ill-suited to modern biology
The “Next-Gen” Clinical Trials System

• Therapeutic individualization based on personal genomics
• Real-time bioinformatics
• HIT network supporting clinical trials and cancer care
• Increased collaboration
• Trial designs focused around multi-targeting
• Redesigned informed consent process
• Fundamentally different regulatory apparatus
• CAN STANFORD LEAD?
Thank You!