

Implementation of Precision Medicine: From Deep Sequencing and Unbiased Screening to Precise Therapeutic Targeting

- Holy Grail: Functional assessment and measurement of tumor biology and therapeutic response in humans *in vivo* (the “nano/bioprobe”) in the correct tissue microenvironment and physiologic context
- A Start: A large scale project focused on developing and applying methods / approaches to primary human cancer cells *ex vivo* or *in vivo* to determine the functional consequences of the constellation of cancer-promoting mutations and determine those which alone or in combination should be targeted in individual patients

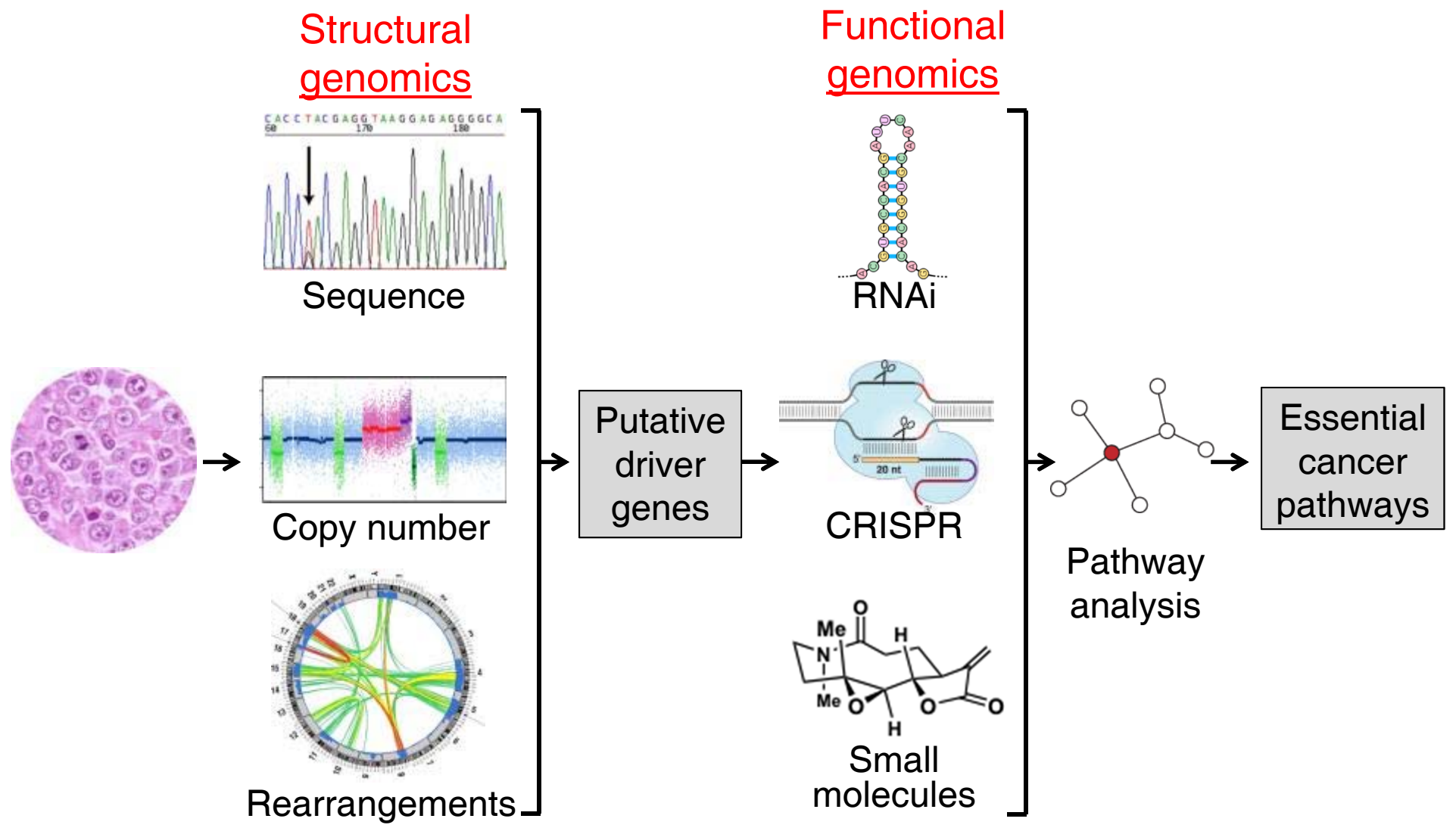
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- Capabilities/Data Sources/Needs:
 - Cancer Cell Genomic Data: TCGA/TARGET datasets, tumors with well-developed NGS datasets existing or to be developed (deep sequencing)
 - Host Genomic Factors: How to assess the contribution of the host genome to tumor biology and response? (Would *in vivo* measurement of functional biology accomplish this indirectly?)
 - Ultimate Goal: Primary human cancer cells/tissues for analysis
 - Unbiased high throughput functional screening using various approaches and platforms (small molecule libraries, drug libraries, repurposed drugs, siRNAs, CRISPR, etc.)
 - How would one address clonal heterogeneity and/or isolate individual clonal populations for analysis and assessment?
 - Integrated informatic platforms for prediction of functional behaviors and therapeutic responses

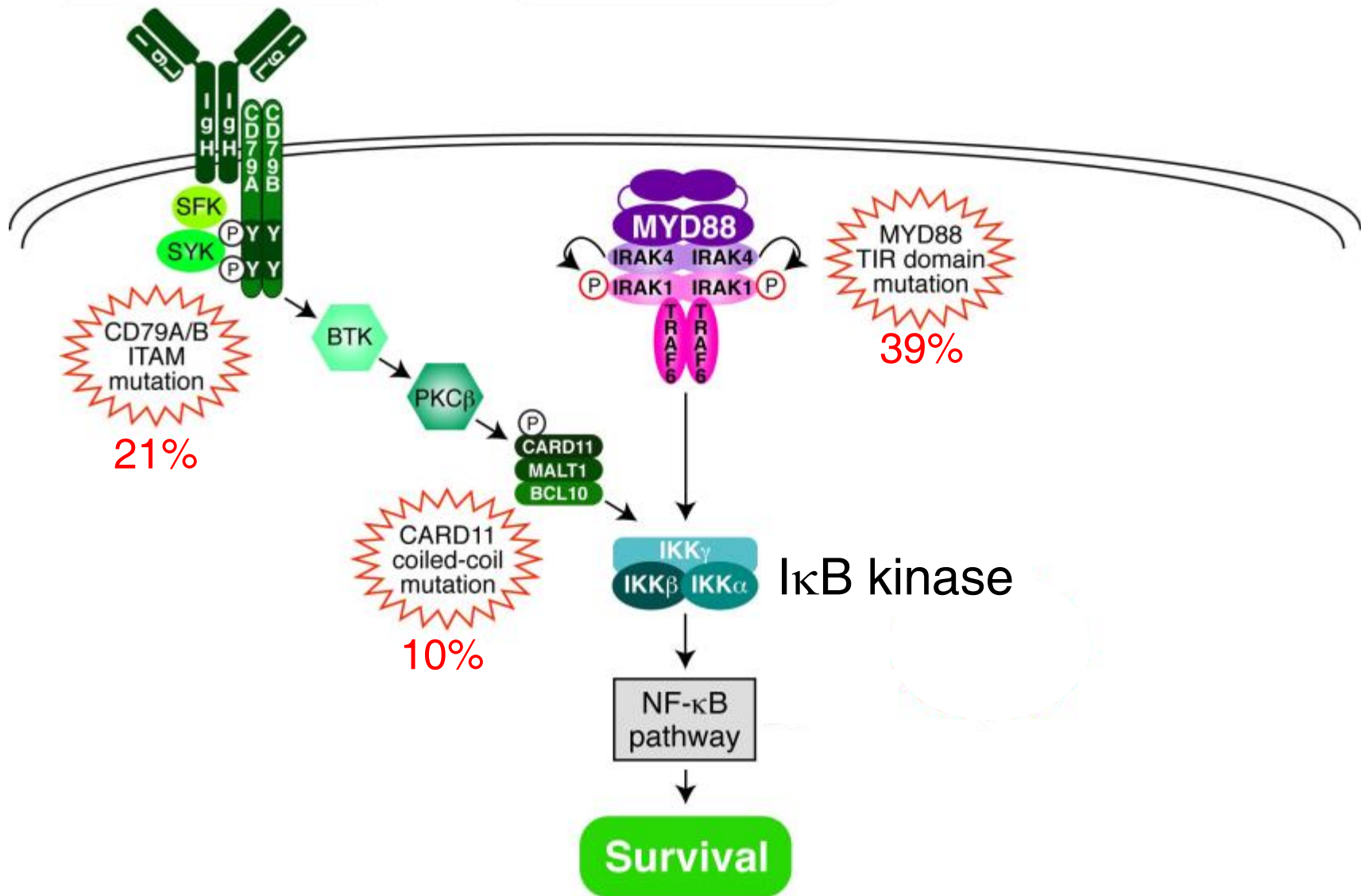
Some Current Efforts

- NCI / Staudt (Lymphoma) and DFCI / Hahn (Brain/Ovary) : Genomic scale shRNA screens in a large number of cancer cell lines.
- Broad / Hahn: Constructing 3000 cDNAs containing mutations found in TCGA data sets to perform gain-of-function experiments.
- NCI CTD2 (Center for Cancer Genomics): 13 groups performing these functional analyses in smaller and more focused scale, including use of small molecules, RNA interference, and most recently CRISPR (<http://ocg.cancer.gov/programs/ctd2>).
- U Oregon / Knight Cancer Center: Beat AML

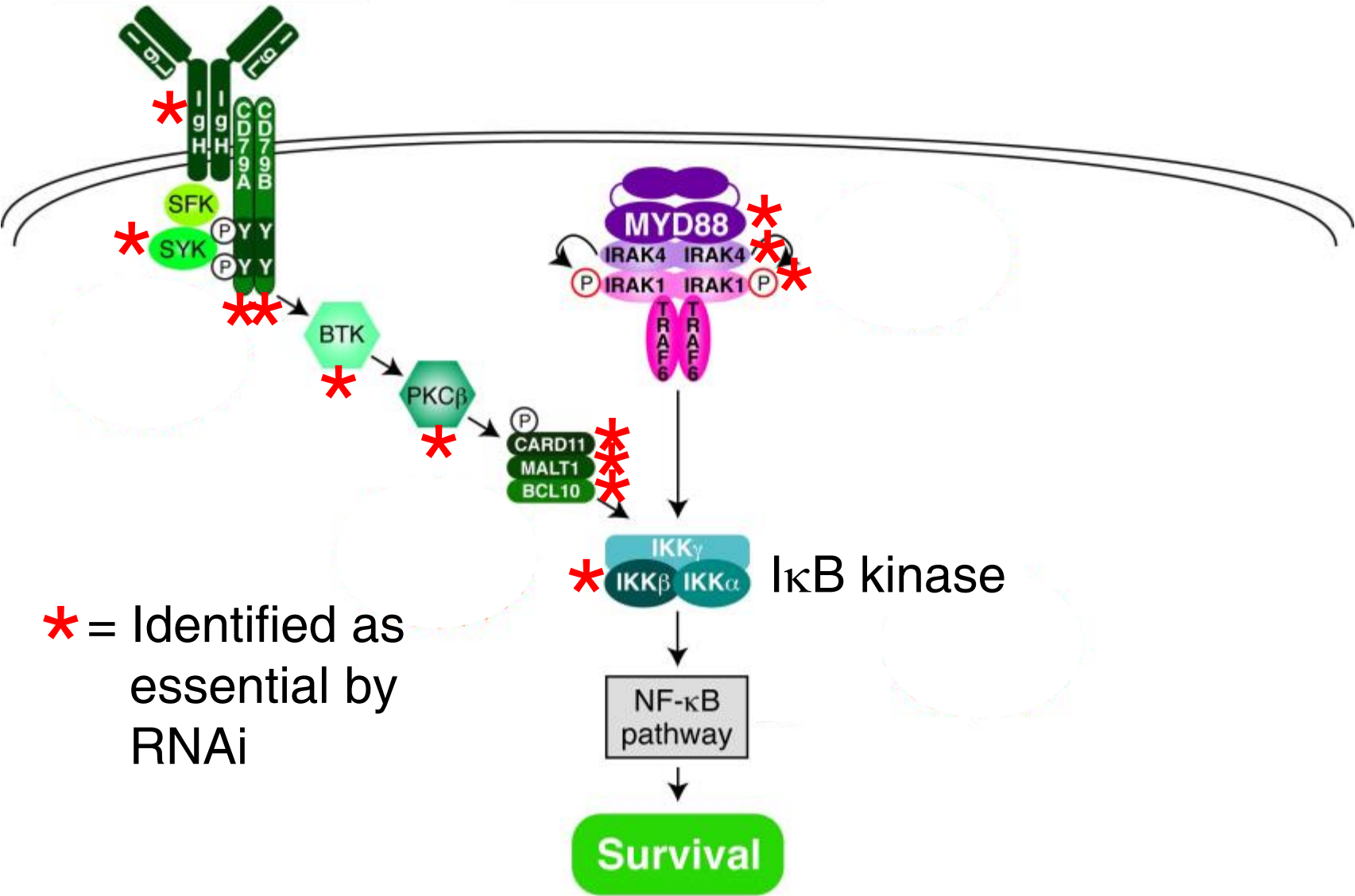
Integration of Functional Genomics and Structural Genomics to Identify Essential Cancer Pathways



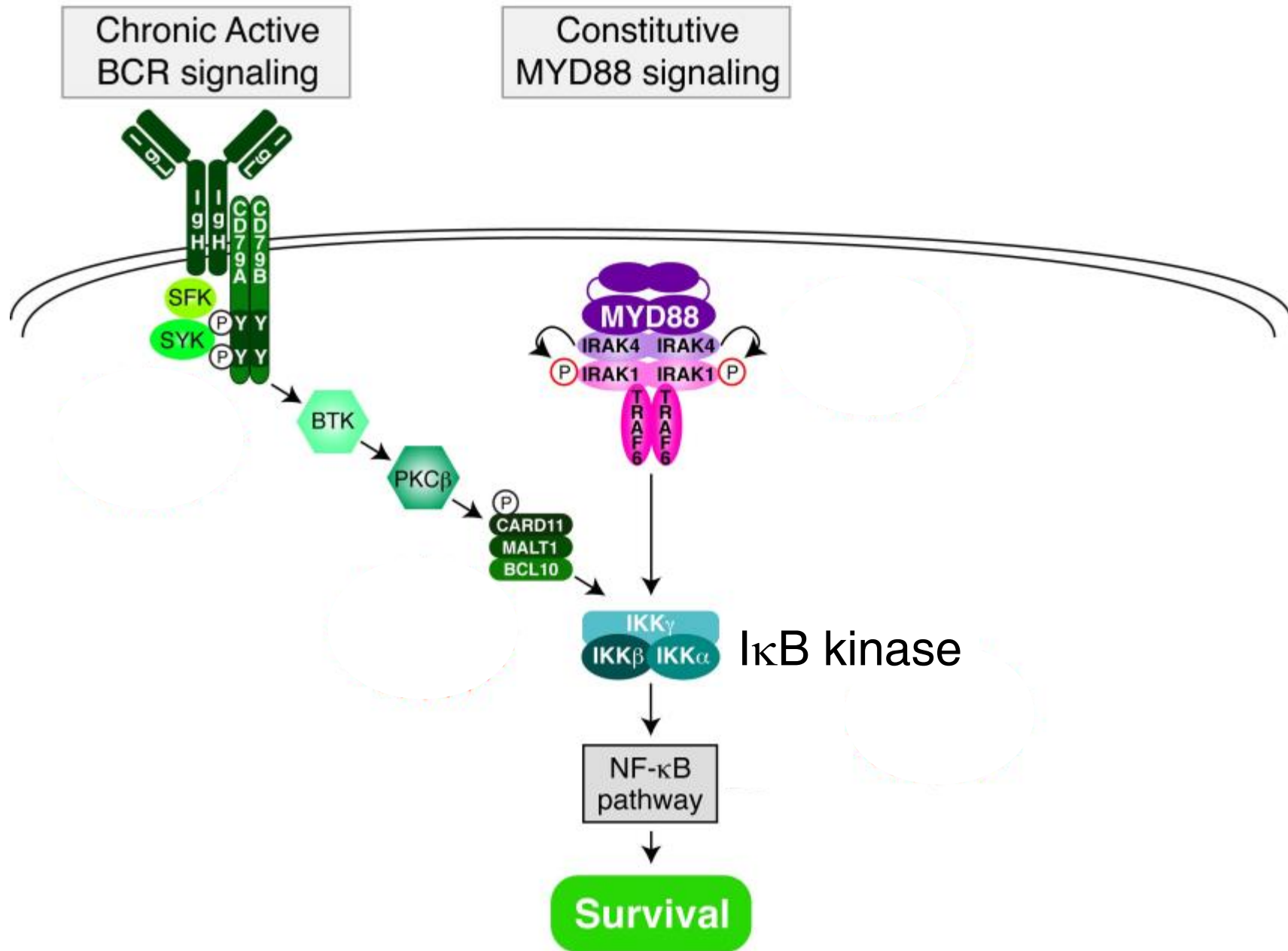
Putative Cancer Drivers in ABC DLBCL From Resequencing



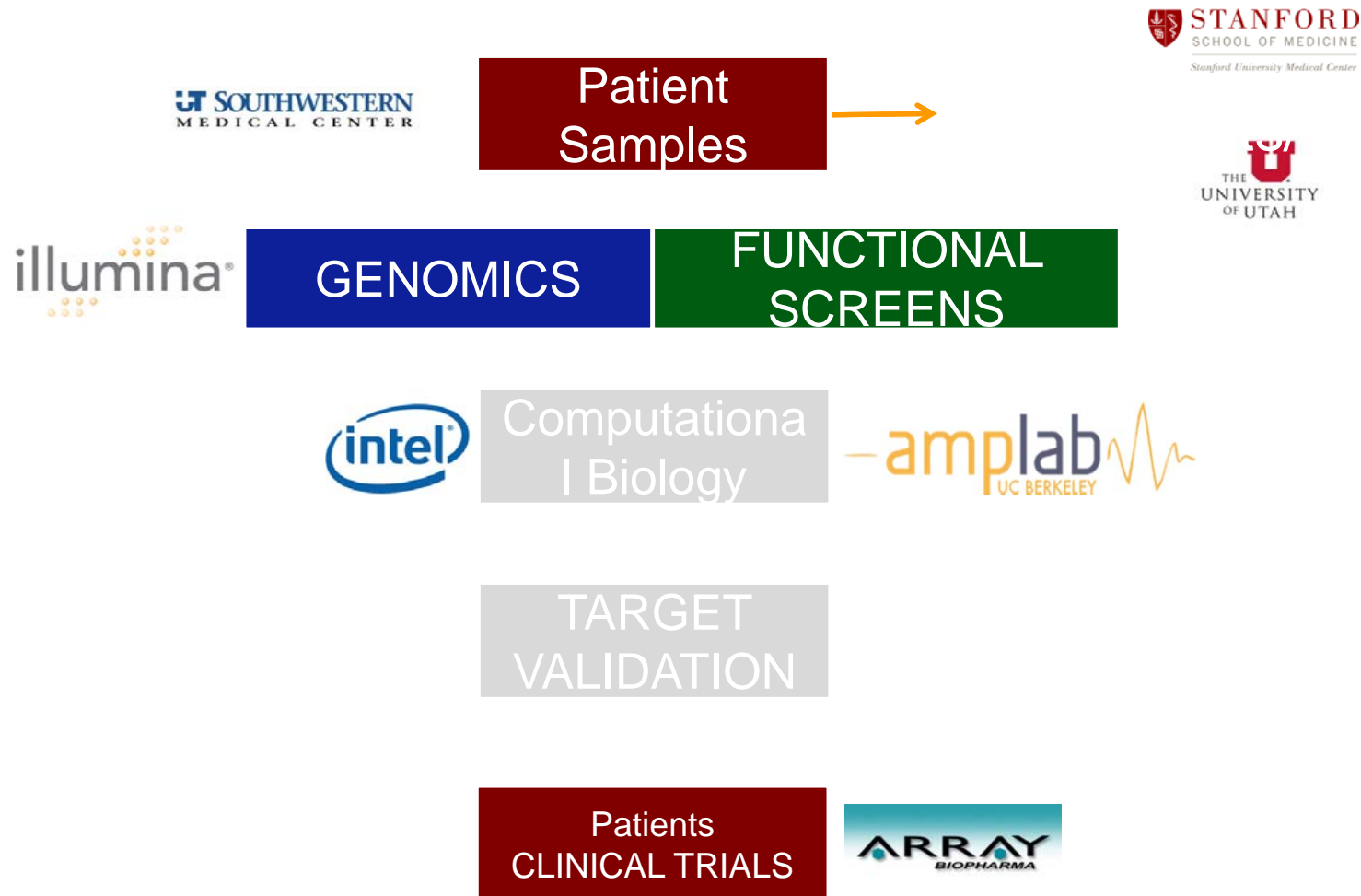
Essential Genes in ABC DLBCL From RNAi Screens



Essential Pathways in ABC DLBCL by Integrative Genomic Analysis



Building Towards “Omically” Guided Therapy and Improving Outcomes for Patients with AML



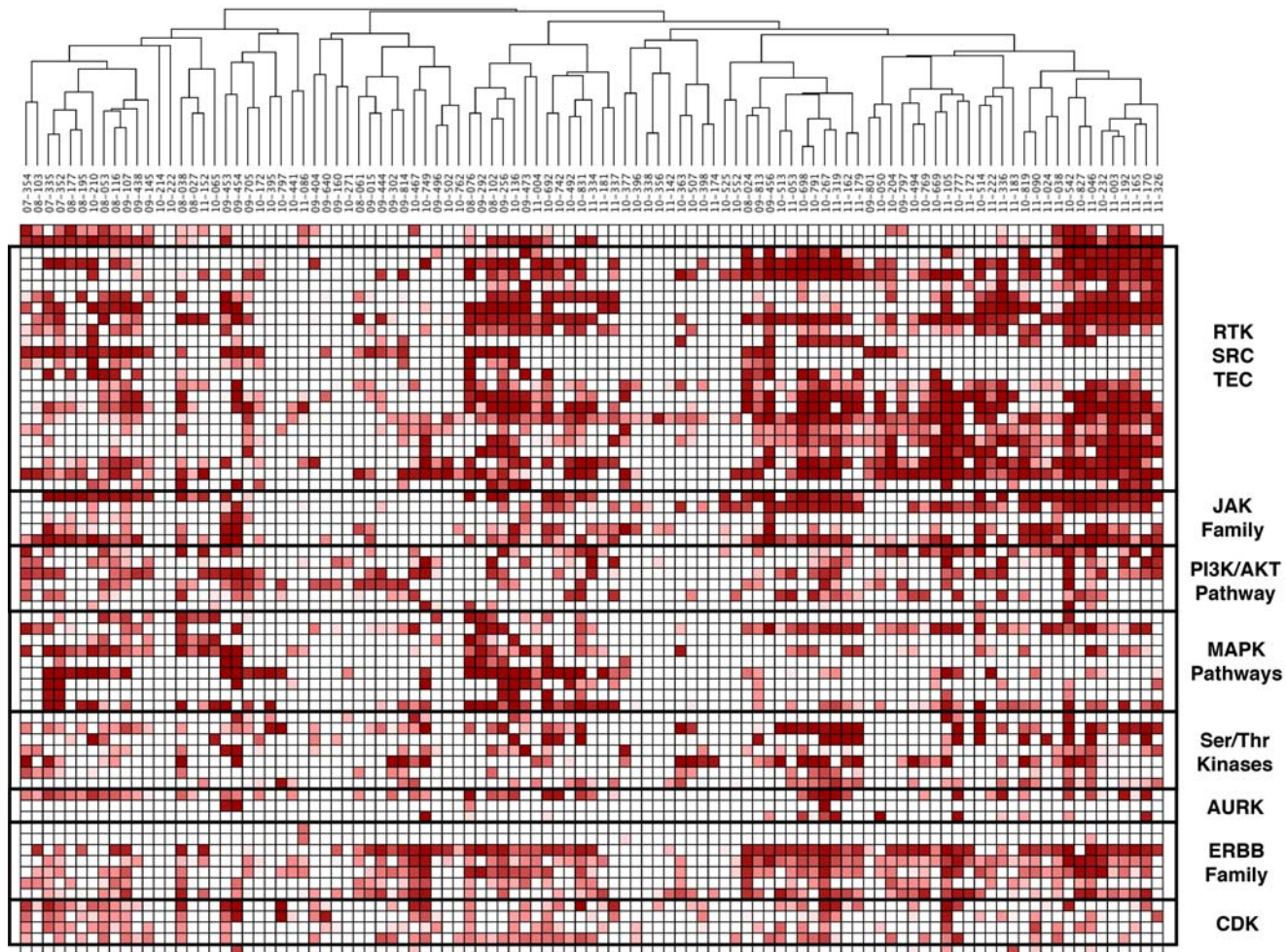
Genomic and Functional Screens

- Whole-genome sequencing (50x primary sample; 30x matched skin biopsy control)
- RNA-seq
- Functional analyses
 - RNAi, kinase inhibitors
- Proteomic analysis
 - Various platforms currently being explored

Data Analysis and Target Validation

- Integration of functional, genomic, and clinical data on every patient
 - LLS SCOR relational database, Oracle
- Pathway analysis and machine learning
 - OHSU Bioinformatics (Shannon McWeeney)
 - Intel
 - David Patterson (AMPLab)
 - David Haussler (PARADIGM)
- Wet-lab validation of transformation, signaling, and clonogenic potential of new oncogenes

Inhibitor Sensitivities of 100 AML Samples

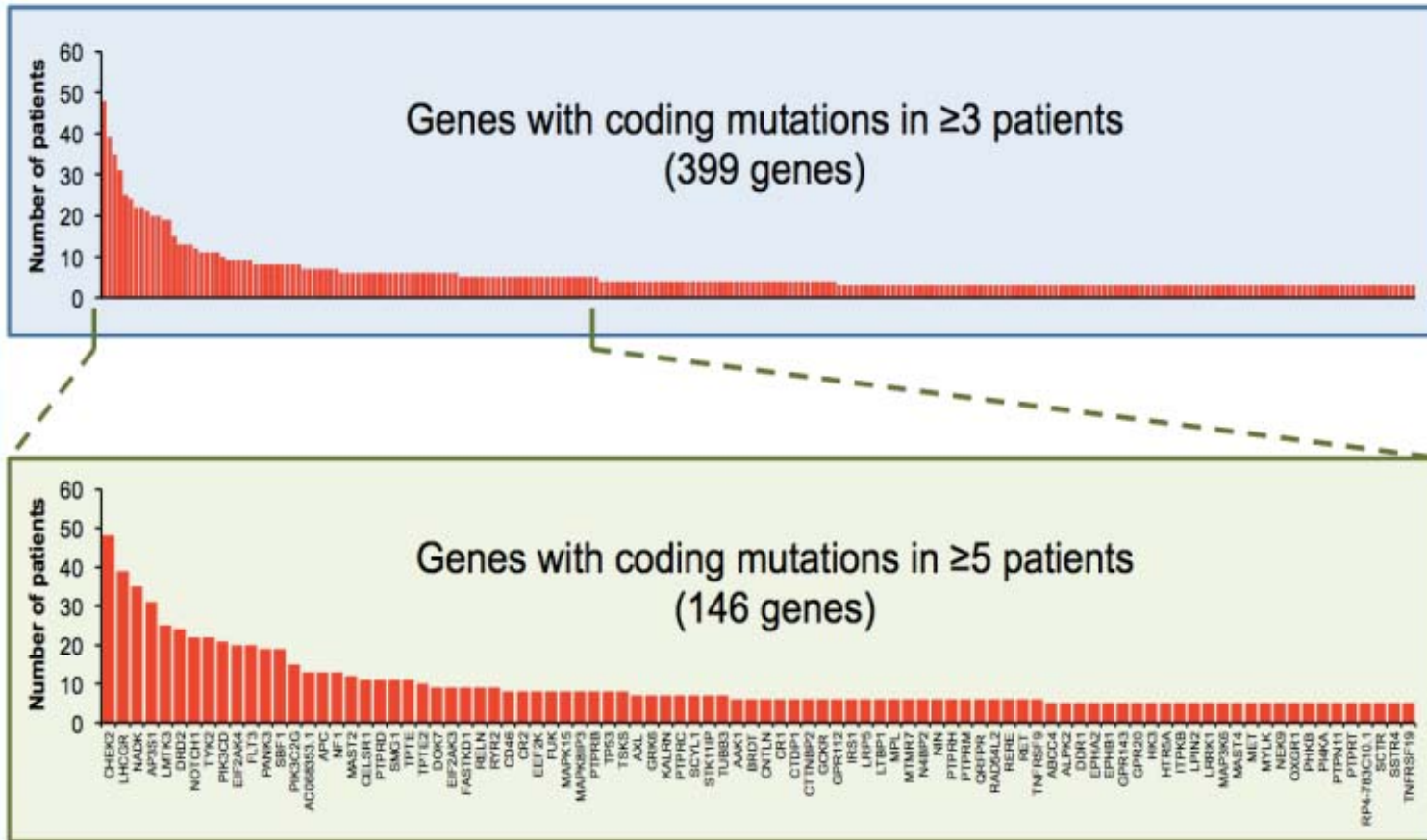


Diversity of drug responses that need to be correlated with tumor genotypes

Lessons From Functional Screening

- Can identify important genes, pathways, drugs in a clinically relevant time frame
- Matching this information with genetic drivers is much more complicated
- Need to integrate with genomics

Few Recurrent, Many Rare Mutations



Top mutated genes in AML
(n=91)

How can we prioritize and understand these data?

Summary of Work to Date

- Functional genomic analysis of >500 patient samples (AML, MPN, ALL)
- Computational strategies developed for data integration
- Wet-lab validation of new oncogenic drivers
- Treatment of individual patients based on these findings
- One clinical trial open, others in development (elaborated in upcoming slides)