National Cancer Institute

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

NCI Center for Cancer Genomics

Our Mission is to develop and apply cutting edge genome science to better treat cancer patients

1. DISCOVERY by genomics and functional genomics

2. Drug Development

3. DNA-based Diagnosis

4.Personalized Treatment

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3 immediate goals of CCG

1. FFPE (formadehyde fixed paraffin embedded)

The critical path to:

- rarer tumors
- minority patient groups
- tumor progression
- drug resistance
- AND The Clinic

Where we are today

TCGA / Target Pipelines 1.0

special, non-routine, “fragile”

- Plunge sample directly into liquid nitrogen in operating room
- -80C freezer storage
- Specialized DNA or RNA preps

Where we're going in 2012

TCGA/Target Pipelines 2.0 = what now happens to every biopsy in every clinic

plunge sample into formaldehyde @room temp

embed in paraffin

slice for pathology

NOW dissect and prep for DNA/RNA: new SOPs

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3 goals of CCG

*2. Adopting personalized tumor diagnosis and treatment

Fast but not foolish is the objective

Where we are today:

- EGFR testing in lung cancer as test
- *How to do this better? Your role?

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3 goals of CCG

*3. Prepare patients and doctors for personal genomics

protect privacy without blocking treatment or research

issues for full-exome or whole genome sequencing

Science Rules!

- neither you nor I can fully control where breakthroughs will be, including with much more money

- seek best match: bottom up (what science community brings us) and top down (what we want)

- Discovery about X might solve your problem Y
- really true in cancer:

Path for Discovering Effective New Treatments: Example from childhood programs

TARGET Discovery Programs

PPTP Preclinical Evaluation

COG Phase 1 Clinical Trial

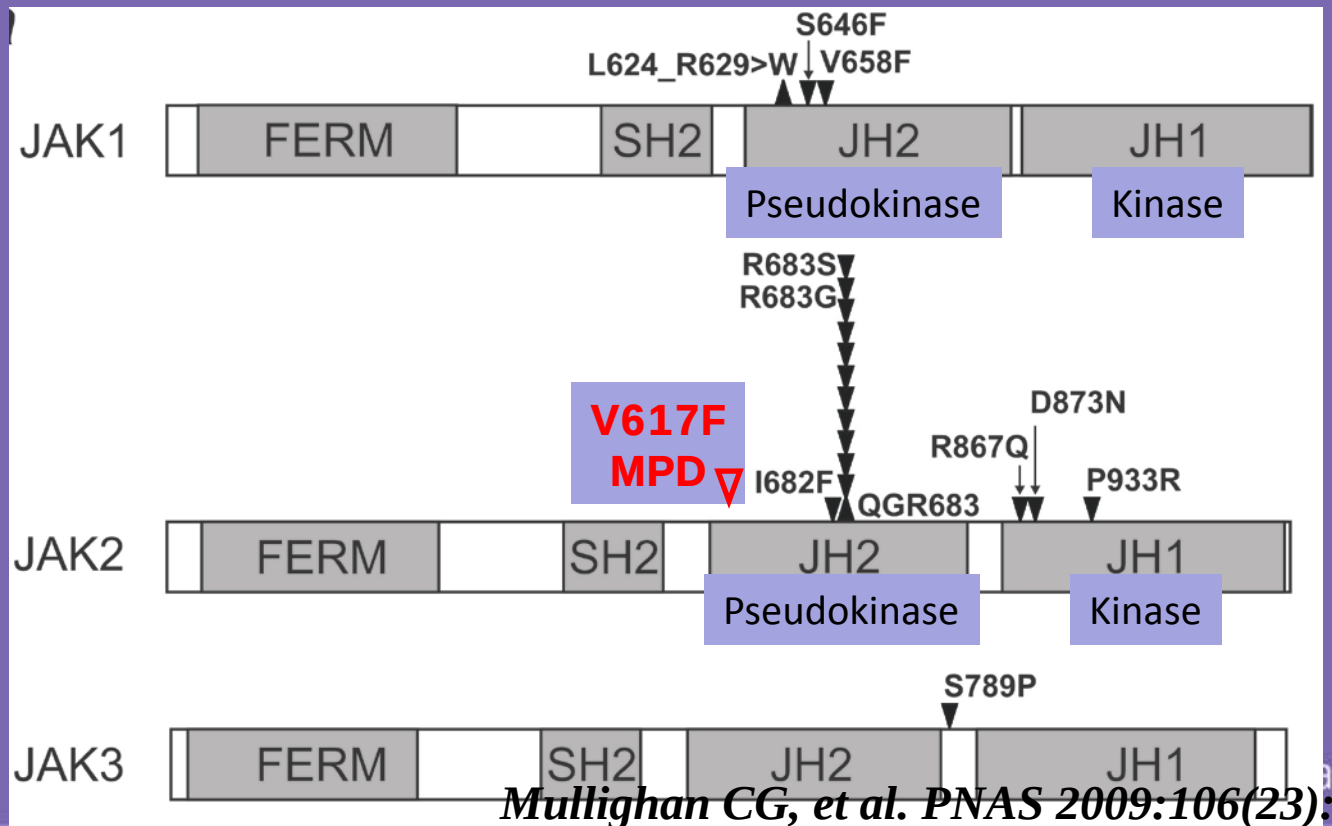
COG Definitive Clinical Trial

TARGET

St. Jude Children's Research Hospital
Pediatric Cancer Genome Project
Washington University

JAK mutations in “BCR-ABL1-like” ALL

- JAK2 (n=16): 10 R683G; 3 non-R683G pseudokinase domain; 3 kinase domain
- JAK1 (n=3): 3 pseudokinase domain
- JAK3 (n=1): uncertain functional consequences



Mullighan CG, et al. PNAS 2009:106(23):9414-9418

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Clinical Translation by COG Consortium

- Phase 1 trial of JAK inhibitor ruxolitinib (INCB18424) in Sept 2010 JAK-ALL kids
- Ruxolitinib in development for adults with myelofibrosis (MF):
  - JAK2 mutations common for this condition
  - NDA filed in June 2011
- Eventual COG plan for combining JAK inhibitor for JAK-mutant ALL in same way that imatinib has been added to standard chemotherapy for BCR-ABL ALL.

“Spice chest” of highly specific drugs is woefully incomplete

Every tumor will need its best match

Combinatorics: a new, complex opportunity

DNA may help predict patient side effects

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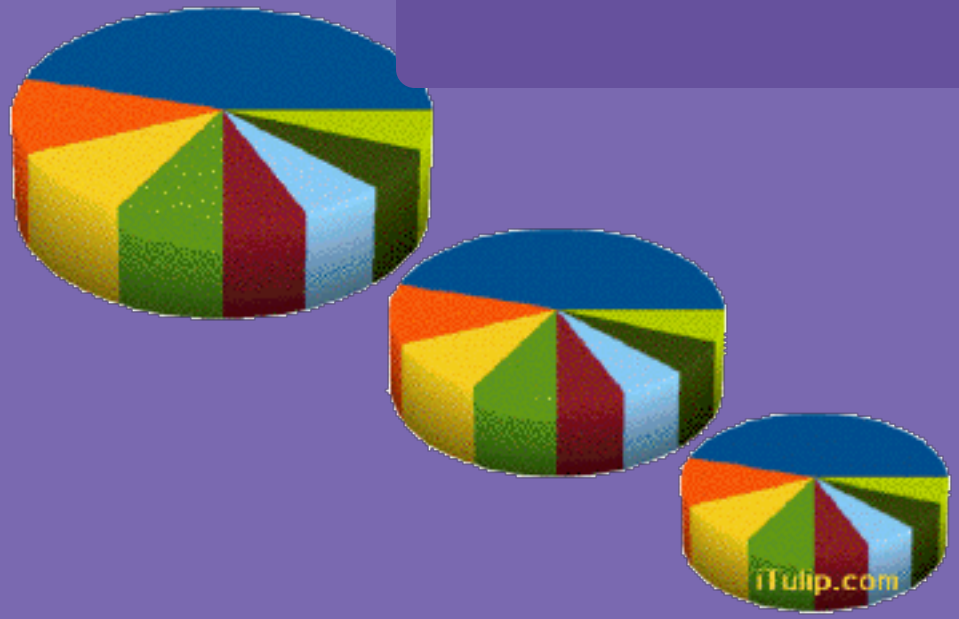
*The Pie is Shrinking

Help!



Perspective on CCG founding

Why now? Why me?

Architecture and function of molecular gene networks

Chromatin immunoprecipitation

mRNA extraction

Methyl-sensitive DNA preparation

Other input preparations

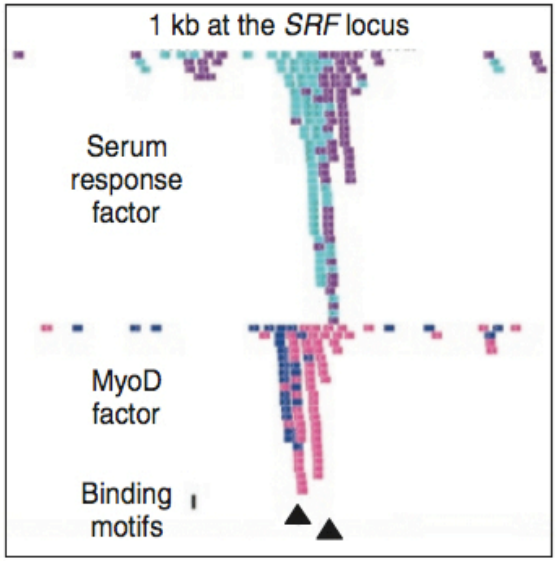
High throughput DNA sequencing

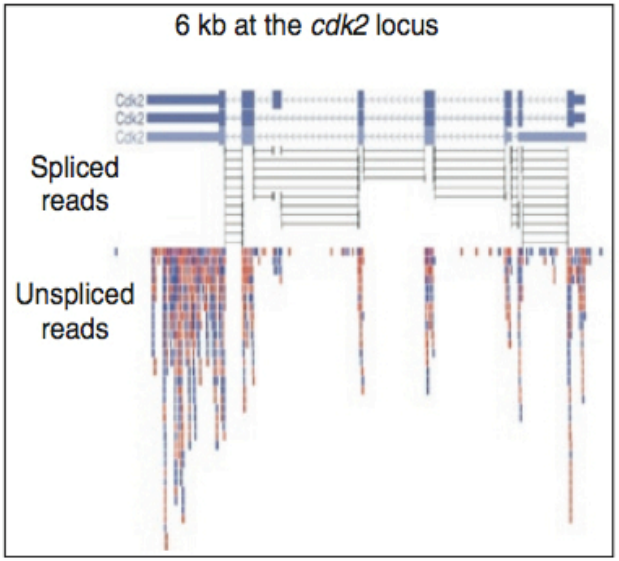
Other (microRNA, 3C, ribonucleoprotein, DNase-hypersensitive sites, nucleosome position, etc.)

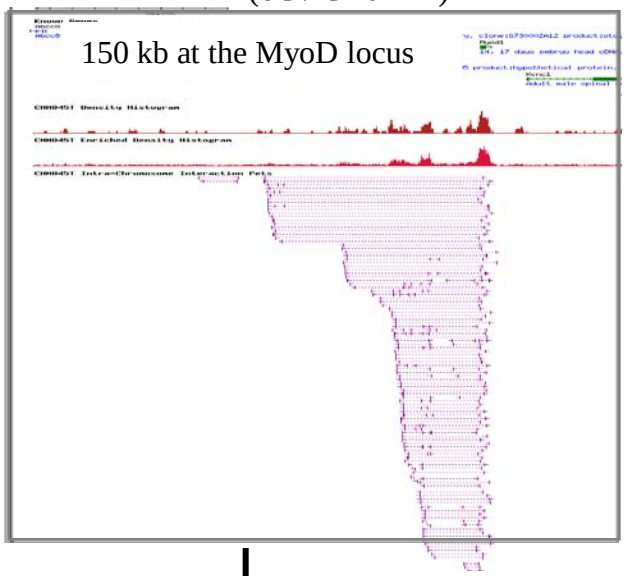
ChIP-Seq

mRNA-Seq

Chromatin Capture (6C / ChiaPET)

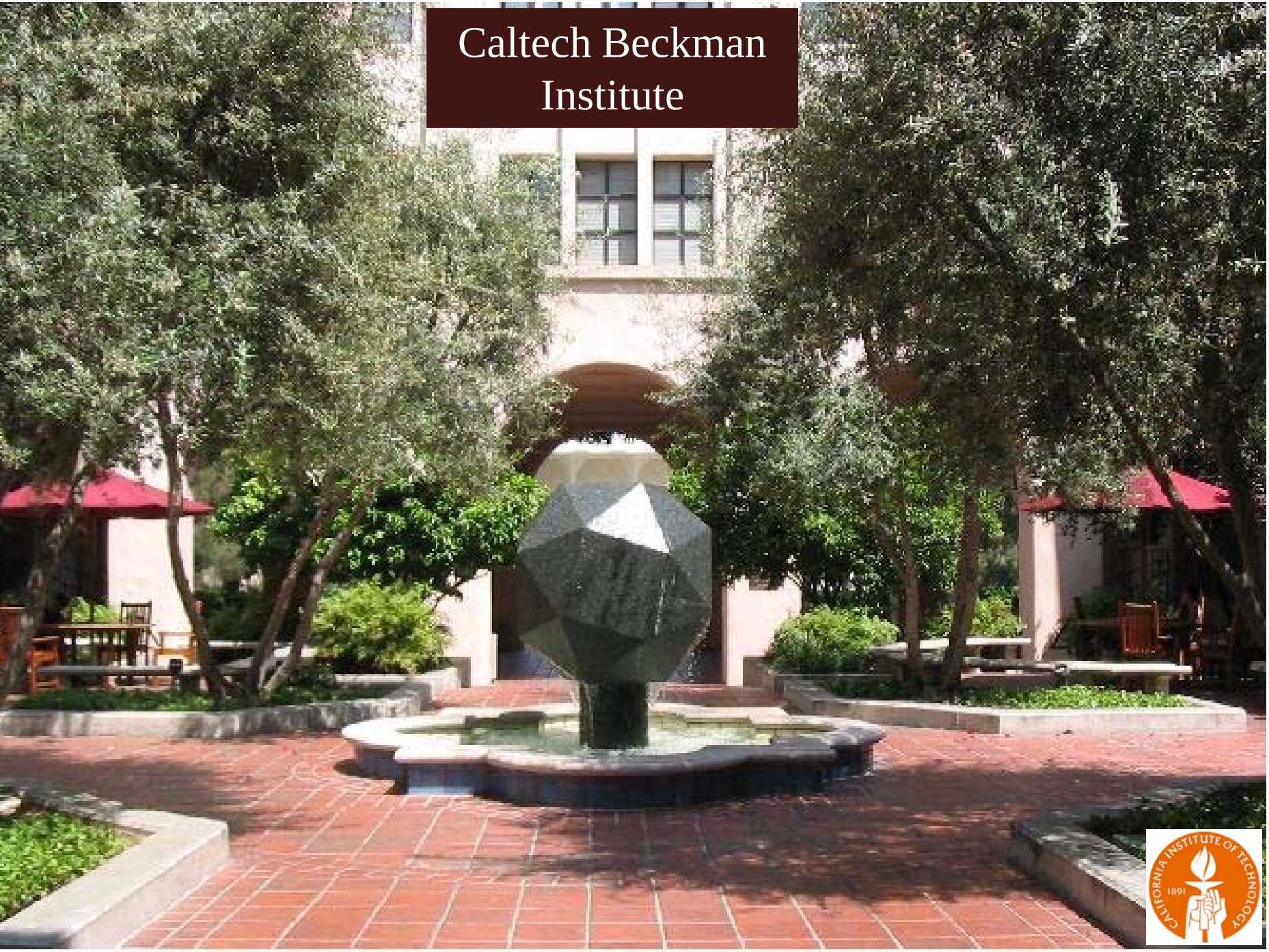






Which factors bind where?
What DNA motifs cause occupancy?

Which genes expressed?
Which isoforms?

Long distance connectivity?
Which regulatory regions interact with which promoters?

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