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Translating the Cancer Genome:
A Drug Discovery Perspective

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Institute for Applied Cancer Science
Department of Genomic Medicine
MD Anderson Cancer Center.

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Agenda

- Barriers to progress in the fight against cancer.
  - Complexity
  - Few successes but many failures
  - Focus on personalized medicine
- Functional Genomics to identify genetic dependencies.
  - Prioritization must be based on both genomic and biological weight of evidence.
- Introduction to the Institute for Applied Cancer Science.
  - How we utilize genomic information to develop the next generation of targeted therapies.
- Question and Answer Session

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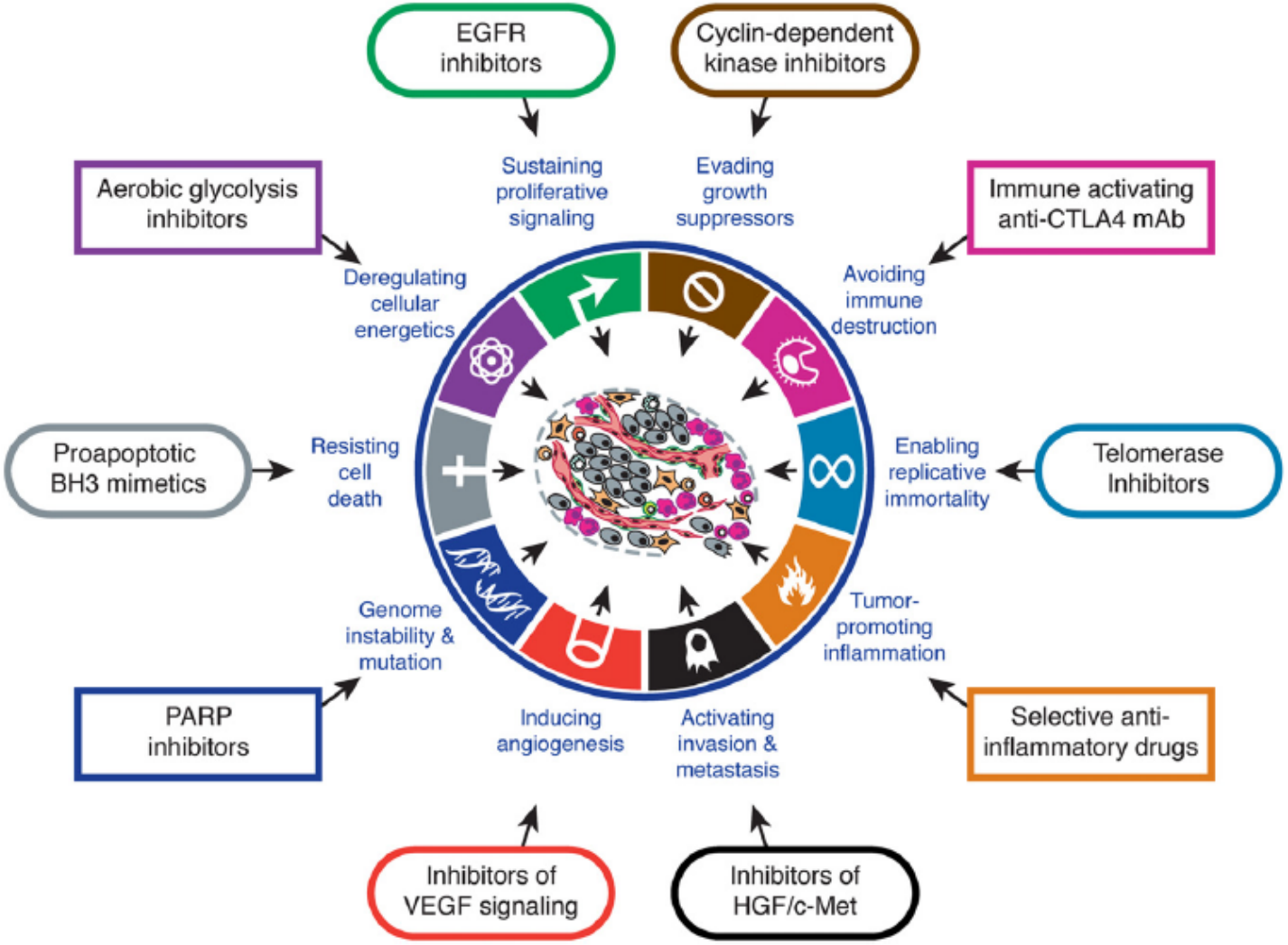
The Hallmarks of Cancer: *Therapeutic Opportunities*



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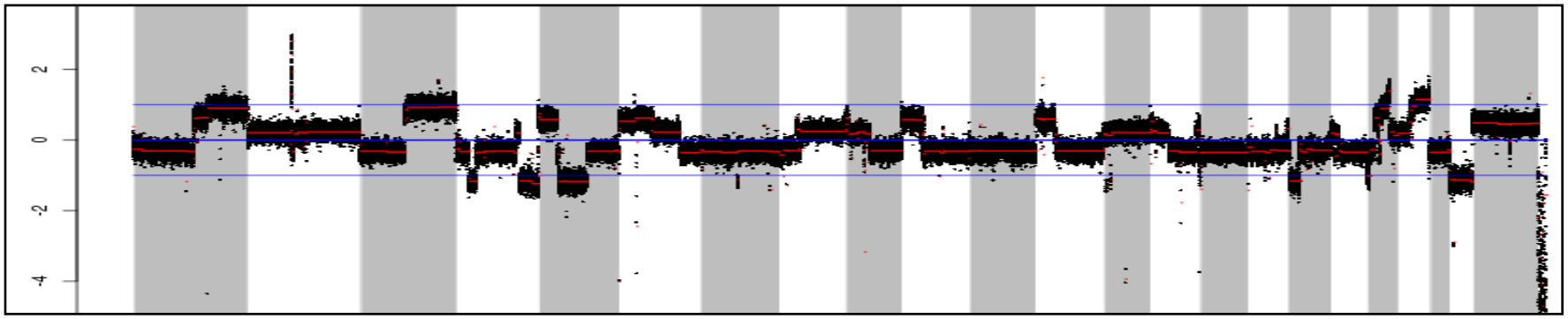
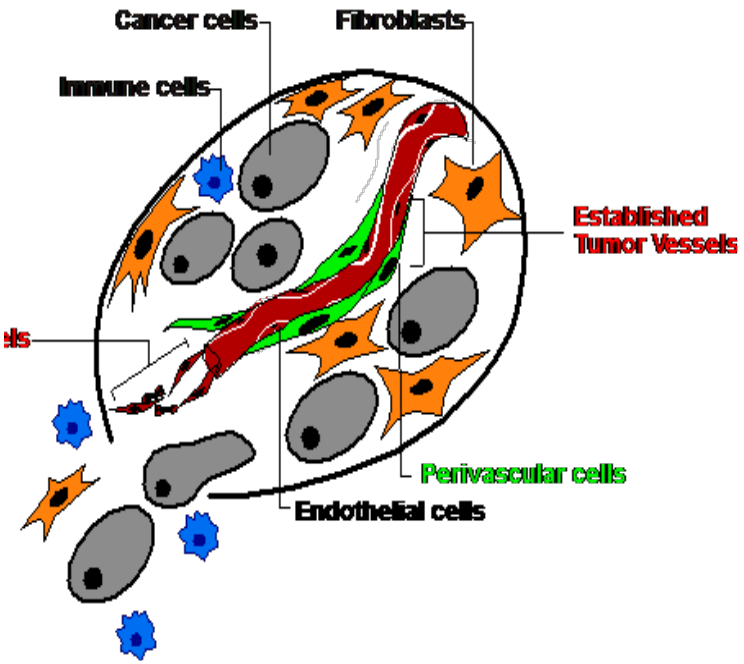
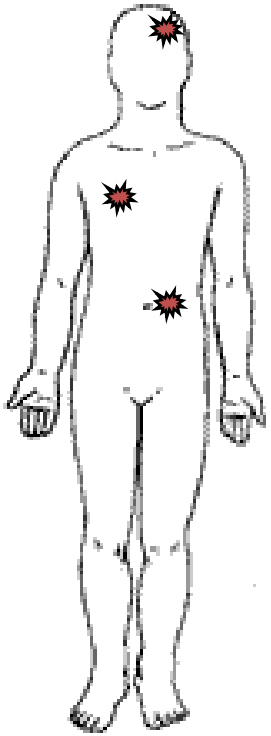
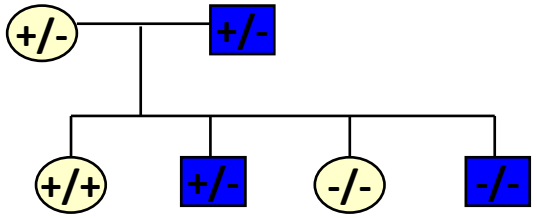
Cancer is Complex

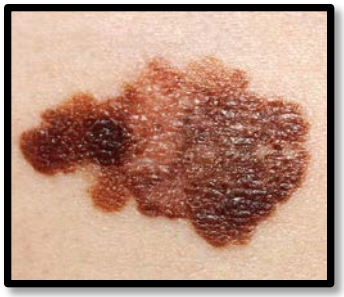




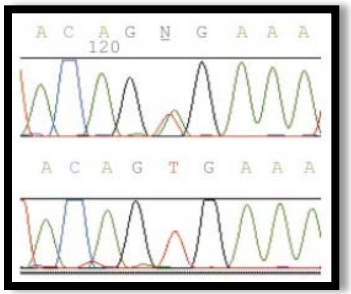




Cancer genomics guides personalized medicine



BRAF V600E



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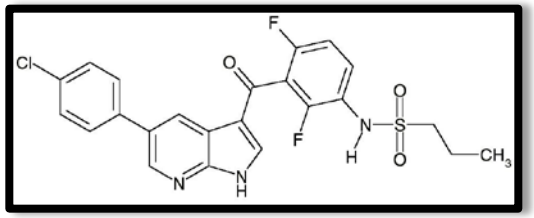
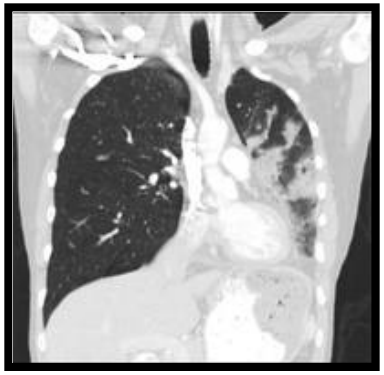
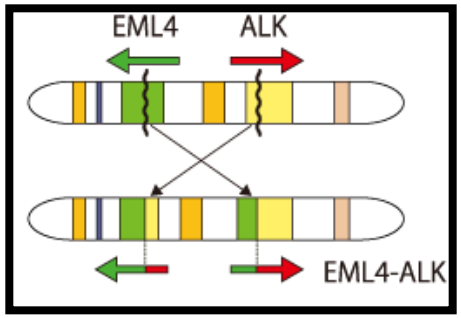
Vemurafenib

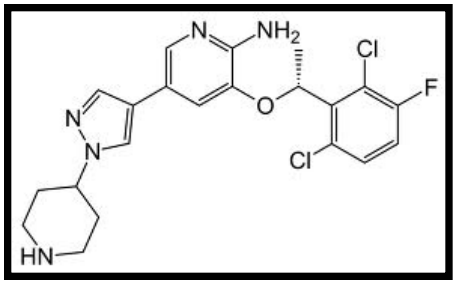


Disease → Pathogenesis → Targeted Therapy





EML4-ALK Fusion



Crizotinib

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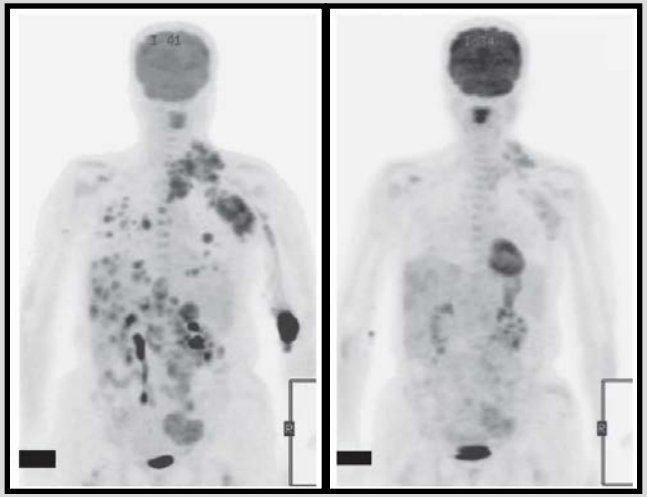
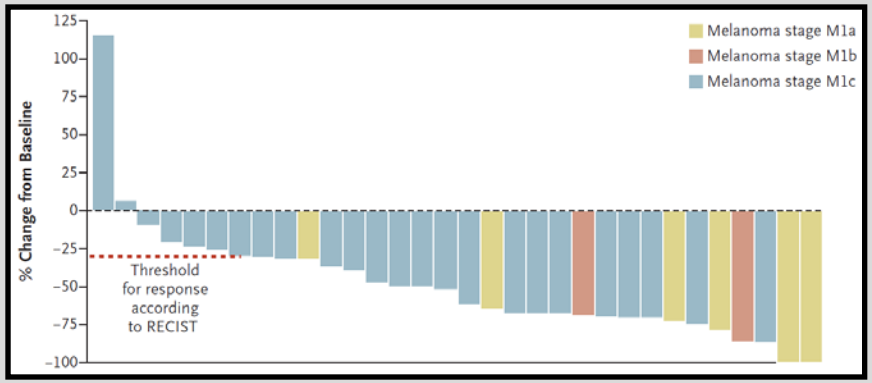
Promise of Personalized Medicine

Vemurafenib

Pre Post

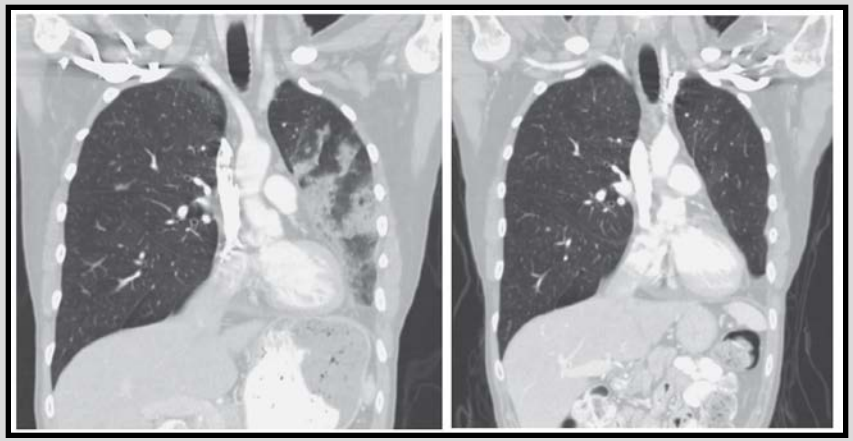


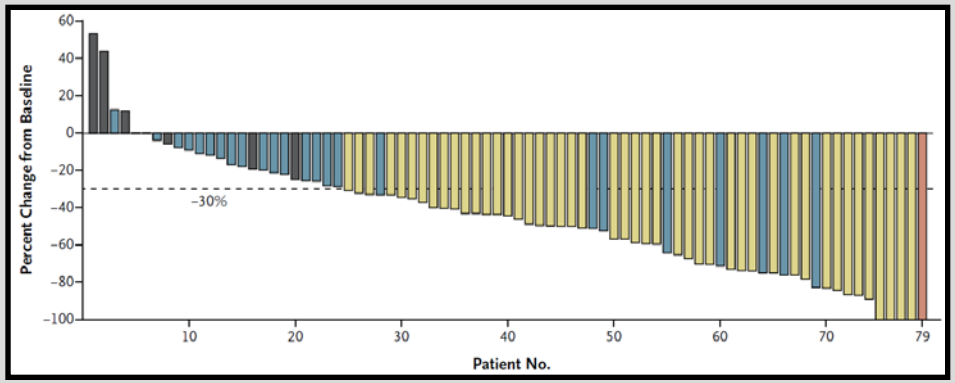


Flaherty et al. NEJM 2010

Crizotinib

Pre Post





Kwak et al. NEJM 2010

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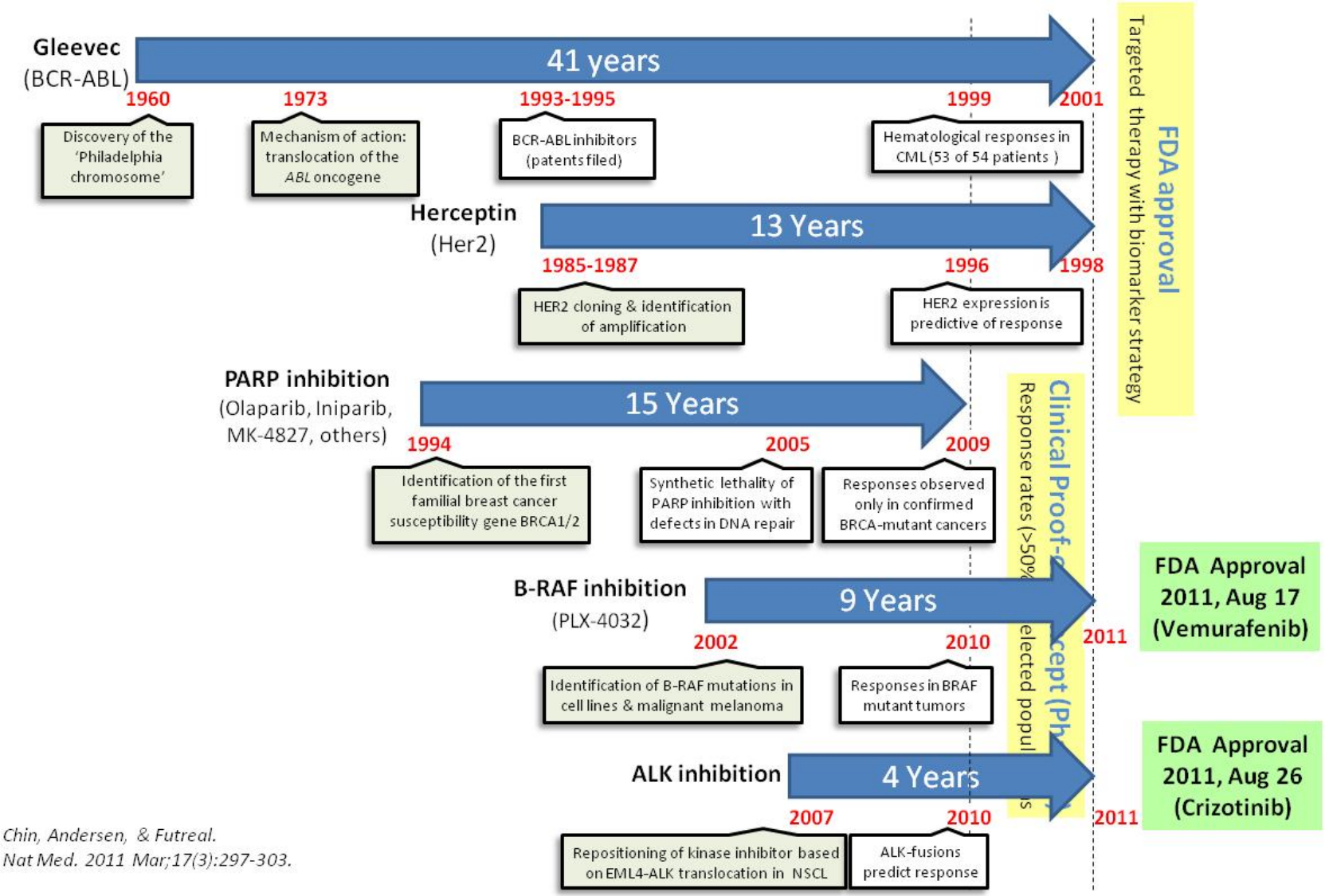
Cancer genetics are accelerating the time from 'target discovery' to 'clinical Proof-of-Concept'



Chin, Andersen, & Futreal.
Nat Med. 2011 Mar;17(3):297-303.

Barriers to progress

- Elemental knowledge of cancer omics.
  - Thinking beyond the genome.
- Limited insights into factors driving cancer.
  - Genetic and functional weight of evidence.
- Poor understanding of the target's "biology"
  - In what context (cellular/genetic) is the target rate-limiting?
- Lack of insight on appropriate combination
  - Tumor will find a way to bypass a single-point intervention
  - Co-extinction is required to shut down a complex highly-redundant network

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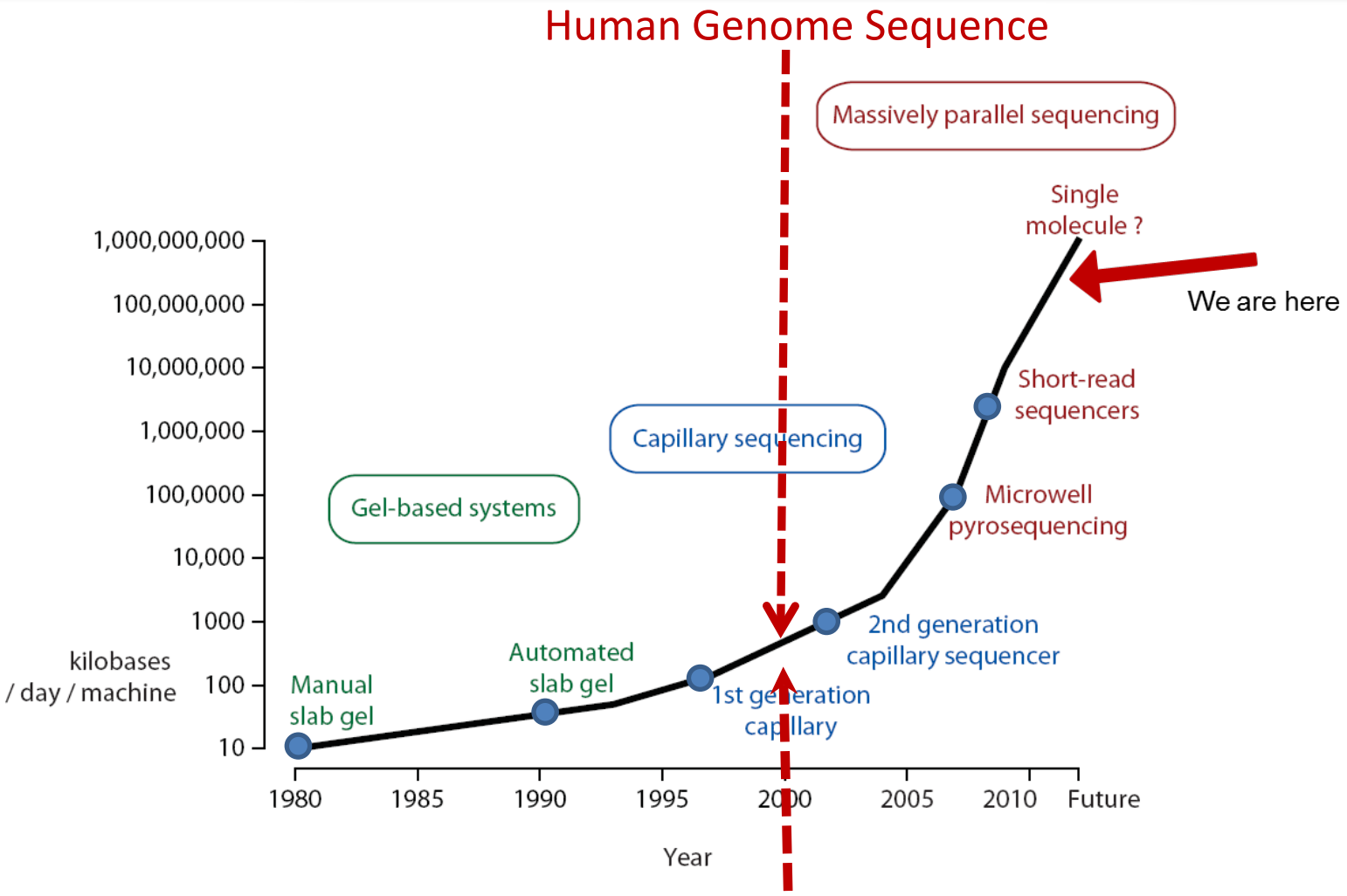
Next Gen Sequencing: Informing personalized medicine



Andy Futreal

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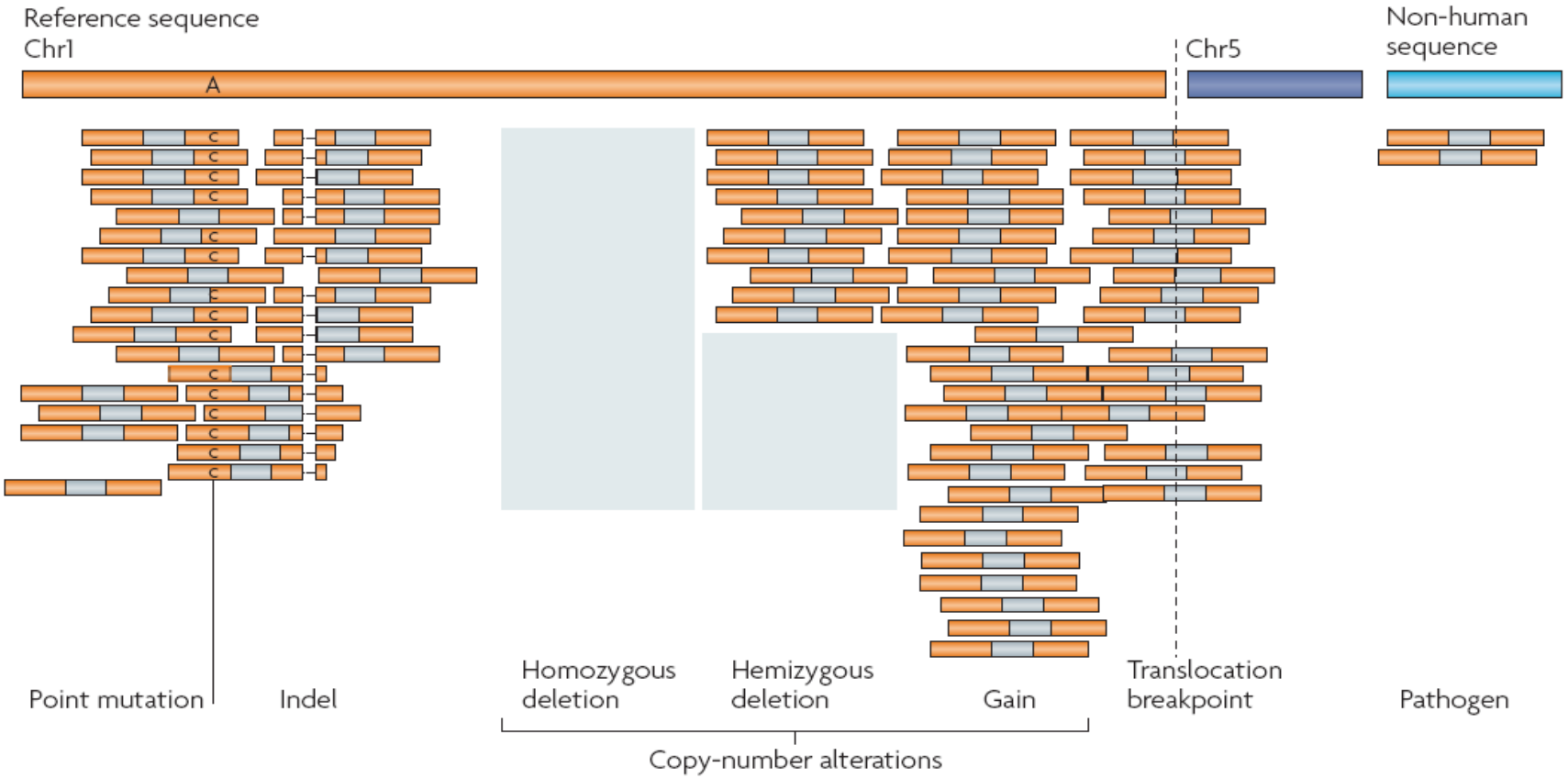
Massively parallel sequencing enables comprehensive genome characterization



Nature Reviews | Genetics

Meyerson, Getz and Gabriel. NRG 2011

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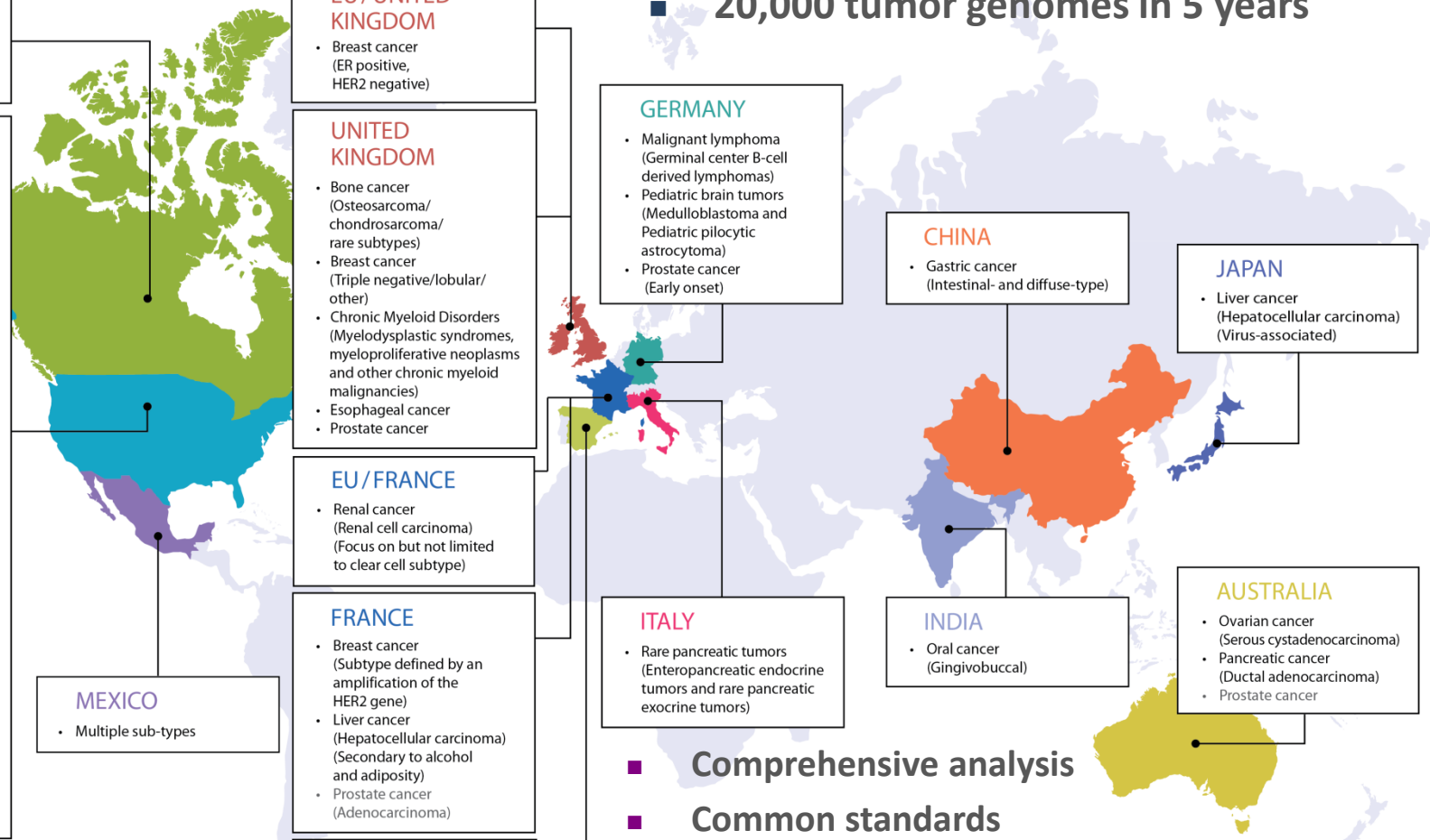
International Cancer Genome Consortium Projects

- 40 project teams in 15 jurisdictions
- 20,000 tumor genomes in 5 years



CANADA
- Pancreatic cancer (Ductal adenocarcinoma)
- Prostate cancer (Adenocarcinoma)

UNITED STATES
- Bladder cancer
- Blood cancer (Acute myeloid leukemia)
- Brain cancer (Glioblastoma multiforme/ lower grade glioma)
- Breast cancer (Ductal & lobular)
- Cervical cancer (Squamous)
- Colon cancer (Adenocarcinoma)
- Endometrial cancer (Uterine corpus endometrial carcinoma)
- Gastric cancer (Adenocarcinoma)
- Head and neck cancer (Squamous cell carcinoma/ Thyroid carcinoma)
- Renal cancer (Renal clear cell carcinoma/ Renal papillary carcinoma)
- Liver cancer (Hepatocellular carcinoma)
- Lung cancer (Adenocarcinoma/ squamous cell carcinoma)
- Ovarian cancer (Serous cystadenocarcinoma)
- Prostate cancer (Adenocarcinoma)
- Rectal cancer (Adenocarcinoma)
- Skin cancer (Cutaneous melanoma)

MEXICO
- Multiple sub-types

EU / UNITED KINGDOM
- Breast cancer (ER positive, HER2 negative)

UNITED KINGDOM
- Bone cancer (Osteosarcoma/ chondrosarcoma/ rare subtypes)
- Breast cancer (Triple negative/lobular/ other)
- Chronic Myeloid Disorders (Myelodysplastic syndromes, myeloproliferative neoplasms and other chronic myeloid malignancies)
- Esophageal cancer
- Prostate cancer

EU / FRANCE
- Renal cancer (Renal cell carcinoma) (Focus on but not limited to clear cell subtype)

FRANCE
- Breast cancer (Subtype defined by an amplification of the HER2 gene)
- Liver cancer (Hepatocellular carcinoma) (Secondary to alcohol and adiposity)
- Prostate cancer (Adenocarcinoma)

SPAIN
- Chronic lymphocytic leukemia (CLL with mutated and unmutated IgVH)

GERMANY
- Malignant lymphoma (Germinal center B-cell derived lymphomas)
- Pediatric brain tumors (Medulloblastoma and Pediatric pilocytic astrocytoma)
- Prostate cancer (Early onset)

ITALY
- Rare pancreatic tumors (Enteropancreatic endocrine tumors and rare pancreatic exocrine tumors)

CHINA
- Gastric cancer (Intestinal- and diffuse-type)

INDIA
- Oral cancer (Gingivobuccal)

JAPAN
- Liver cancer (Hepatocellular carcinoma) (Virus-associated)

AUSTRALIA
- Ovarian cancer (Serous cystadenocarcinoma)
- Pancreatic cancer (Ductal adenocarcinoma)
- Prostate cancer

- Comprehensive analysis
- Common standards
- Public data release
- Coordination & comparison

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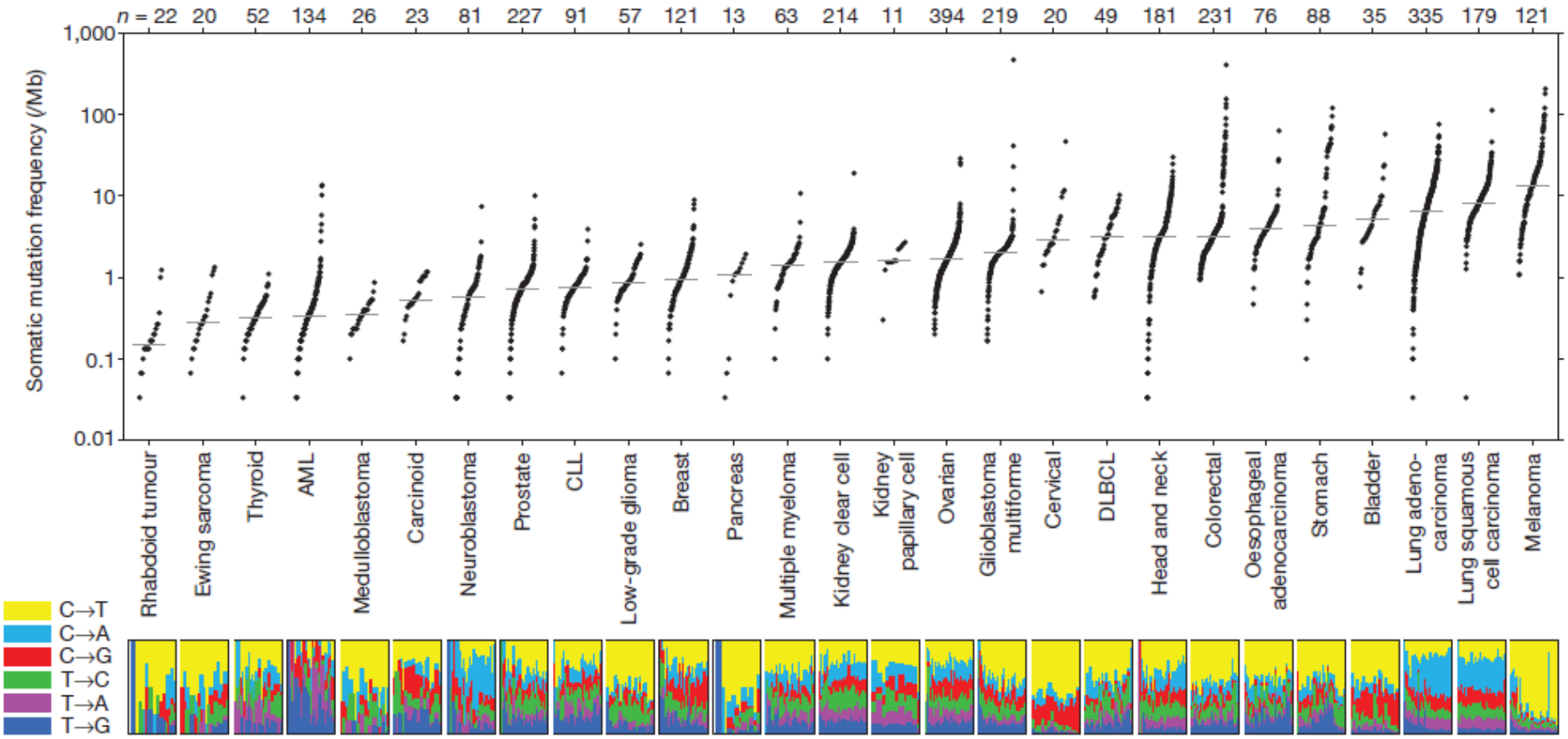
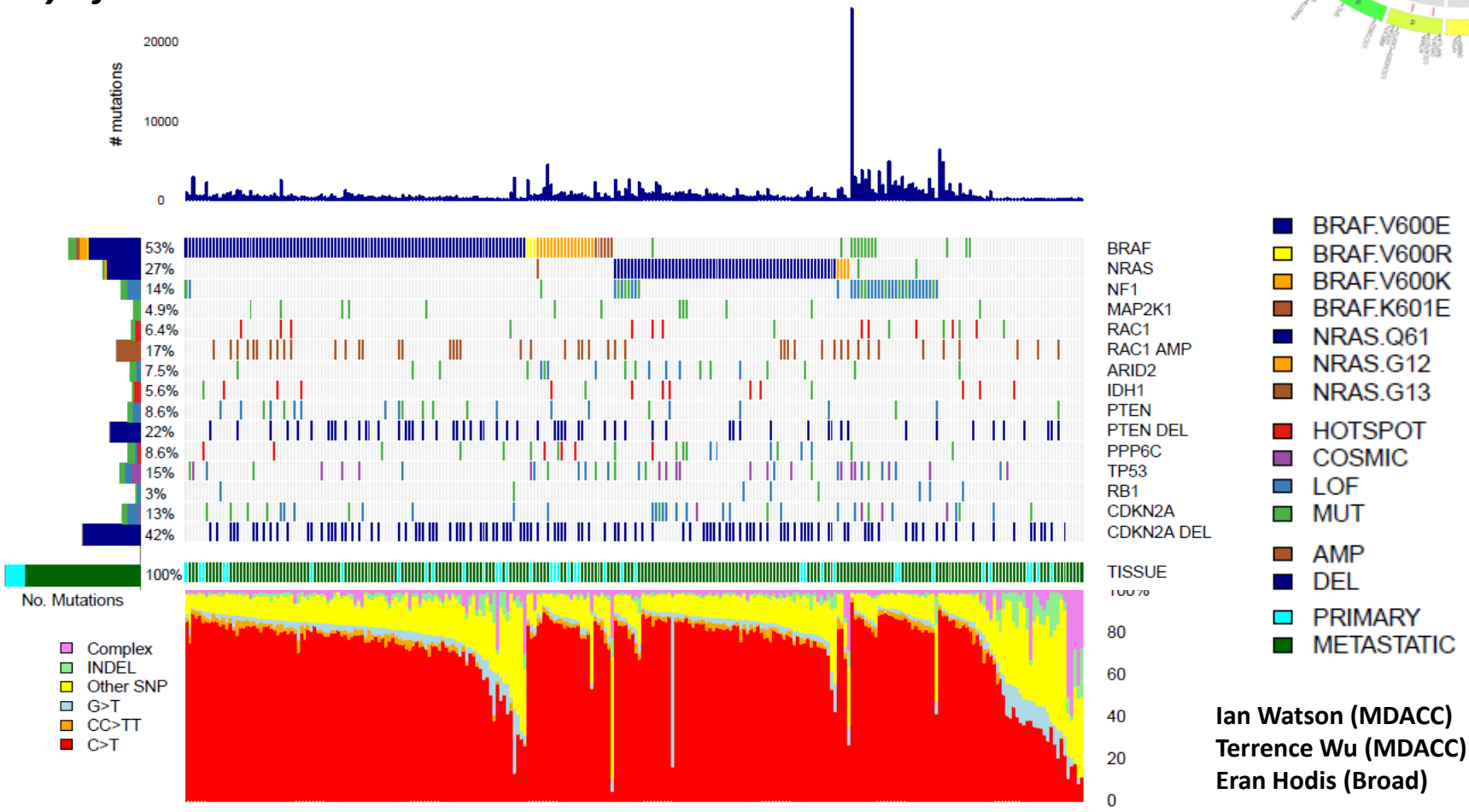
The landscape of somatic mutations in human cancer



Lawrence et al. Nature 2013

Melanoma TCGA: Landscape of somatic mutations

Courtesy of Ian Watson



Ian Watson (MDACC)
Terrence Wu (MDACC)
Eran Hodis (Broad)

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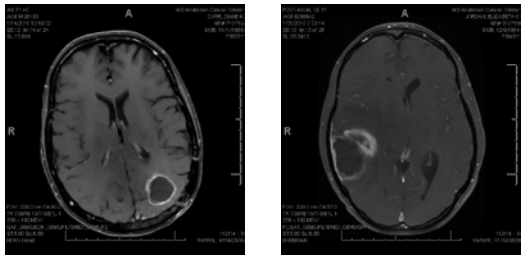
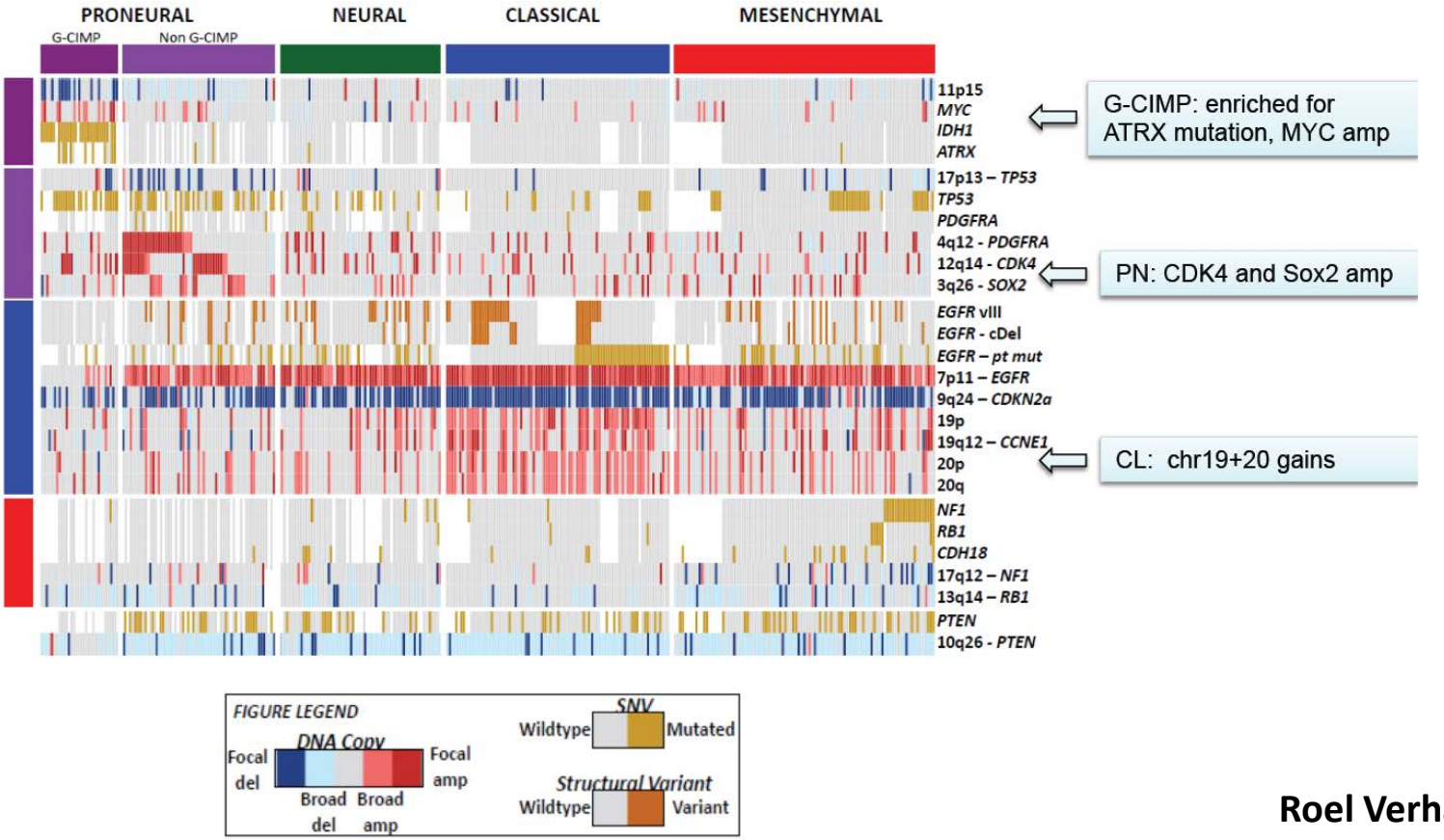
Subtype specific genetic alterations inform GBM pathogenesis





Roel Verhaak

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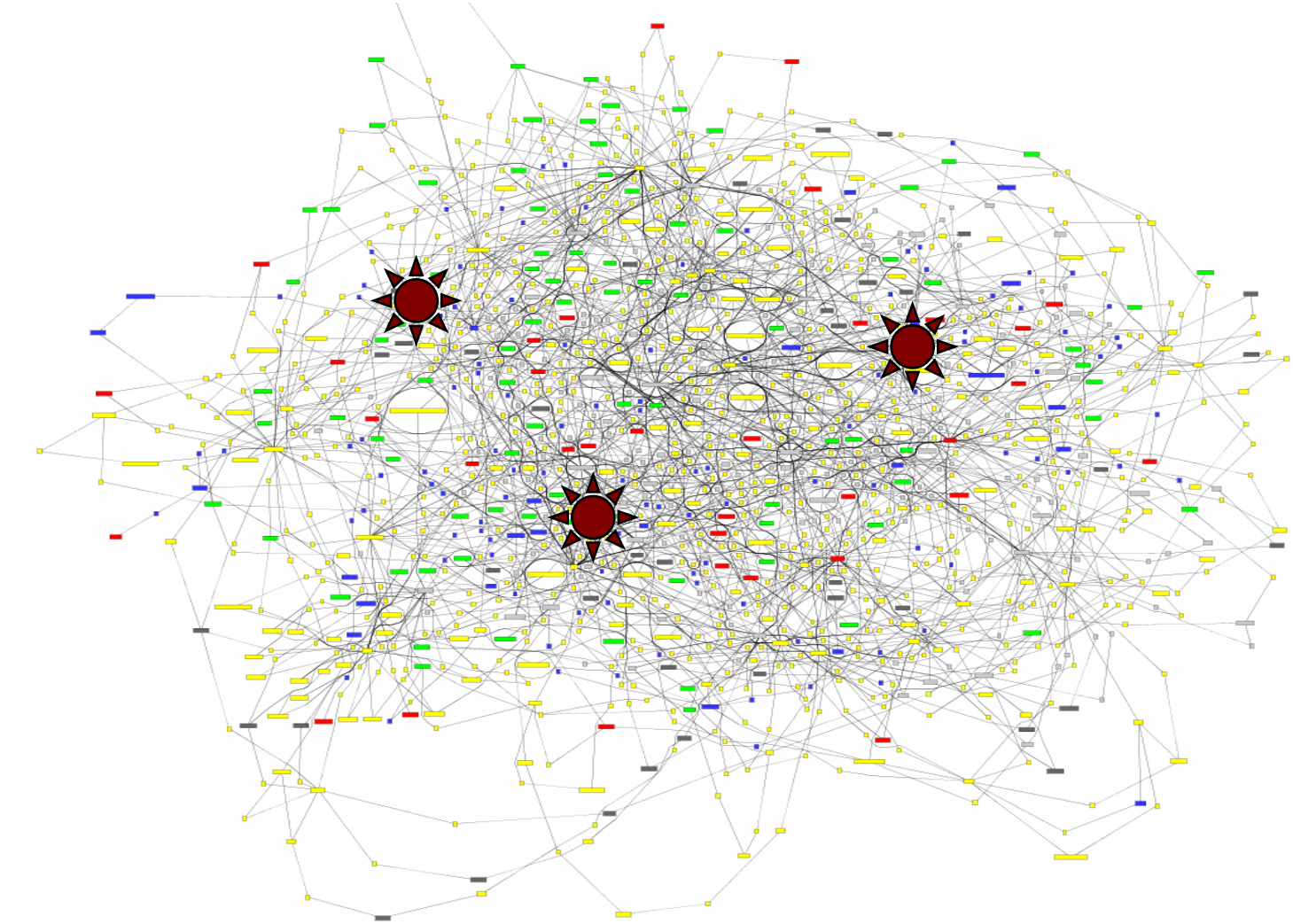
Cancers possess myriad mutations that cooperate to maintain tumor survival



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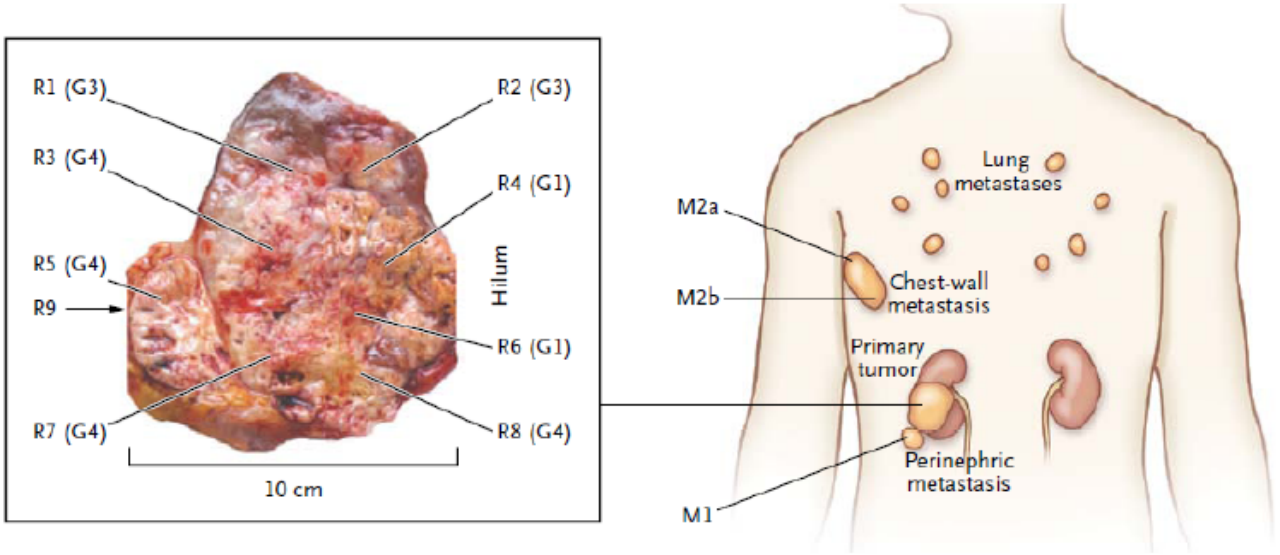
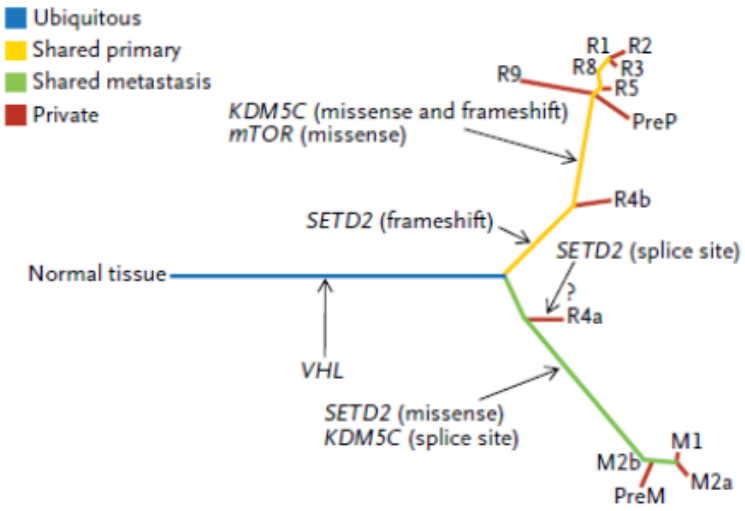
Cancer Genomics informs on clonal evolution





Gerlinger et al. NEJM 2012

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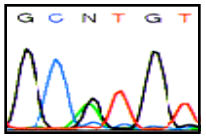
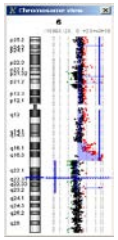
Atlas: Comprehensive Omic Profiling Ongoing

Dr. Gordon Mills

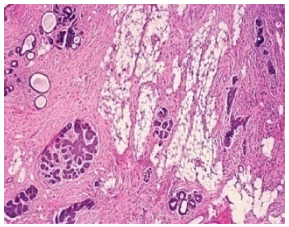
Epigenetics
(DNA methylation)

Tumor genotyping
(mutations, sequencing, amplifications, deletions)



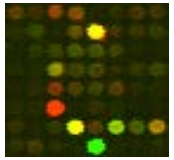


Tumor phenotype

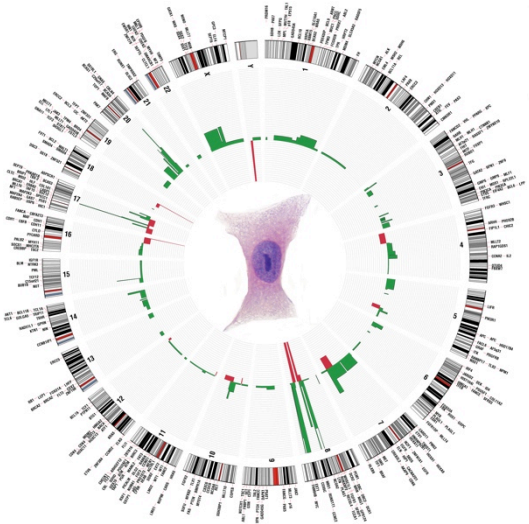


Tumor cells
Stroma cells
Lymphocytes

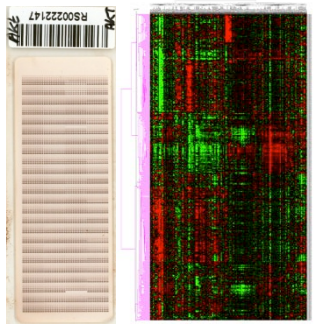
Expression profiling
(mRNA, miRNA)



INTEGRATIVE ANALYSIS



Clinical Outcomes



Functional Proteomics

Barriers to progress

- Elemental knowledge of cancer omics.
  - Thinking beyond the genome.

- Limited insights into factors driving cancer.
  - Genetic and functional weight of evidence.

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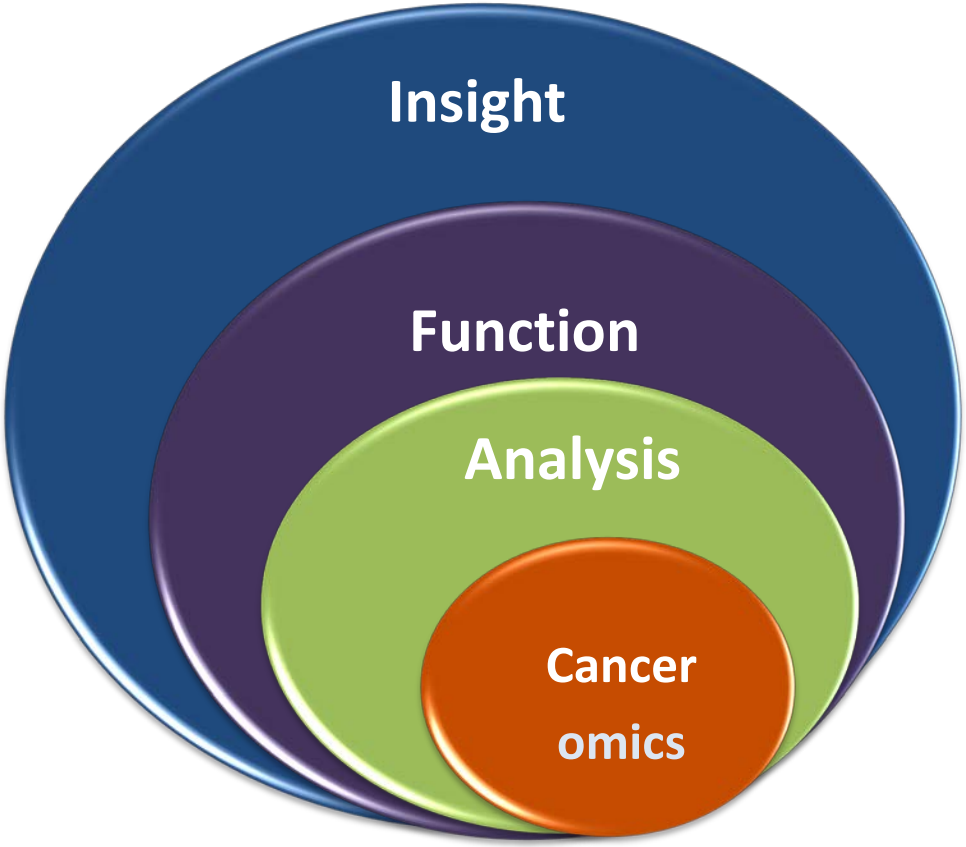
Translating the Cancer Genome:



Deep biology to inform on mechanism of action

Functional genomics to assign disease relevance

Bioinformatic and comp biol platforms to prioritize drivers vs. passengers.

Comprehensive "omic" profiling Genome, Epigenome, Proteome, etc.

The genome will inform the right targets and the right patients for the right drugs, ONLY when interpreted in context of the biology

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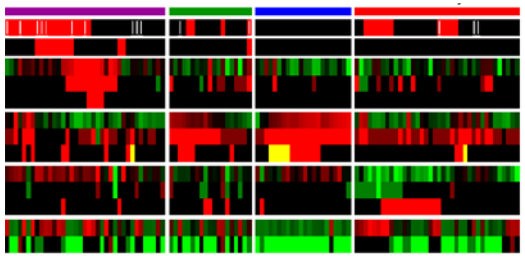
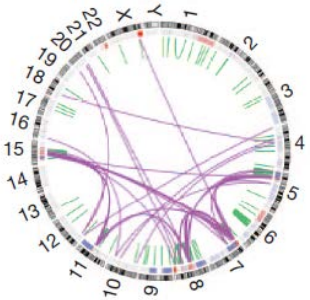
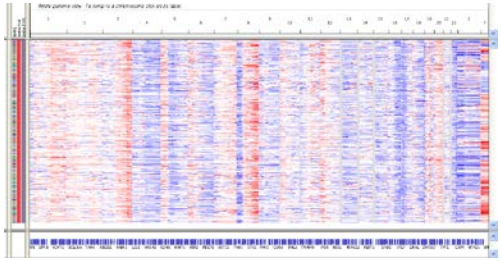
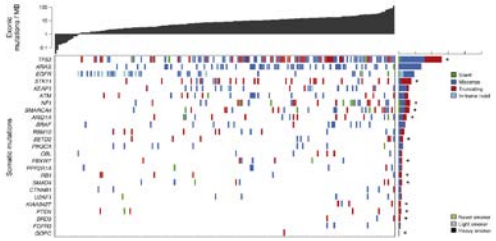
The complexity of cancer genomes necessitates a systematic approach to target discovery





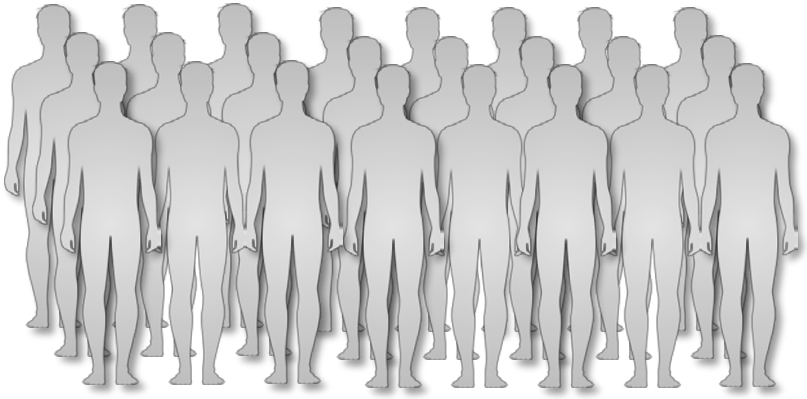




- Need to complement structural characterization with functional annotation.
  - Hundreds to thousands of candidates; drivers vs. passengers
  - Relative importance of one driver vs. another
  - Context-specific actions of specific genetic elements

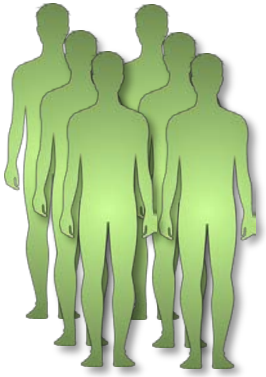
Target ID through functional genomics

Systematic approach with patient-centric focus

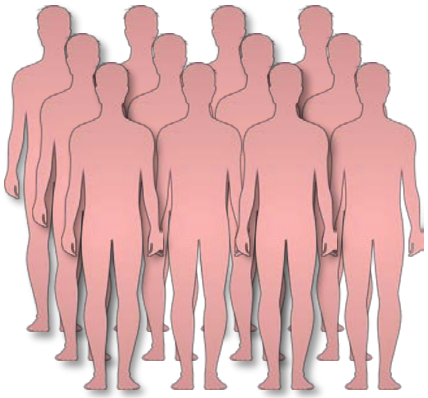


Identifying the context in which a target is rate limiting

Target A



Target B



Target C

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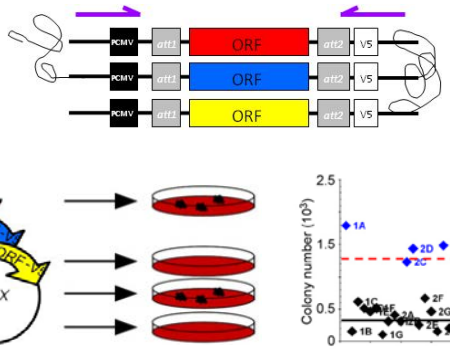
Building a "Functional" Genome Atlas

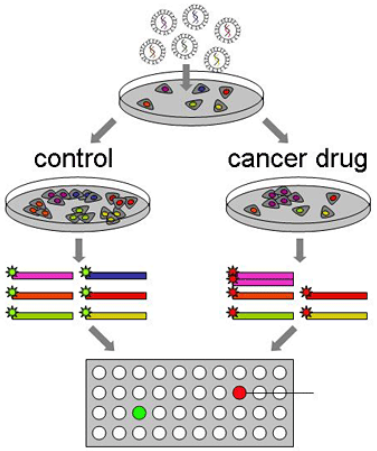
- **Inform on genetic sufficiency**
  - Is a target a driver of disease pathogenesis?
- **Inform on genetic dependency**
  - Is target activity or expression required for tumor growth?
- **Inform on mechanisms of resistance**
  - Guide hypothesis driven drug-drug combinations

Tools for systematic functional analysis

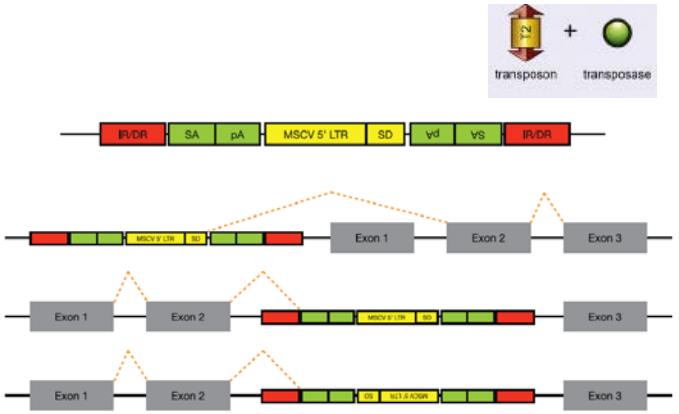
ORF Libraries



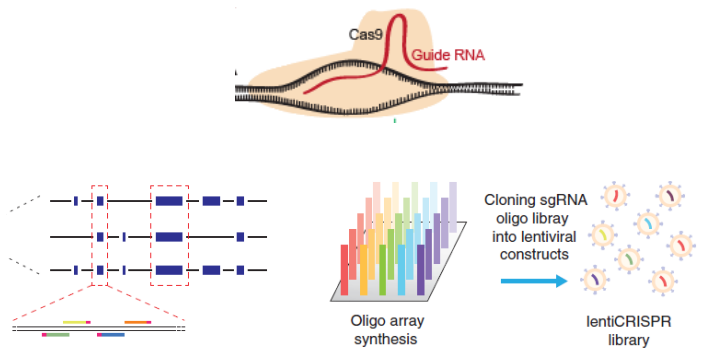
shRNA Libraries



Systematic Mutagenesis

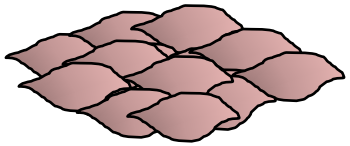


CRISPR Libraries



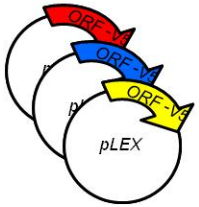
Functional interrogation of cancer genomes

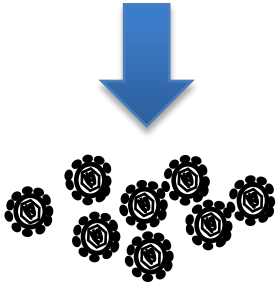
Primary Engineered Cell Lines



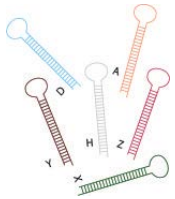
Generic Cancer Cell Lines

ORF Libraries

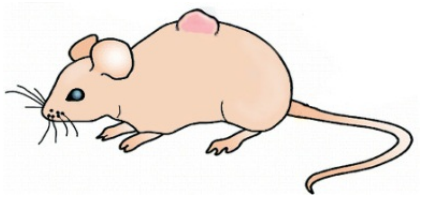




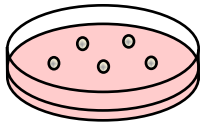
shRNA Libraries



Cancer Phenotypes

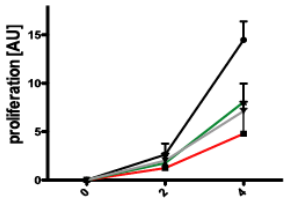


In vivo Tumorigenicity Metastasis

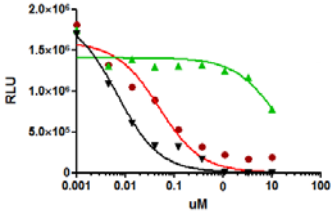


Anchorage Independent growth

Invasion Migration



Proliferation Apoptosis



Drug Resistance

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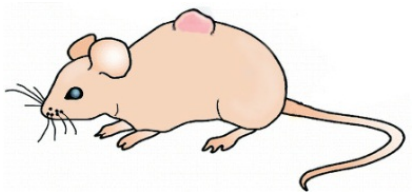
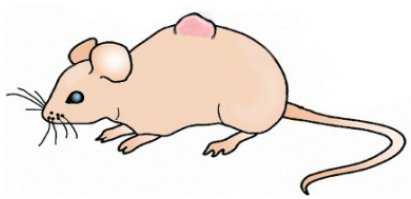
Development of target cell models with defined genetic elements

Primary Human Cell

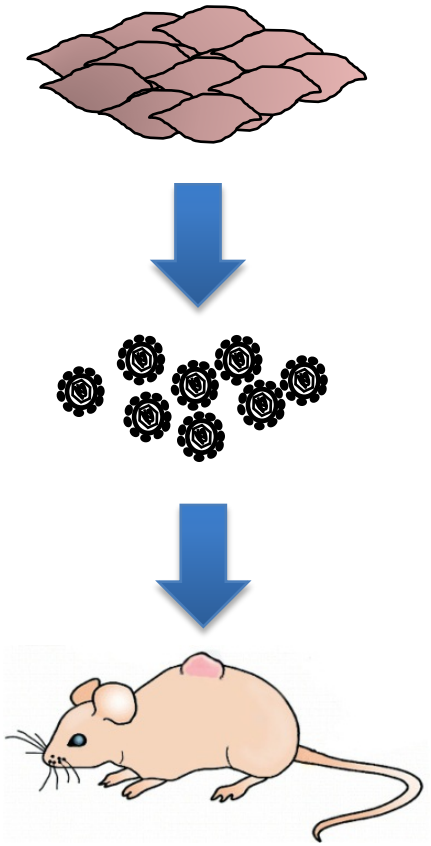
	Embryonic Kidney Cells	**Melanocytes**
	Hahn et al, 1999	
Immortalization	hTERT	hTERT
	+	+
Cessation of Growth Arrest Anti-apoptosis	SV40 LT/ST	p53DD + $CDK4^{R24C}$
	+	+
Mitogenic Stimuli	$HRas^{v12}$	$BRAF^{V600E}$ + “Gene X”





Tumor Cell

Context specific screen design



Target Cells

Library of GEOIs

Phenotype

Genetic Context:
Capture "Definable"
Subtypes

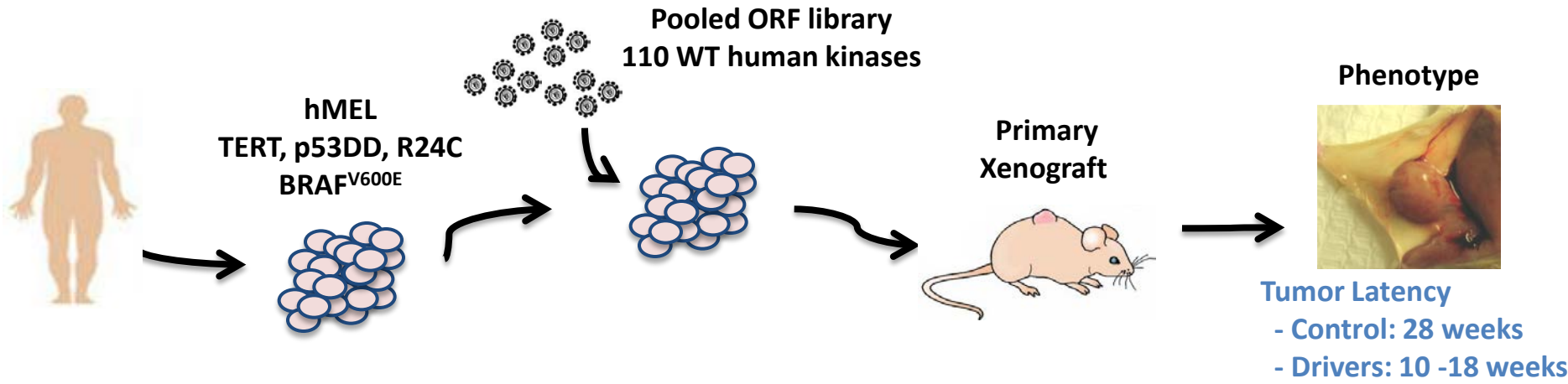
Enzyme classes
Pathway components
WT, AMP, MUT ORFs

In vivo tumorigenesis

In vivo functional genetic screen:

- Systematically assign biological relevance to GEOIs
- Define lineage, genetic, and microenvironmental influences on gene function.
- Clinical Path hypothesis built in to screen design.

Functional Genomics Discovery Platform:
Systematic approach to target identification

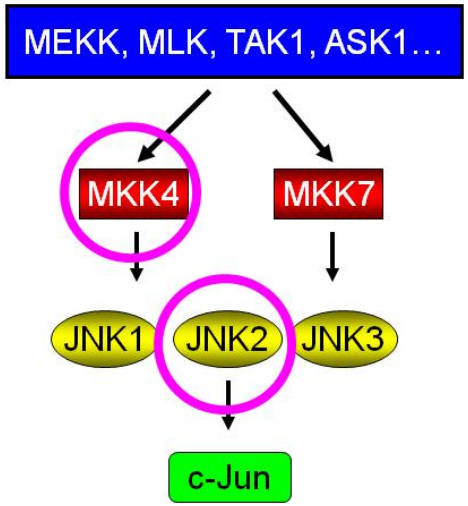


In vivo screen to identify genes that cooperate with BRAF during melanoma genesis

Primary Screen Results

	Injections	Tumors	Ave. Latency
GFP	10	0	N/A
Pool 1	10	0	N/A
Pool 2	10	2	18 wks
Pool 3	10	1	17 wks
Pool 4	10	4	14 wks
Pool 5	10	1	18 wks
Pool 6	10	6	10 wks
Pool 7	10	5	11.5 wks
Pool 8	10	3	13 wks

Multiple in vivo hits in JNK-pathway



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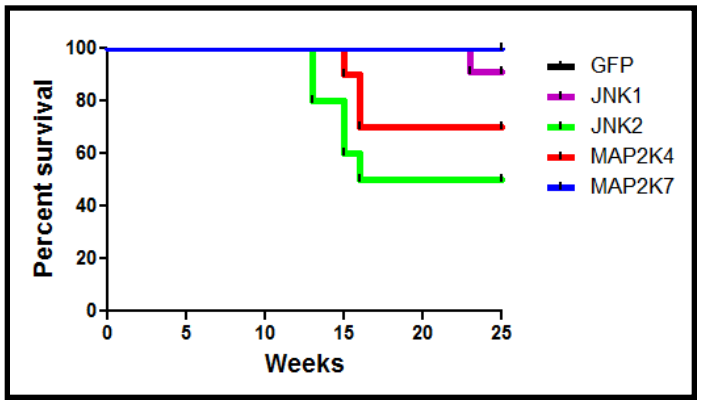
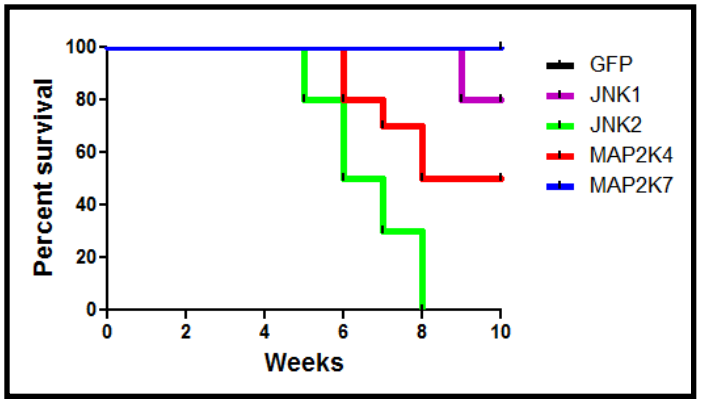
JNK2 overexpression transforms BRAF mutant human and mouse melanocytes

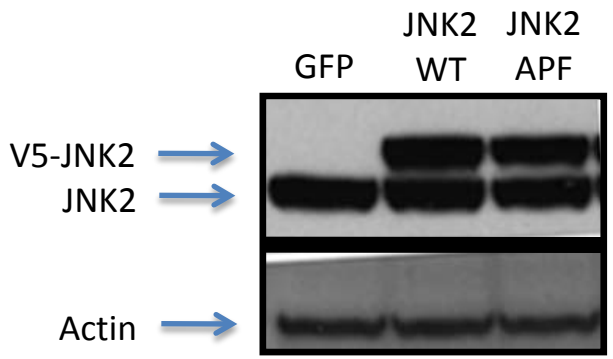
hMEL-BRAF



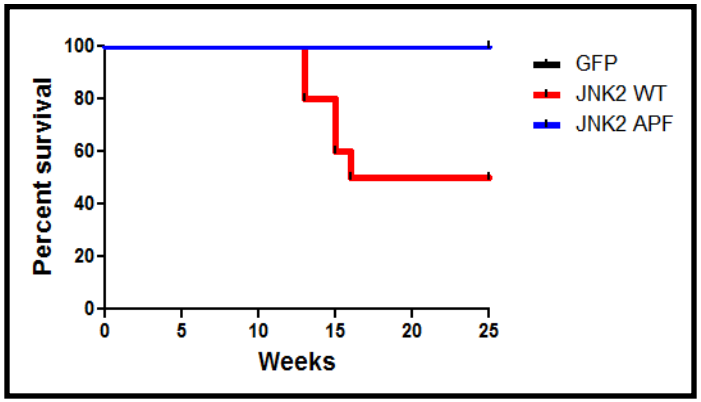
mMEL-BRAF



JNK2 kinase activity is required for transformation



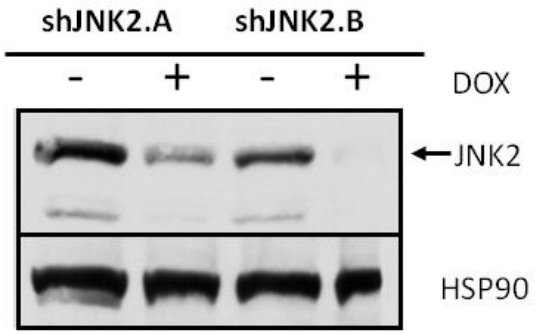
hMEL-BRAF



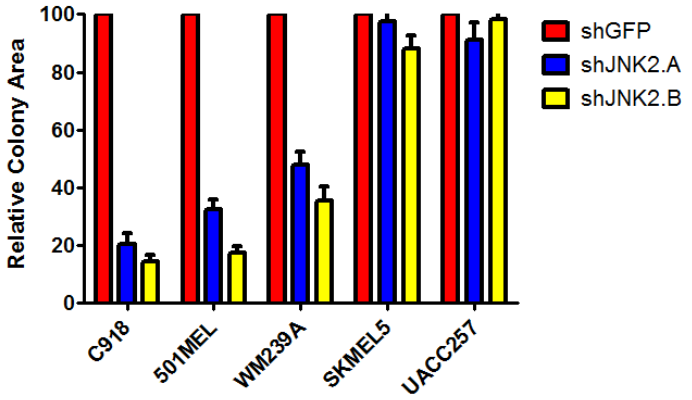
JNK2 is required for the growth of human melanoma cell lines.

Genetic Validation

M619

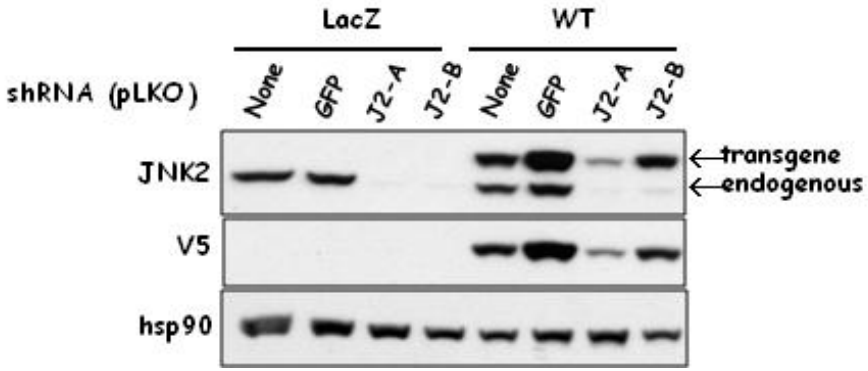


3D Growth

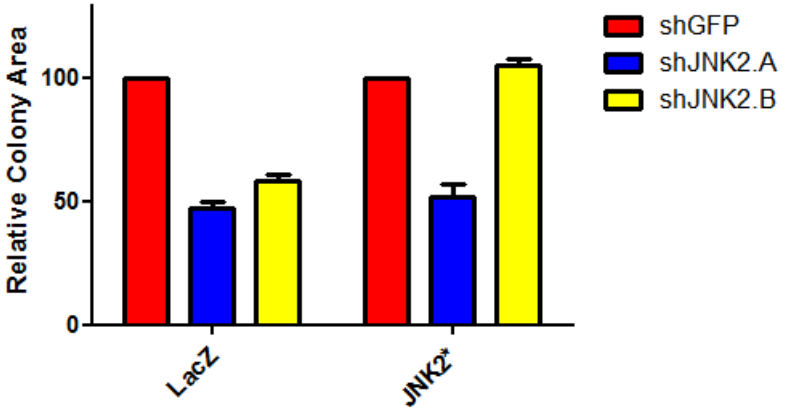


cDNA rescue to confirm on-target activity

WM239A



WM239A: 3D Growth



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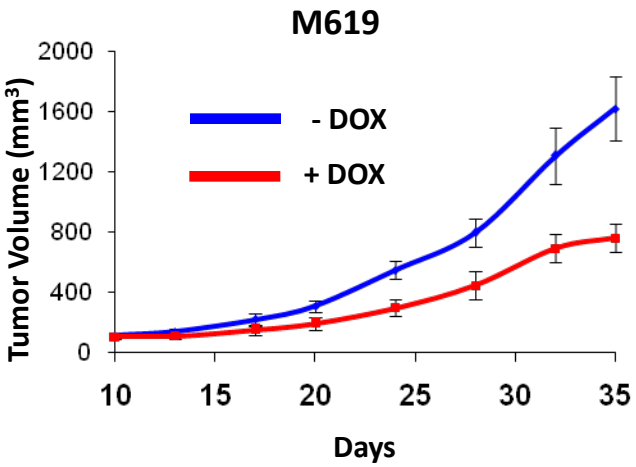
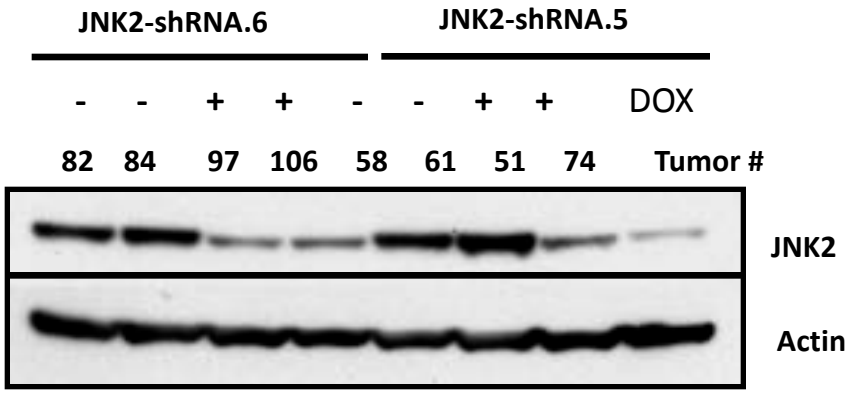
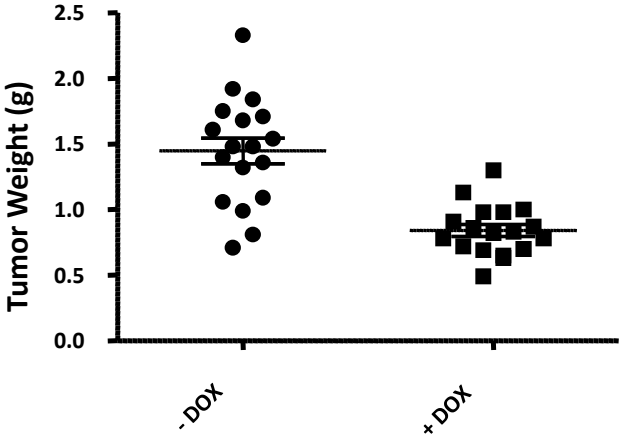
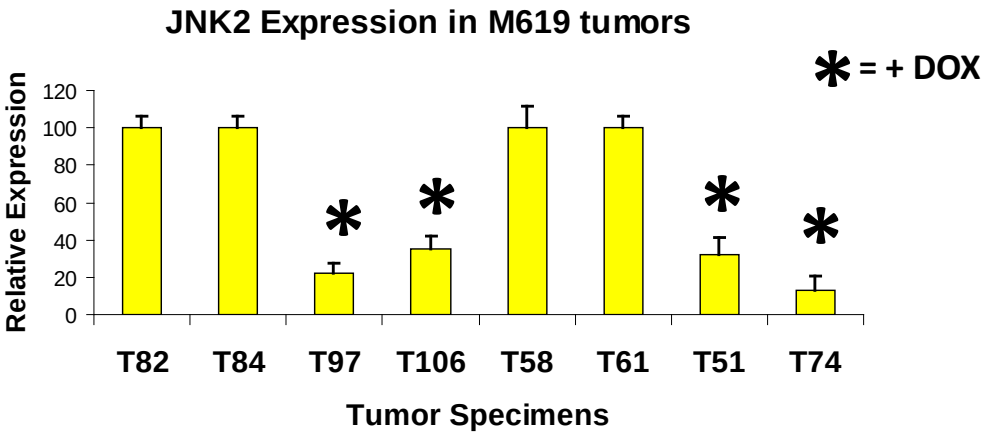
In vivo POC: JNK2 KD inhibits growth of established melanoma xenografts



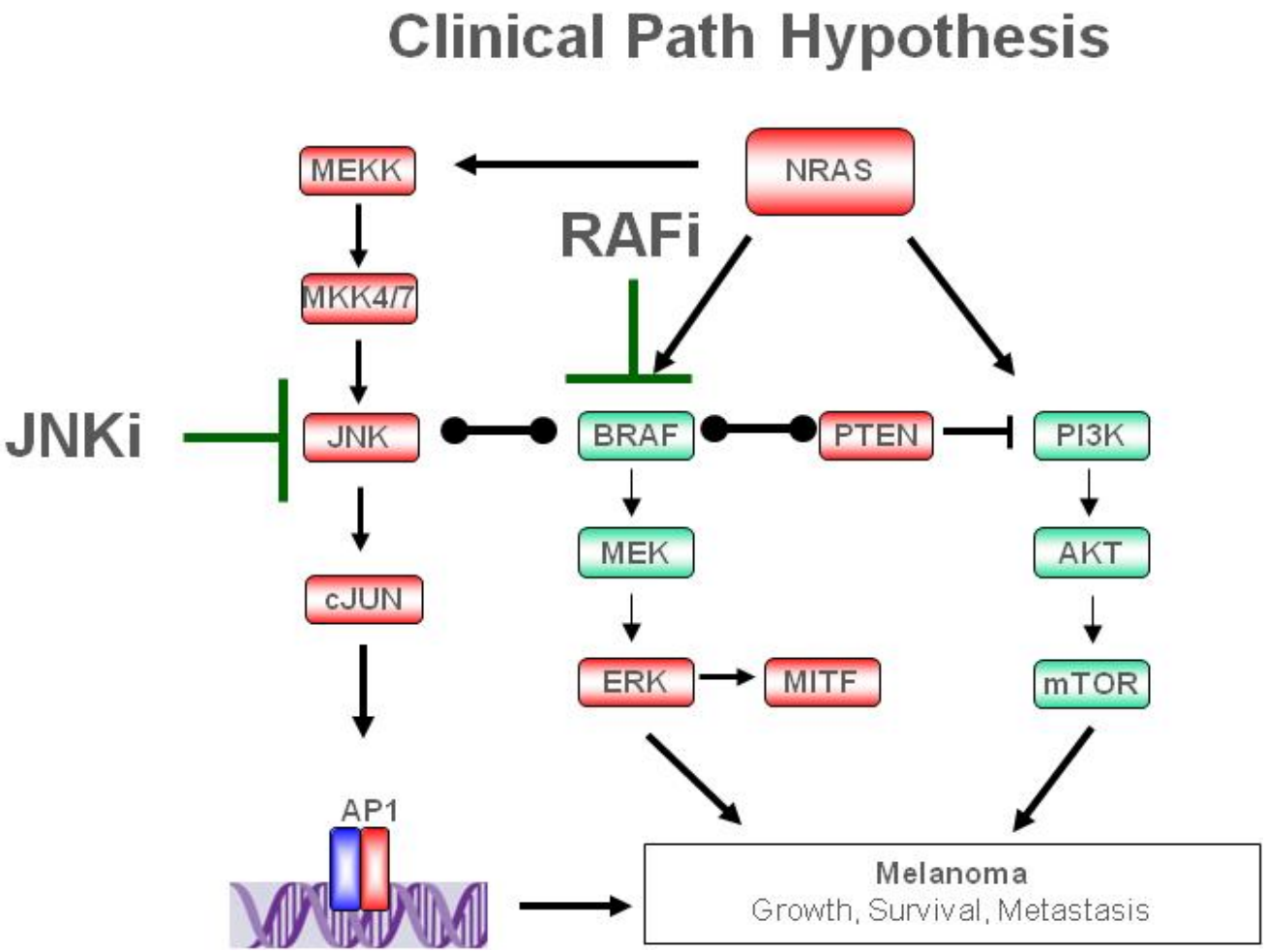






JNK2 expression is required to maintain the growth of human melanoma xenograft.

BRAFi + JNK2i may be effective in treating NRAS* melanoma



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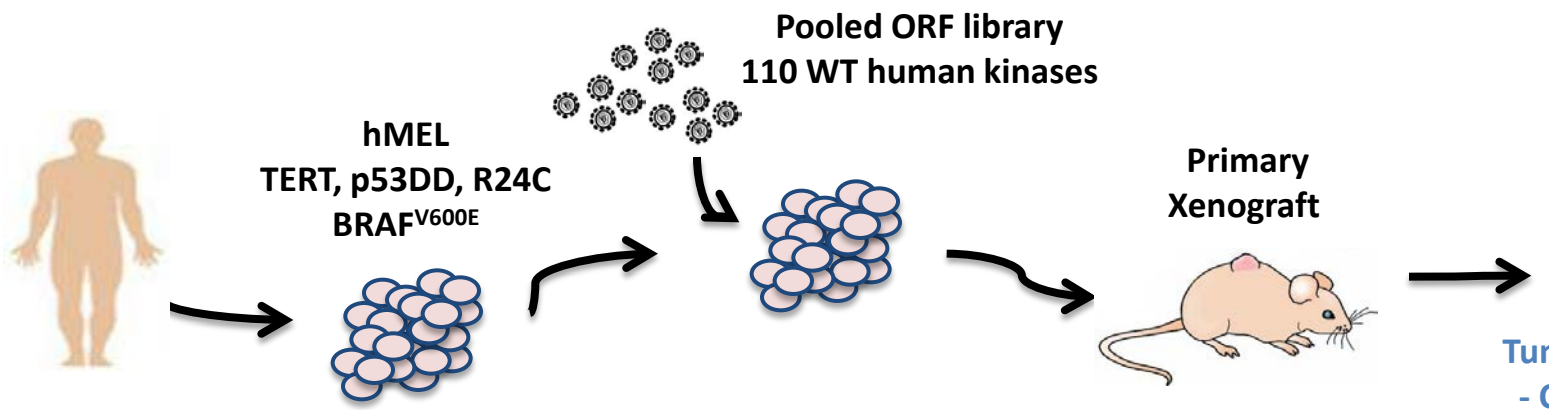
Functional Genomics Discovery Platform:
Systematic approach to target identification



Tumor Latency
- Control: 28 weeks
- Drivers: 10 -18 weeks

In vivo screen to identify genes that cooperate with BRAF during melanoma genesis

Primary Screen Results

	Injections	Tumors	Ave. Latency
GFP	10	0	N/A
Pool 1	10	0	N/A
Pool 2	10	2	18 wks
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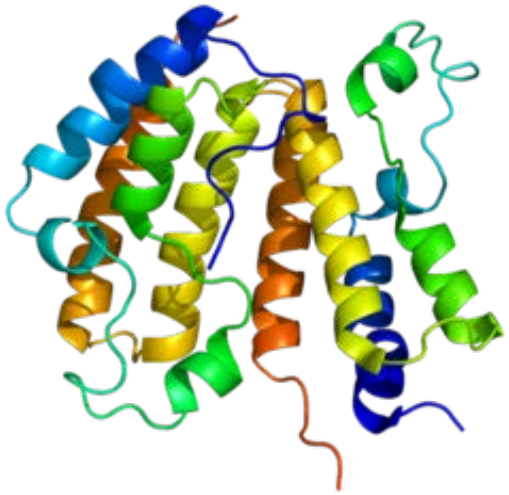
Pool 4	10	4	14 wks
Pool 5	10	1	18 wks
Pool 6	10	6	10 wks
Pool 7	10	5	11.5 wks
Pool 8	10	3	13 wks

Role for BRD3 in BRAF* Melanoma



Functional Genomics Discovery Platform:
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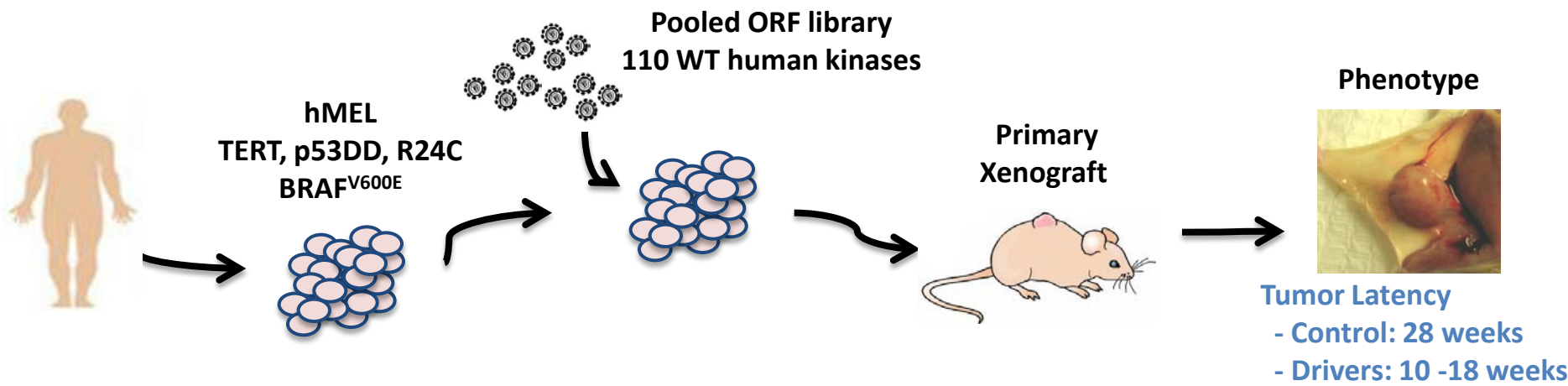
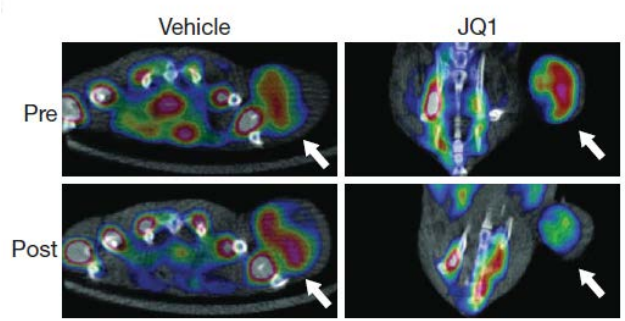


BRD3

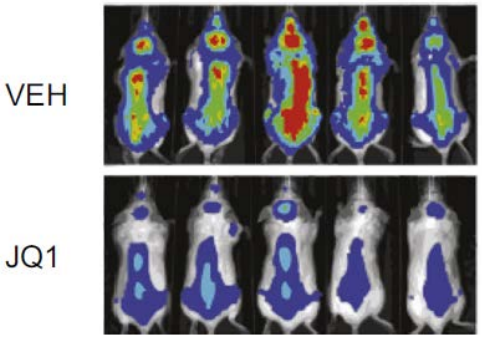
- Member of the BET bromodomain family of epigenetic "readers"
  - BRD2, BRD3, BRD4, BRDT
- Couples histone acetylation to transcription.

NUT Midline Carcinoma



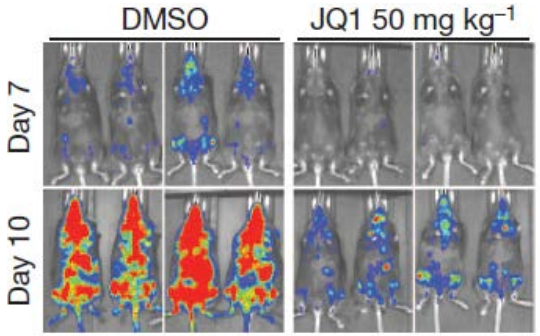
Filippakopoulis et al. Nature 2010

Multiple Myeloma



Delmore et al. Cell 2011

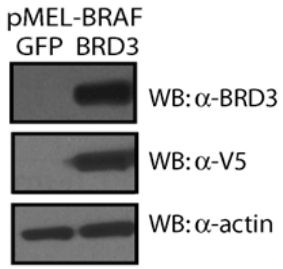
AML

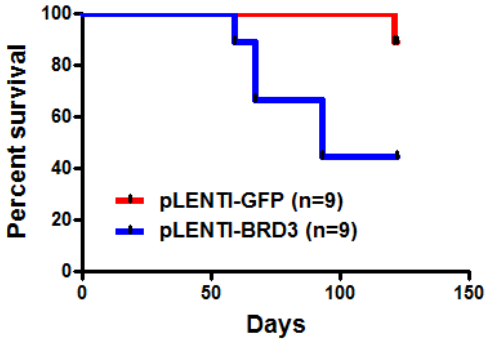


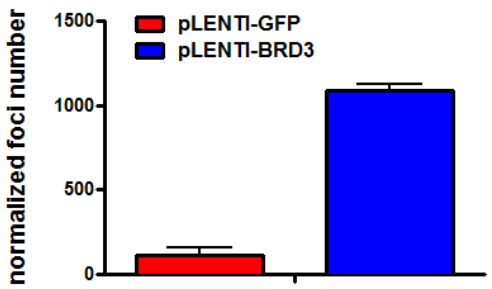
Zuber et al. Nature 2011

BRD3 is a Novel Melanoma Oncogene

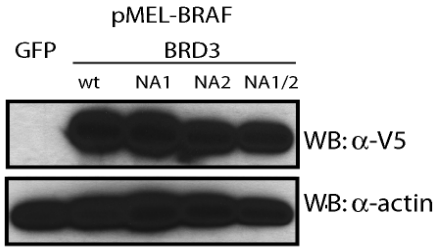
BRD3 overexpression cooperates with BRAF to transform melanocytes

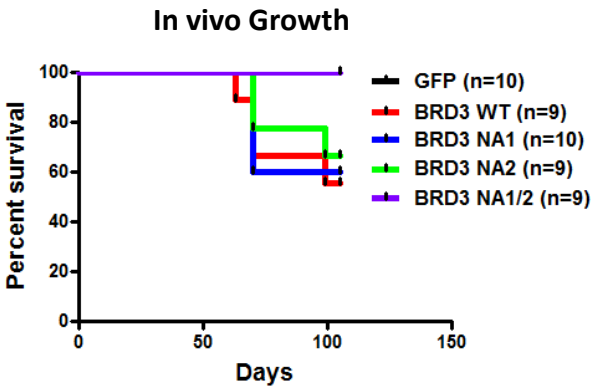


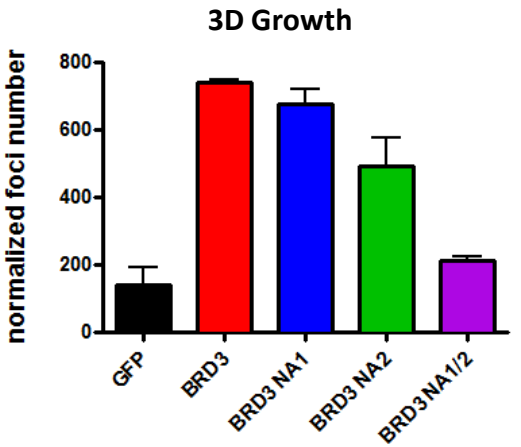




Bromodomain integrity is required for BRD3-induced melanoma genesis







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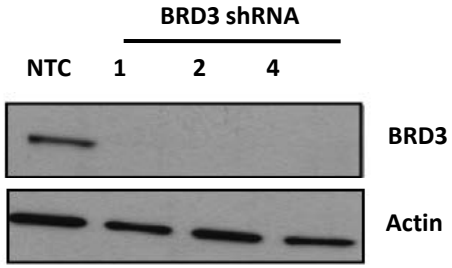
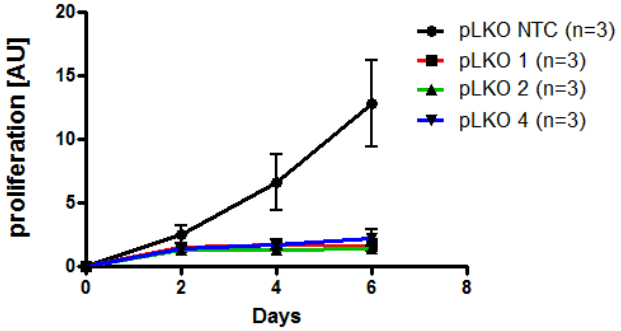
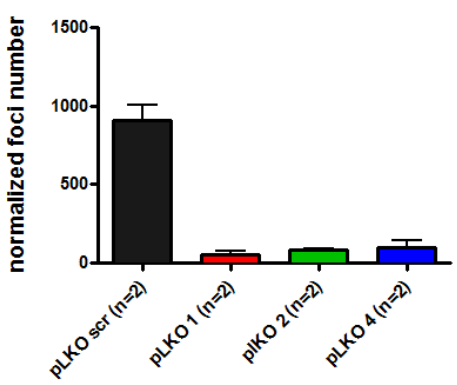
BRD3 is Required for the Growth of BRAF Mutant Human Melanoma Cell Lines

BRD3 KD inhibits growth of BRAF melanoma cell lines*

Genetic Validation

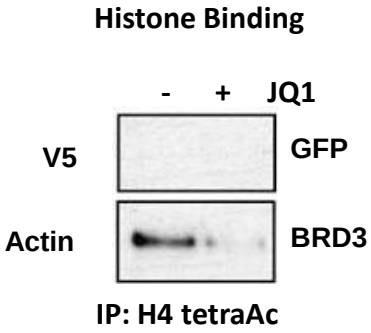


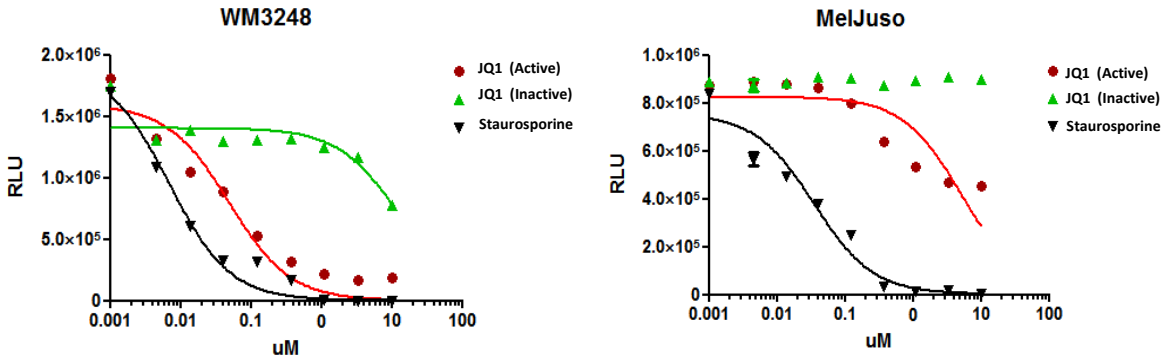




Melanoma cell lines are differentially sensitive to BRD3 inhibition

Pharmacological Validation





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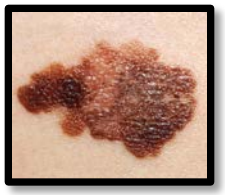
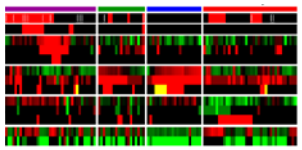
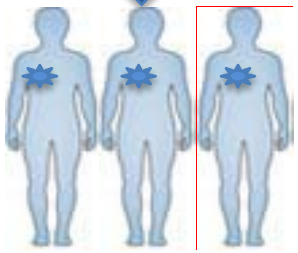
Context-specific genetic screening platform identifies novel actionable targets



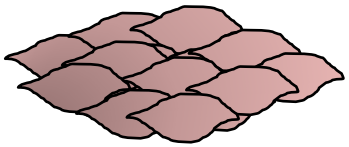


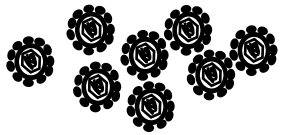


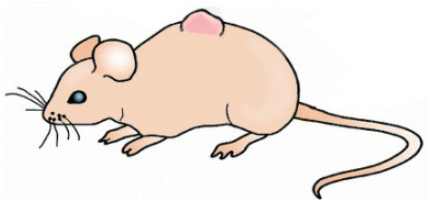
Target Cells
Capture "Definable" Subtypes

Library of GEOIs
Cancer specific Libs.
cDNAs or shRNAs

Phenotype
In vivo tumorigenesis
Metastasis







Unbiased approach informs non-obvious clinical path hypotheses

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Cancer Target Discovery and Development (CTD^2) Network 2012-2013

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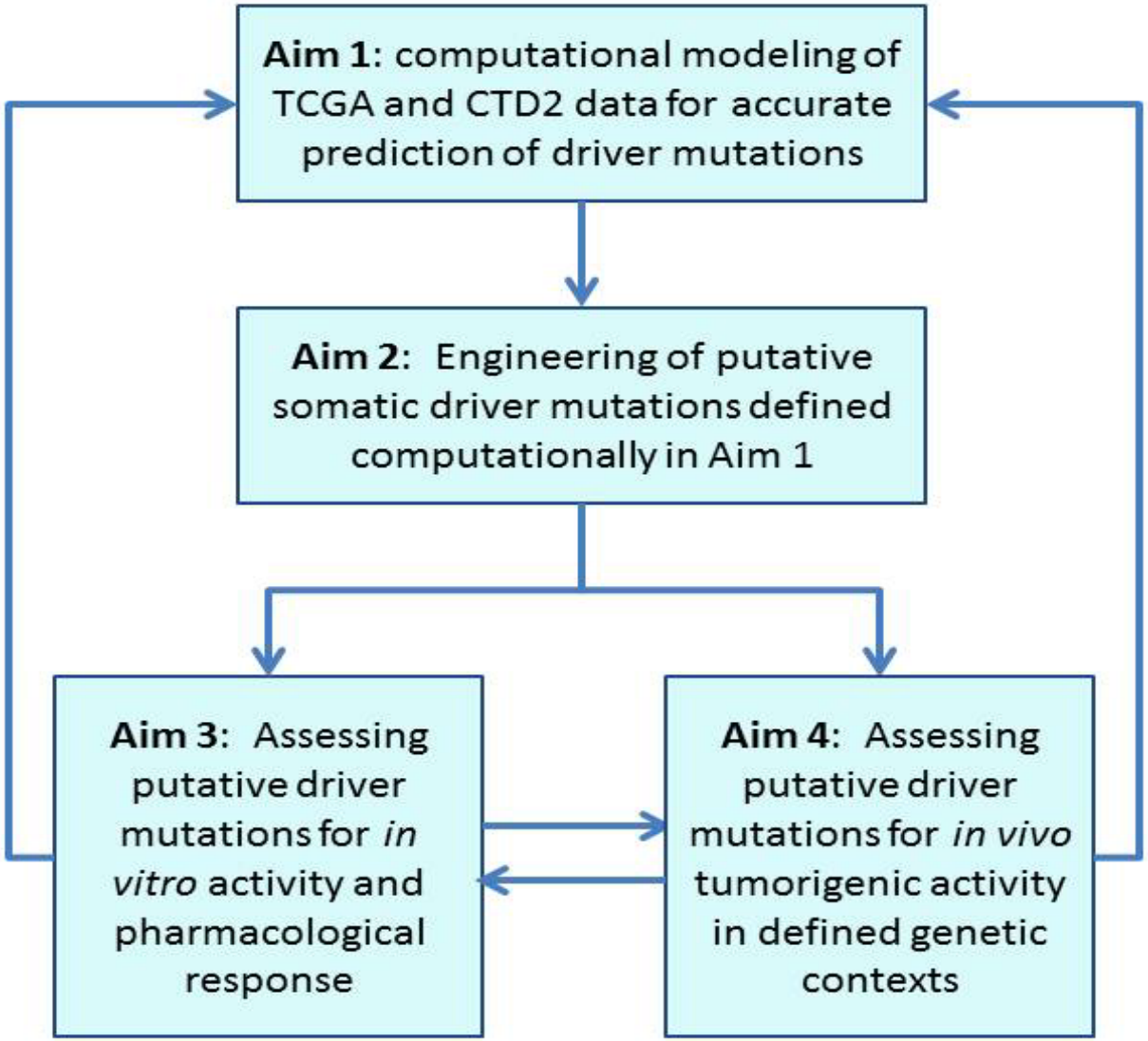
MDACC/BCM CTD2 Program



Cancer Target Discovery and Development Network

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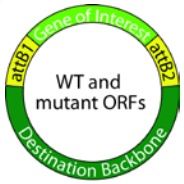
OFFICE of CANCER GENOMICS

Data sets

- MDACC
- TCGA
- ICGC
- Patients

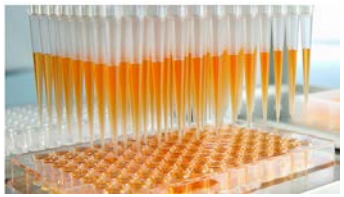
Interative algorithms to identify POTENTIAL DRIVER ABERRATIONS

Construct mutant ORFs >200/month

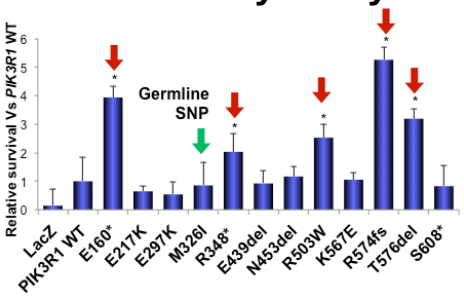


Lentiviral vector: WT or mutated ORF or shRNA for KD

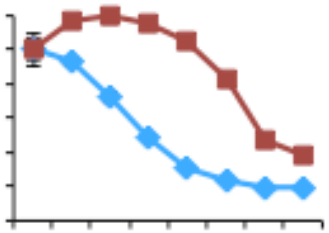
Introduce into "addicted" sensor cell line (Ba/F3, MCF10A, tumor lines)



Cell viability assay

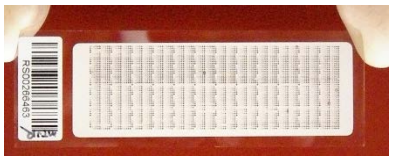


Select potential drivers



Sensitivity to "informer" targeted therapeutic library

Establish "driver addicted" stable cell lines



RPPA to define signaling network

Integrate functional proteomics and drug screen DRUGS AND MECHANISMS

Context Specific In Vivo Screens

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Building a "Functional" Genome Atlas

- **Inform on genetic sufficiency**
  - Is a target a driver of disease pathogenesis?
- **Inform on genetic dependency**
  - Is target activity or expression required for tumor growth?
- **Inform on mechanisms of resistance**
  - Guide hypothesis driven drug-drug combinations

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Context-specific tumor dependencies guide personalized medicine

NSCLC	**EGFR**	**Erlotinib**
NSCLC	**EML4-ALK**	**Crizotinib**
Melanoma	**BRAF**	**Vemurafenib, Debraf.**
Breast	**HER2**	**Trastuzumab**
BRCAness	**PARP**	**Olaparib, BMN, etc**

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Synthetic Lethality: A Mechanism to Identify Novel Targets

Classical Synthetic Lethality

Genetics		Phenotype
A	B	Viable
A	B	Viable
A	B	Viable
A	B	Lethal

Genetic Synthetic Lethality

Genetics		Phenotype
A	B	Viable
A	B	Lethal

Pharmacological Synthetic Lethality

Genetics			Phenotype
A	B	⊣	Viable
A	B	⊣	Lethal

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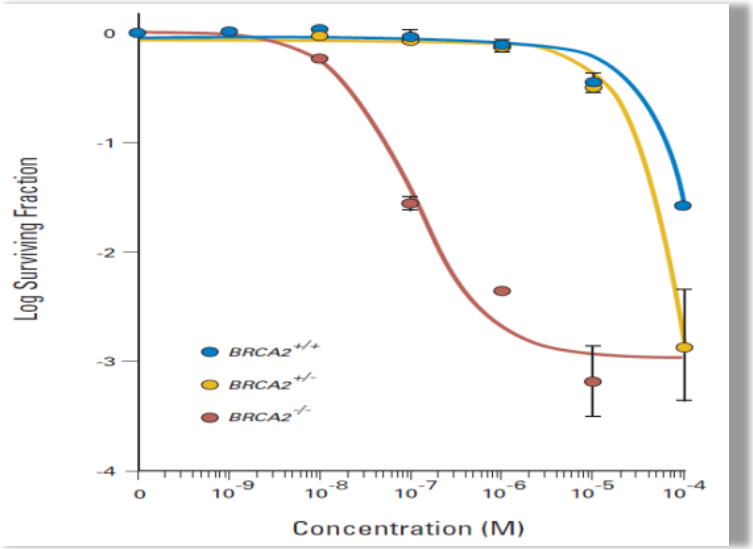
Targeting PARP in tumors with germline BRCA mutations

Pharmacological Synthetic Lethality

Genetics			Phenotype
BRCA1	PARP	⊣	Viable
BRCA1	PARP	⊣	Lethal



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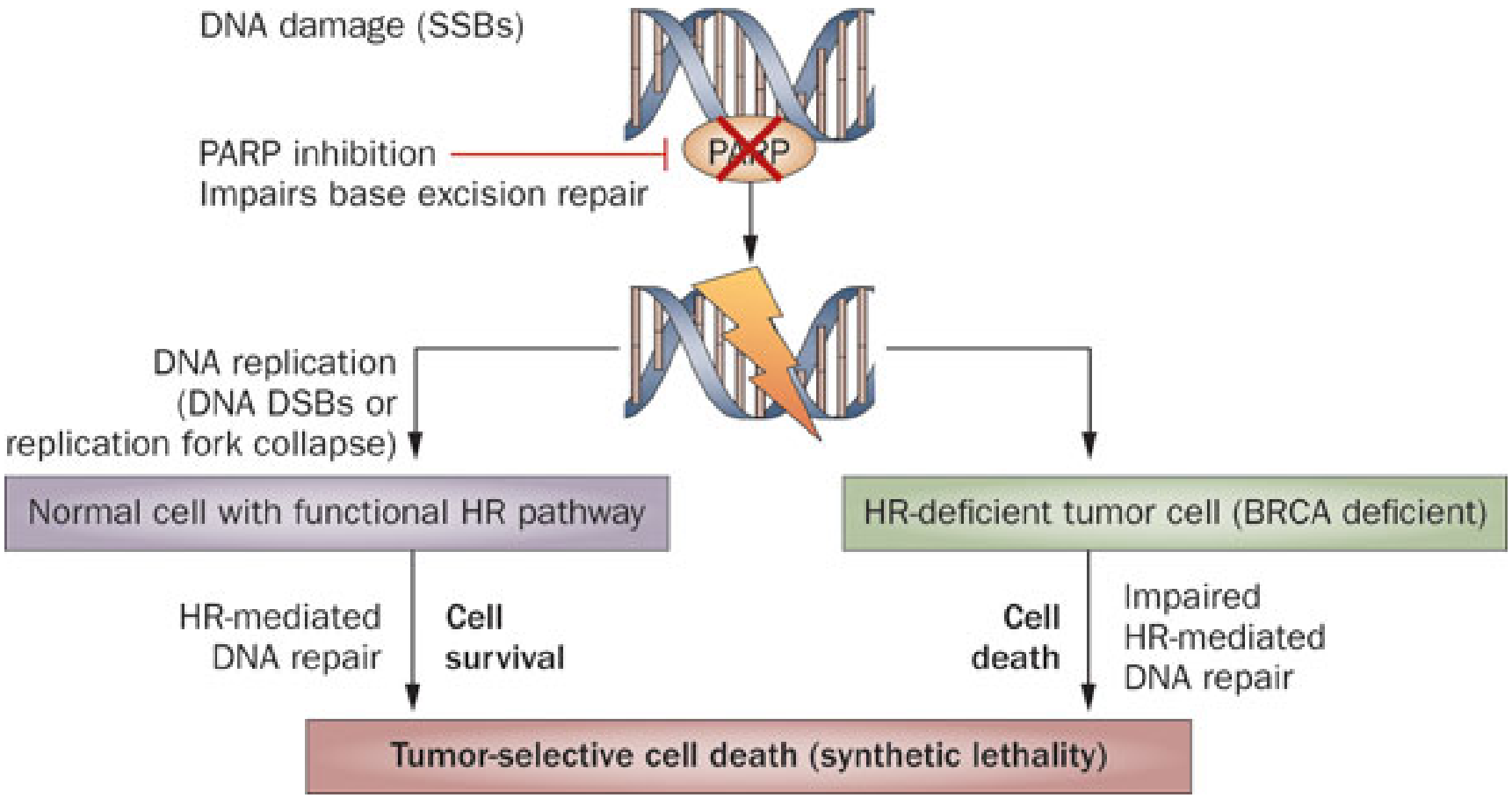
Mechanism of PARP Synthetic Lethality



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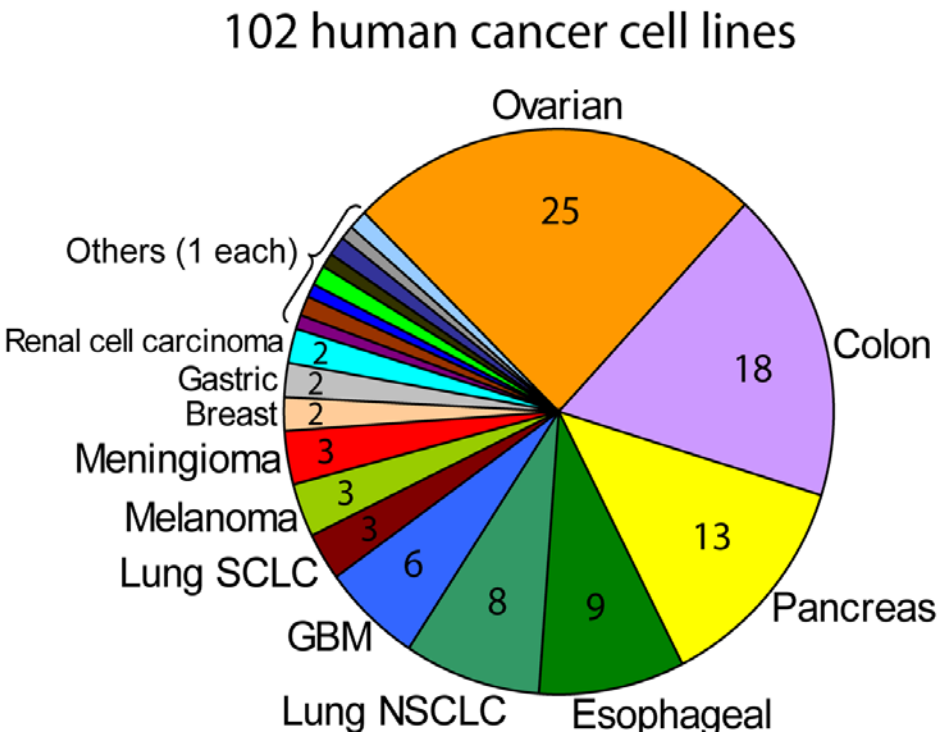
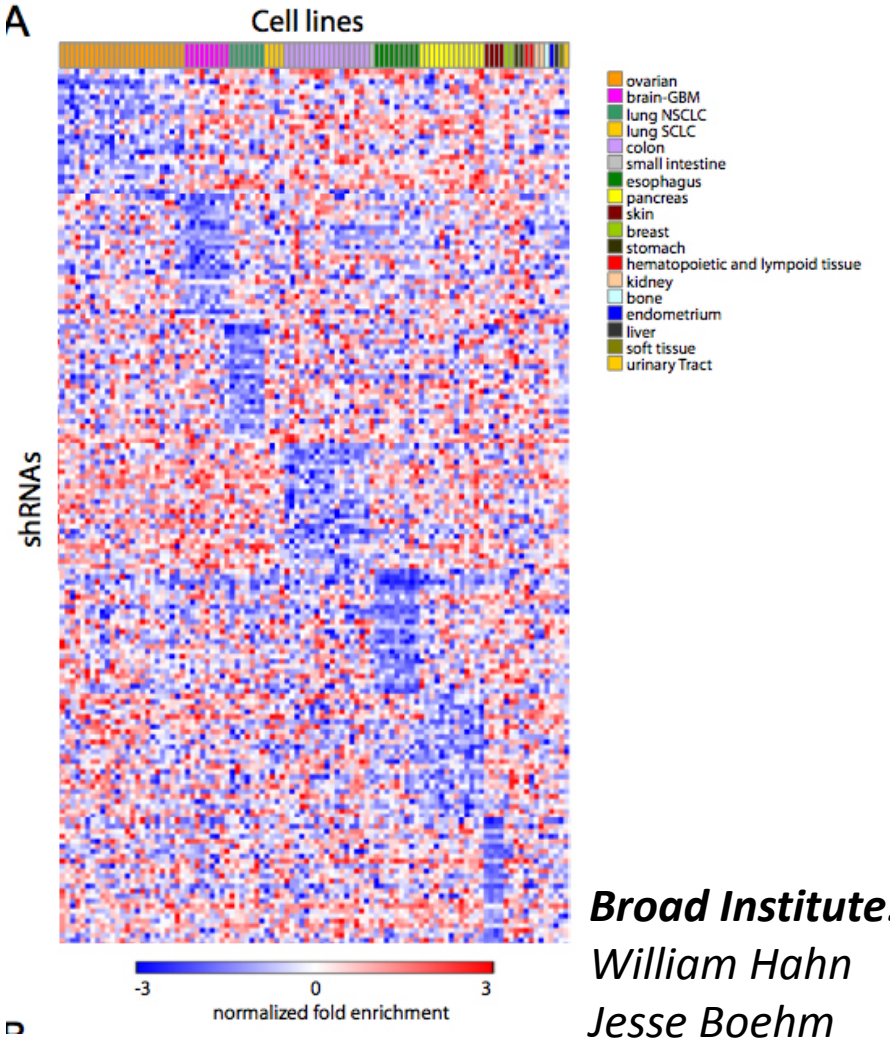
Genome Scale LOF Screens to Identify Genetic Dependencies

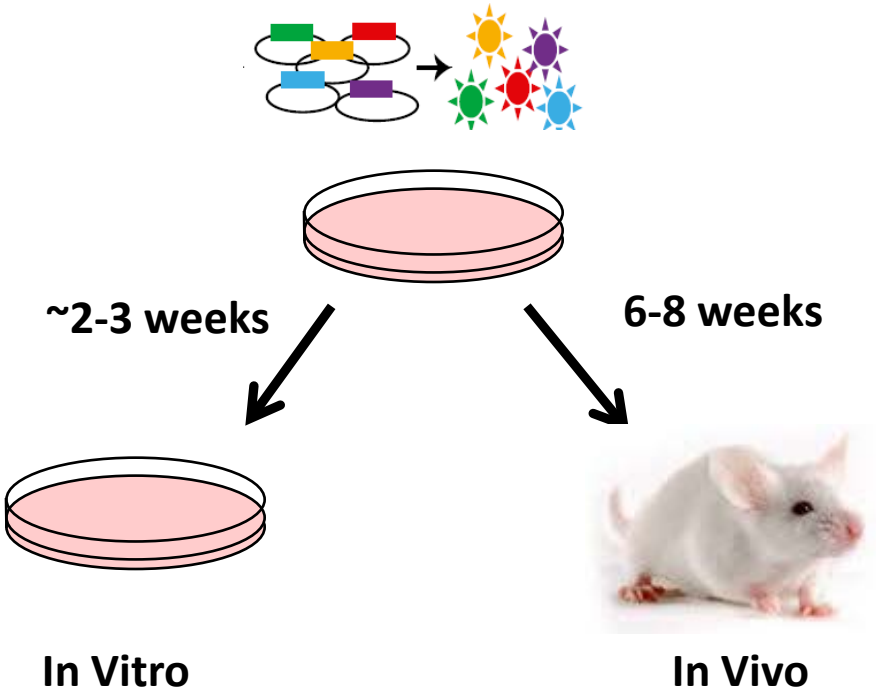




Broad Institute:
William Hahn
Jesse Boehm
Dave Root

Cheung et al. PNAS 2011

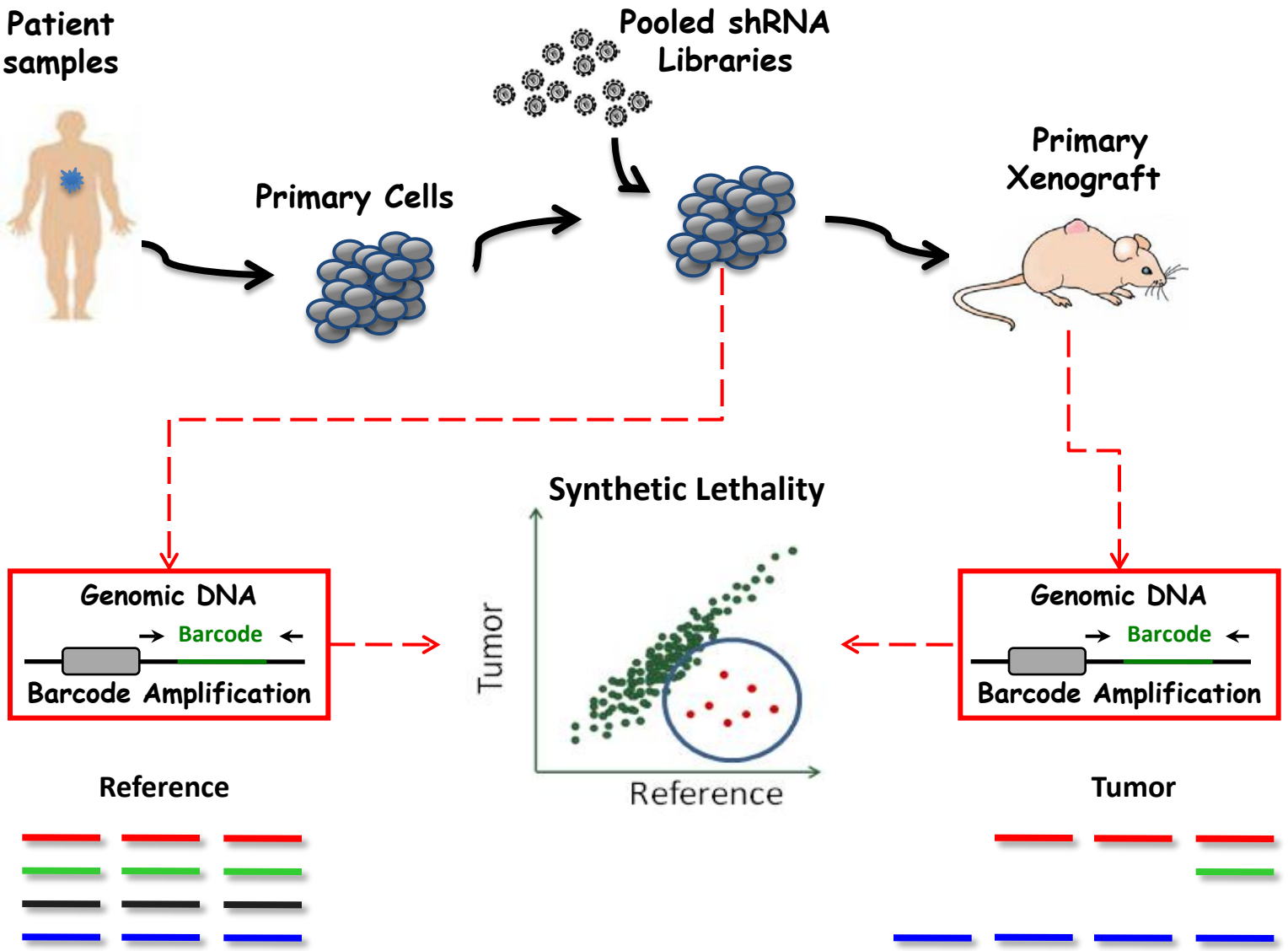
Development of *in vivo* synthetic lethality screens



	In vitro	In vivo
Library Complexity	Genome Scale	Focused
Target Cells	Inclusive	Dependent on TIC Frequency
Capacity	10's-100's	10's
Microenvironment	None	Intact

Functional Genomics Discovery Platform:

In vivo LOF platform to identify genetic vulnerabilities



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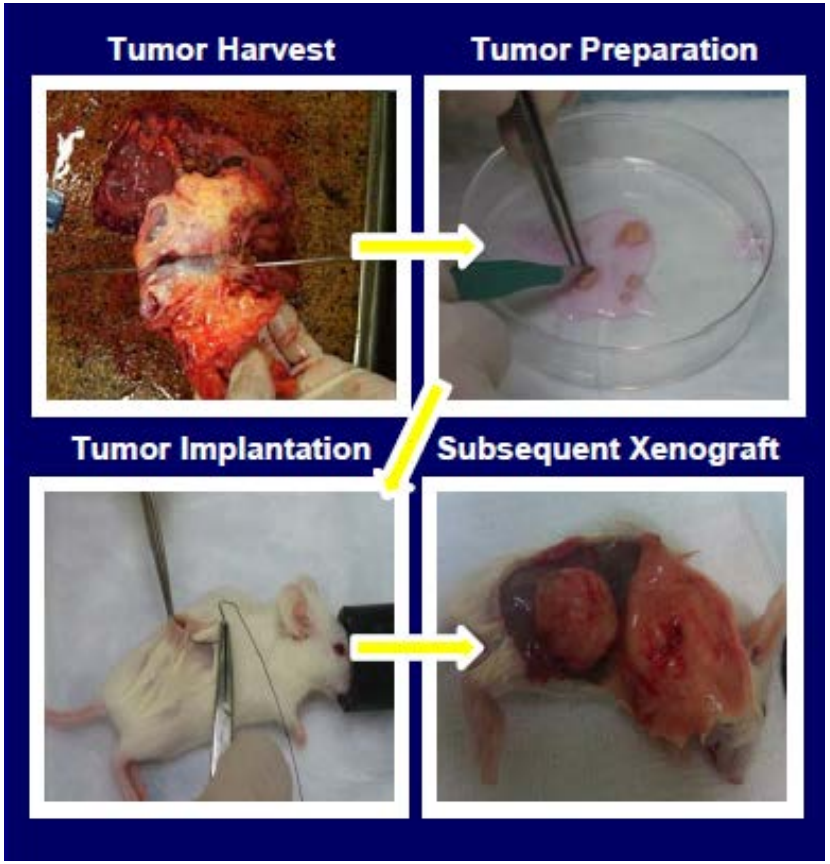
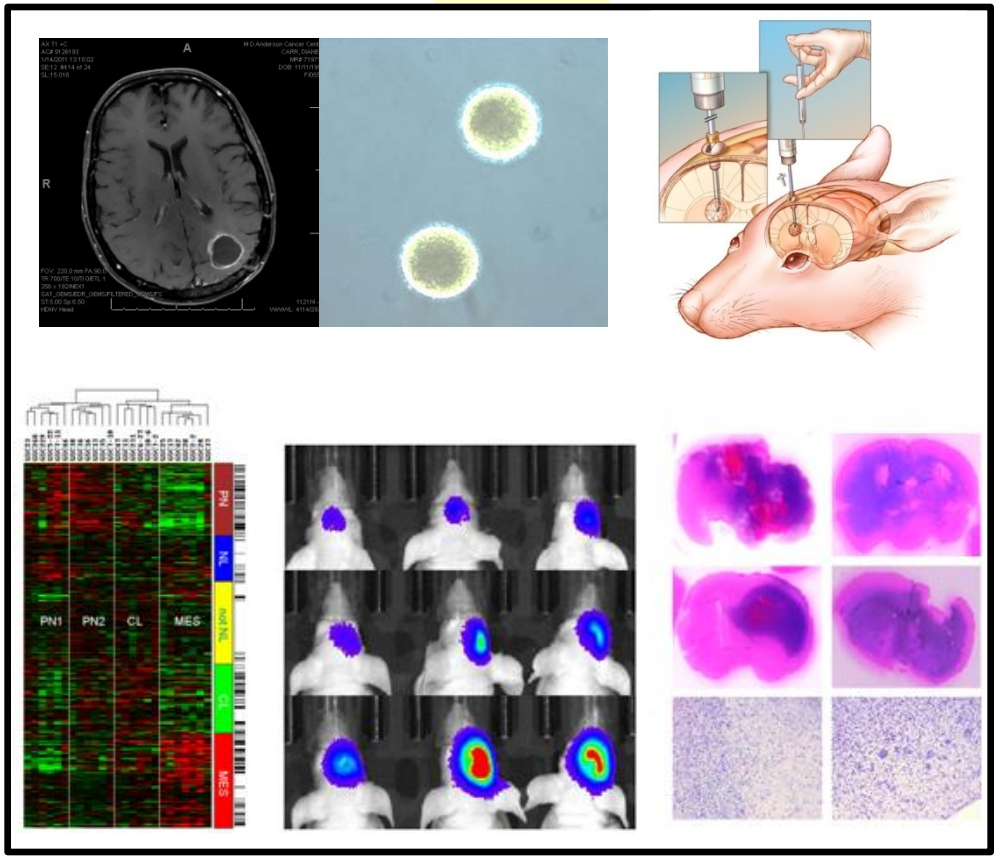
IACS Functional Genomics Platform:
Leveraging the clinical infrastructure at MDACC

PDAC



Jason Fleming, Mathew Katz, Anirban Maitra

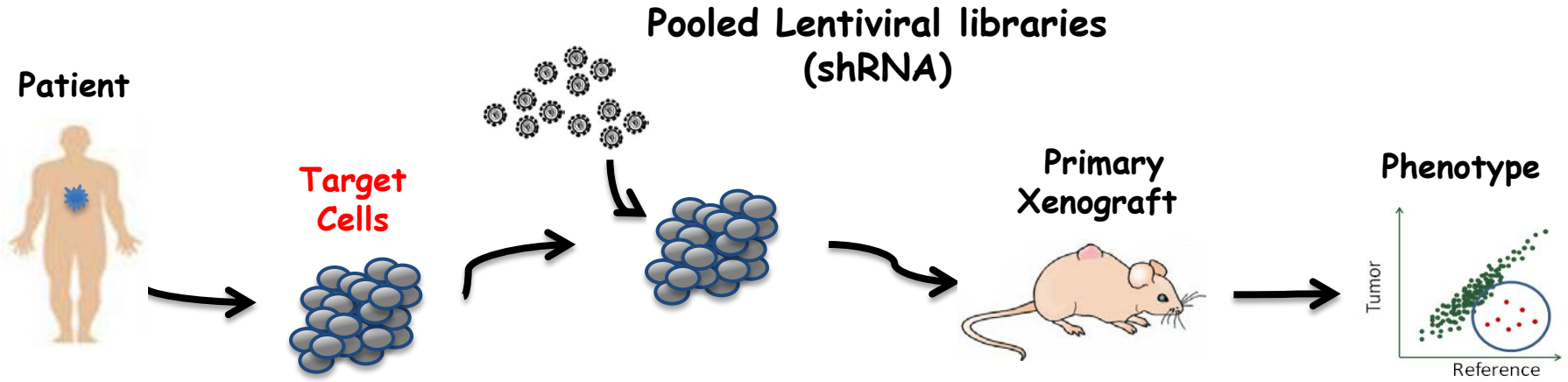
GBM



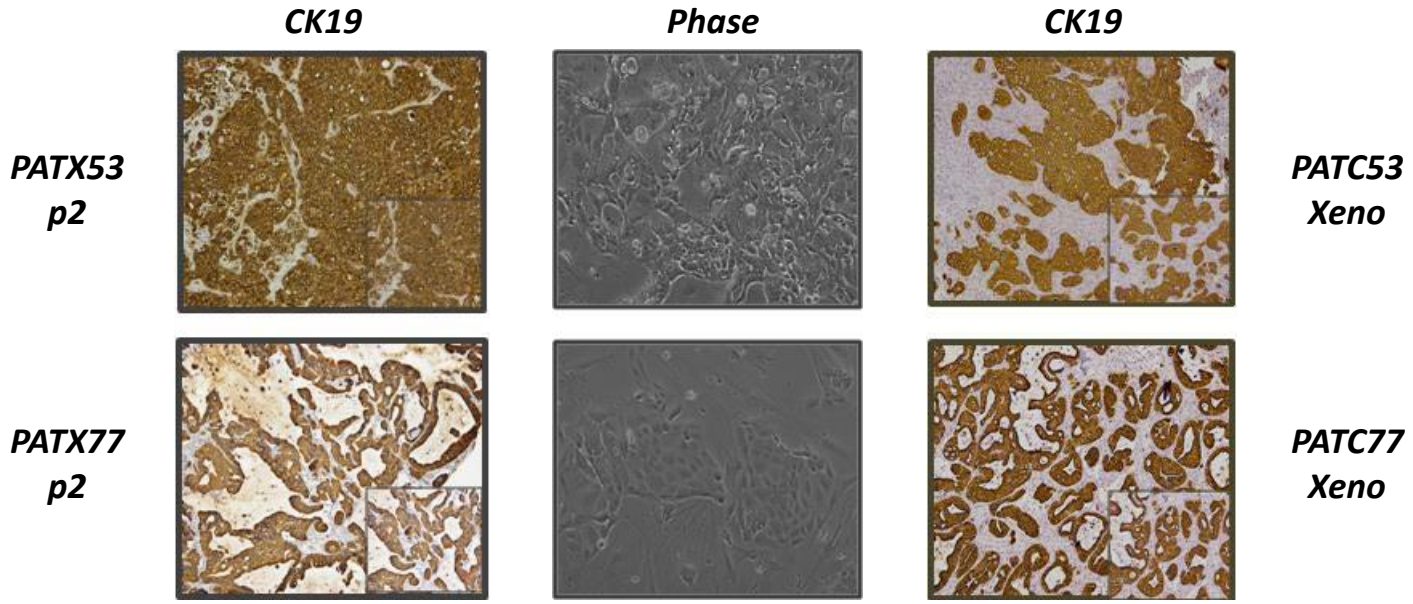
Fred Lang, Erik Sulman, Roel Verhaak

Genomics annotated patient-derived models available across multiple indications

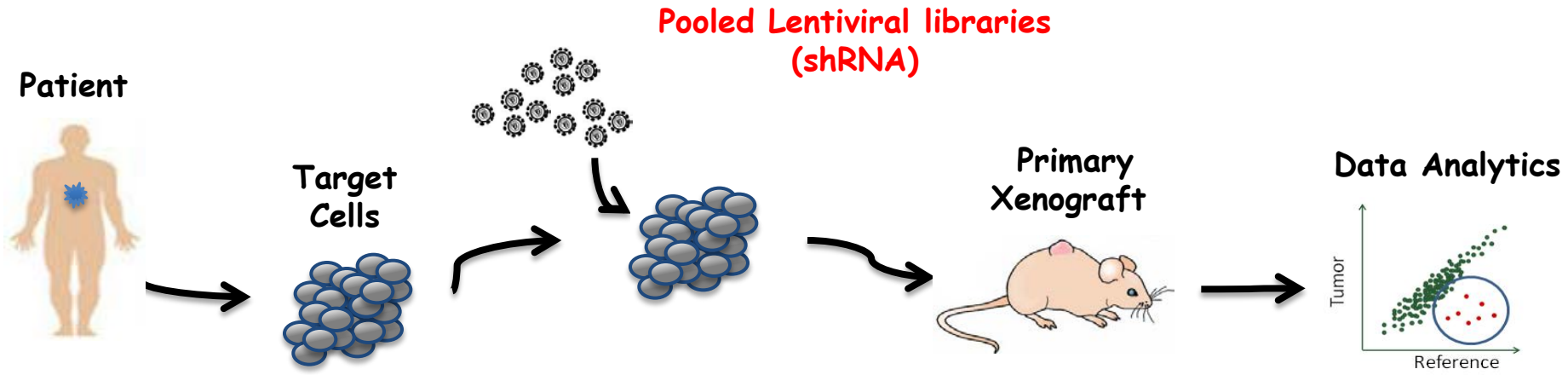
Functional Genomics Discovery Platform:
Target cell isolation/optimization



Human PDAC primary cultures (PATC)



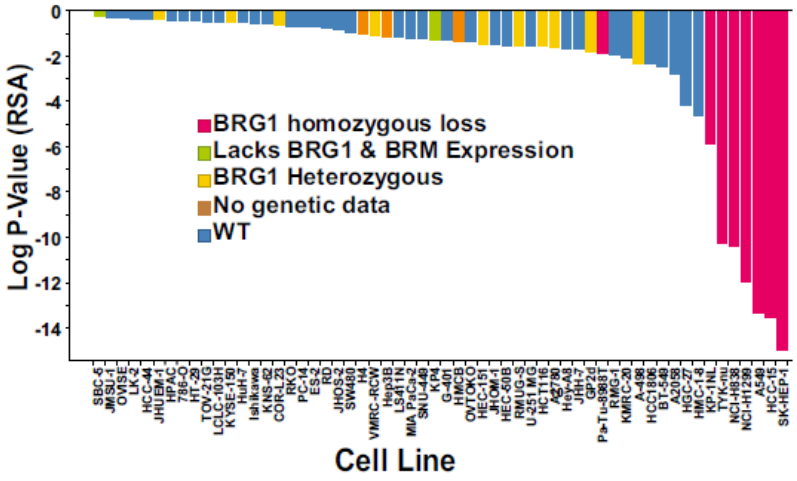
Functional Genomics Discovery Platform:
Pooled shRNA Library Development



Deep Coverage shRNA Libraries (DECODER)

- Custom design of pooled shRNA libraries.
- Complexity of 10-20 shRNAs per gene.
- Engineered with unique molecular barcodes.
- Compatible with Illumina Sequencing.

BRG1/BRM synthetic lethality



Hoffman et al PNAS 2014

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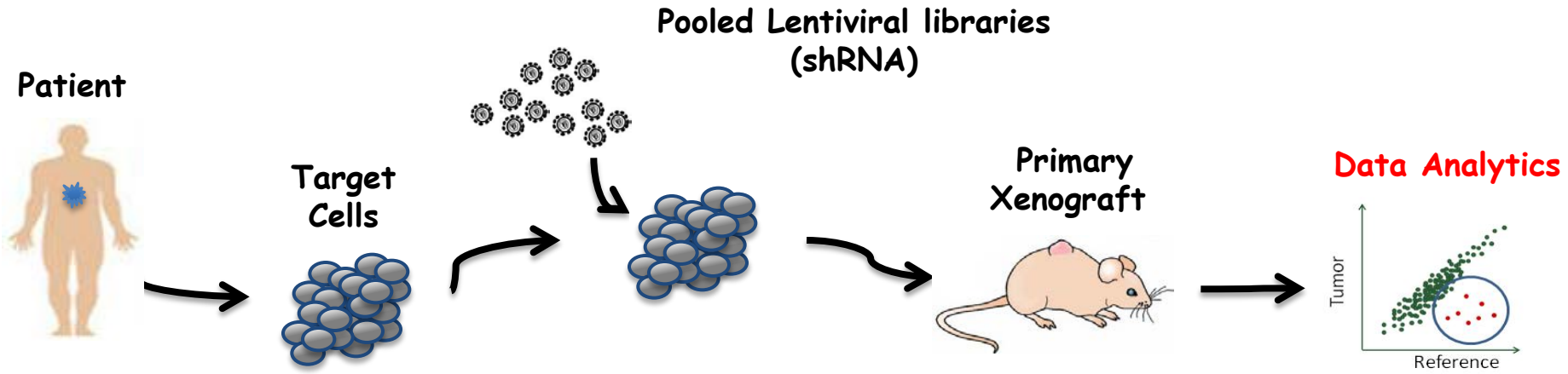
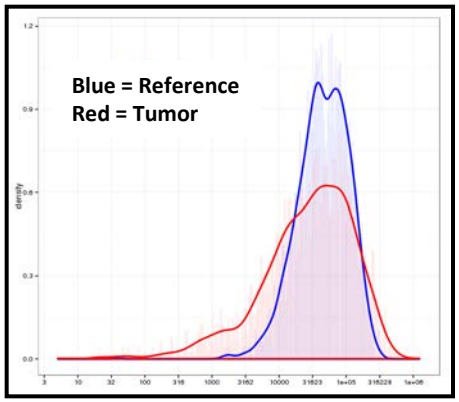
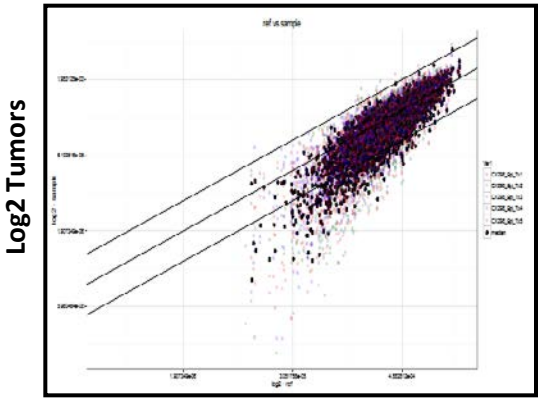
Functional Genomics Discovery Platform:
Data analytics and hit prioritization



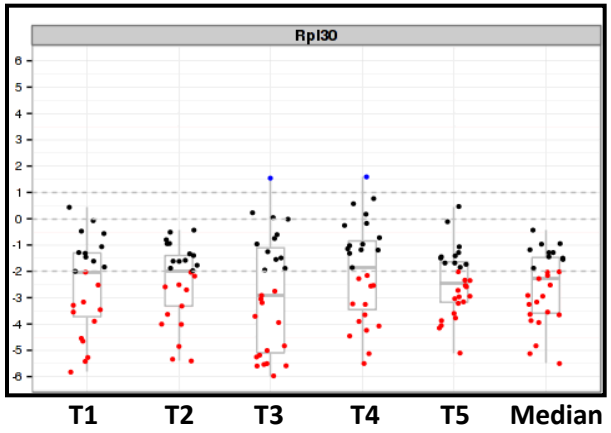
shRNA (Barcode) Distribution



shRNA (Barcode) Comparison



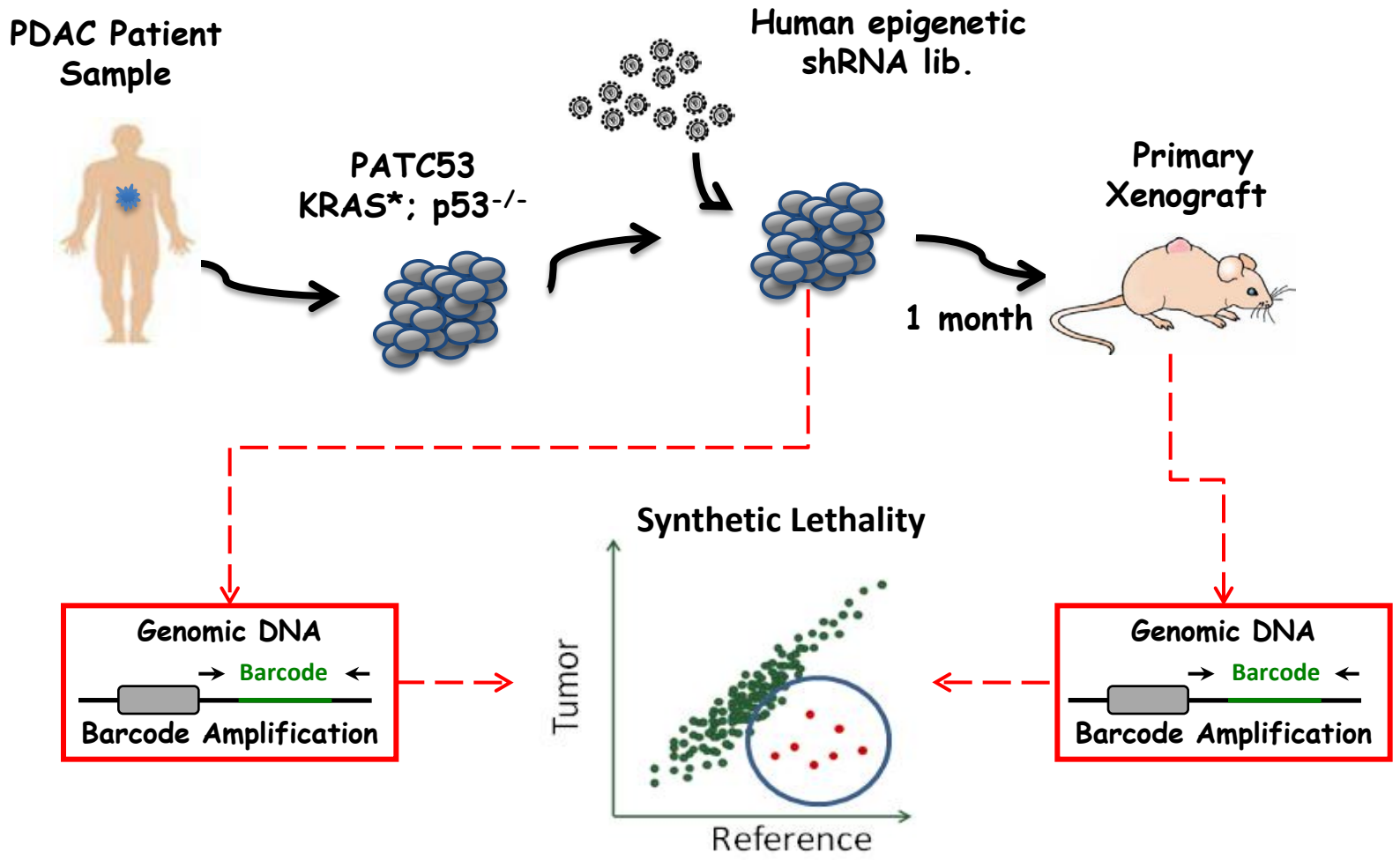
shRNA score across experimental replicates



Analysis confirms in vivo enrichment and depletion of shRNAs across experimental replicates

Sahil Seth

In vivo LOF screen to identify epigenetic vulnerabilities in human PDAC



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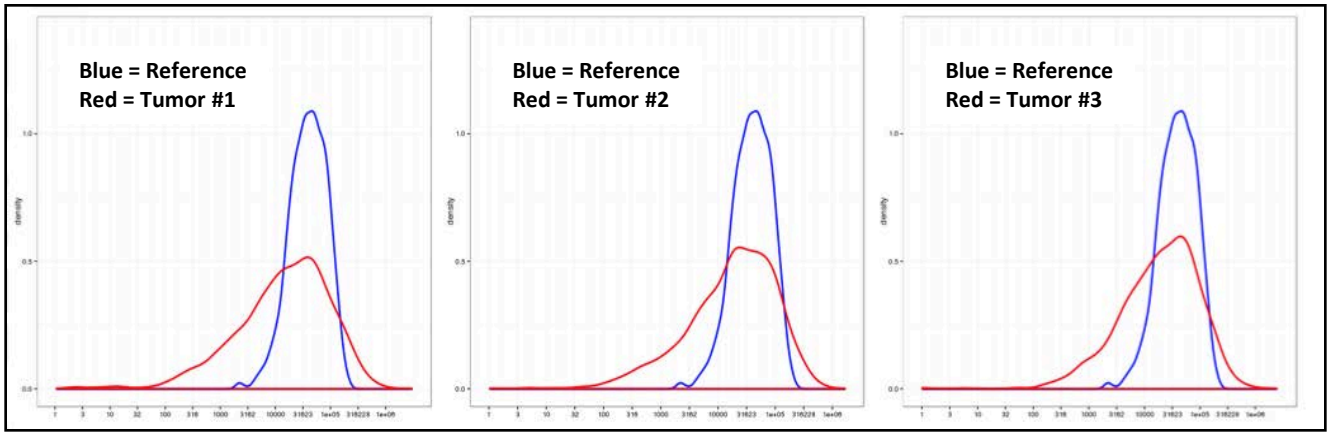
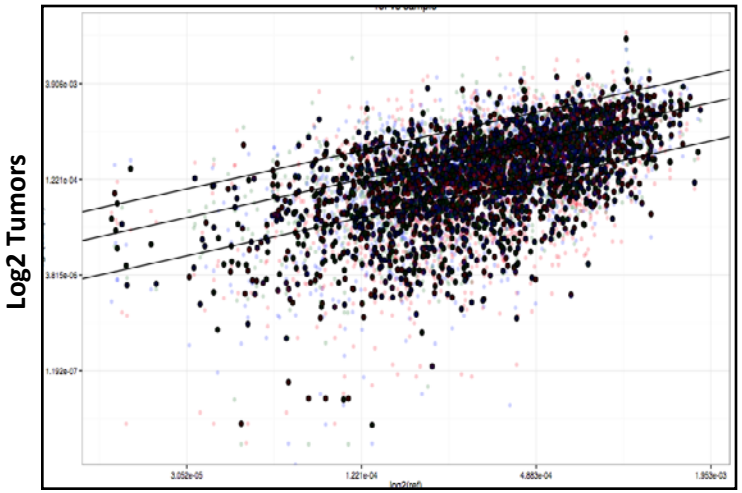
In vivo LOF screen to identify epigenetic vulnerabilities in human PDAC

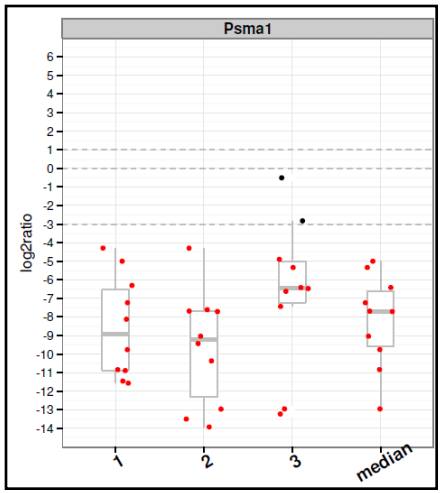
shRNA distribution across experimental replicates



shRNA abundance tumor vs. ref



shRNA depletion in Pos. Control



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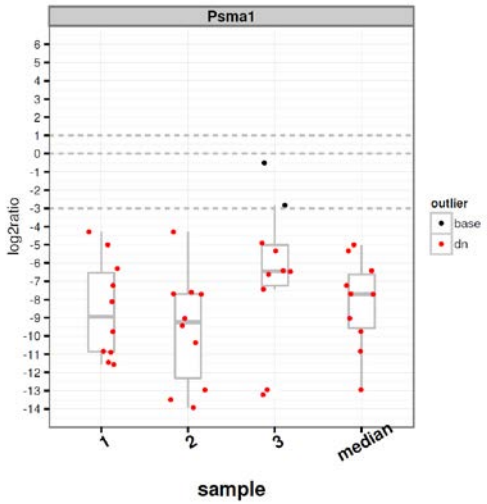
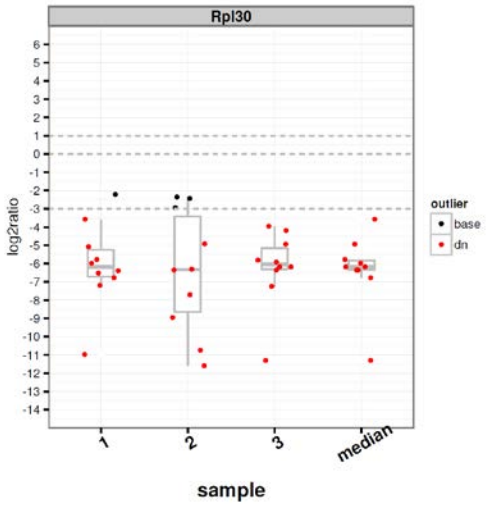
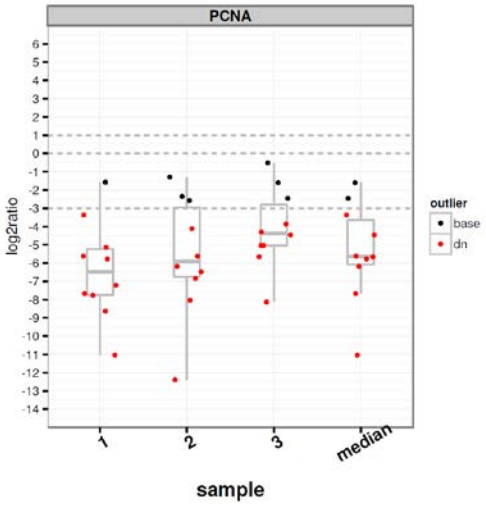
In vivo LOF screen identifies epigenetic vulnerabilities in human PDAC

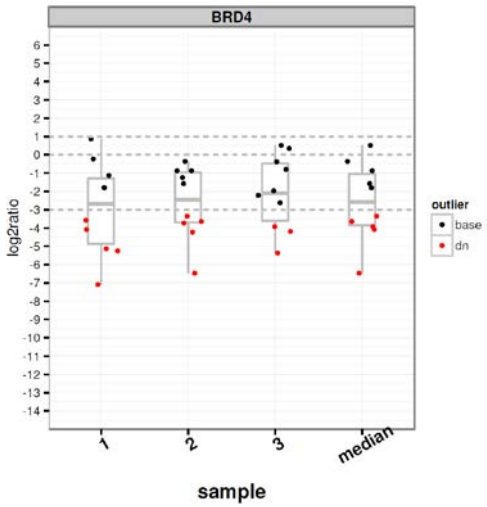
Positive Controls

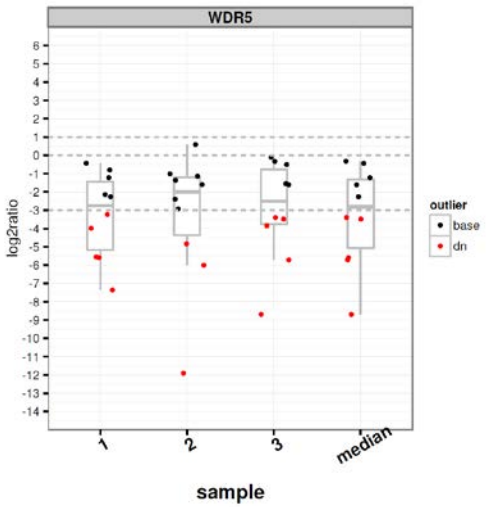


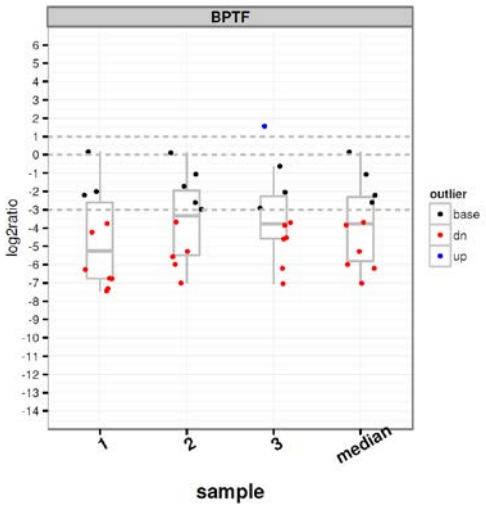




Selected Primary Screen Hits







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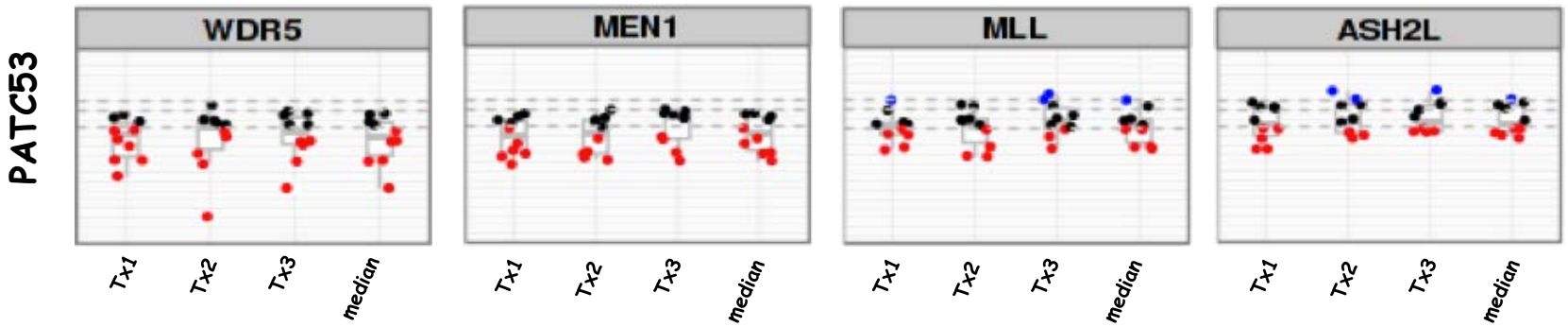
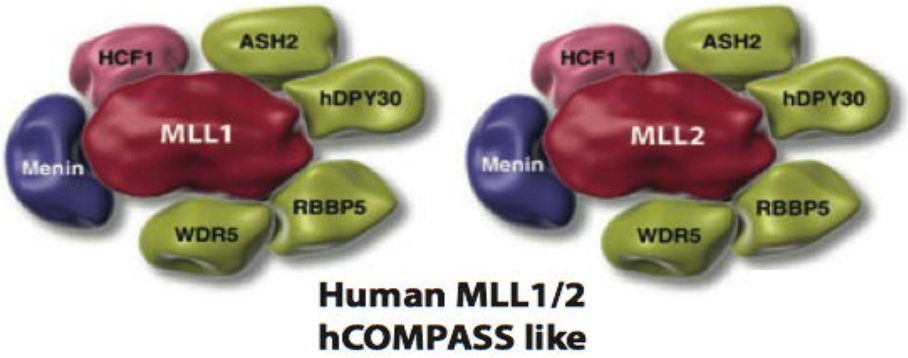
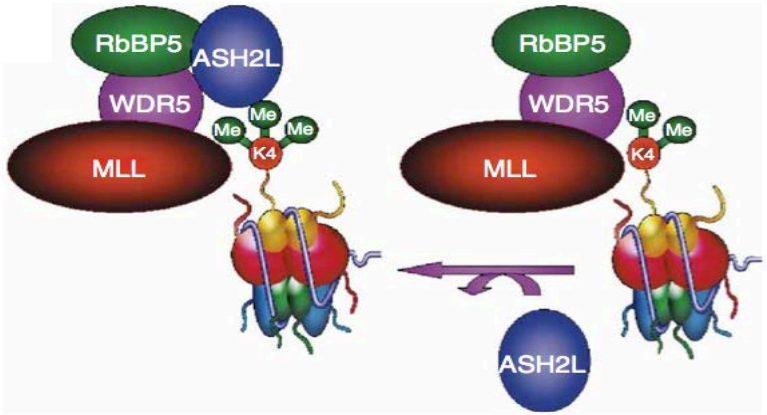
Multiple members of the COMPASS complex are essential for PDAC growth

- COMPASS complex screen hits -





Shilatifard A. *Annu. Rev. Biochem* 2012



Steward M. *Nat. Struct. Mol. Biol.* 2006

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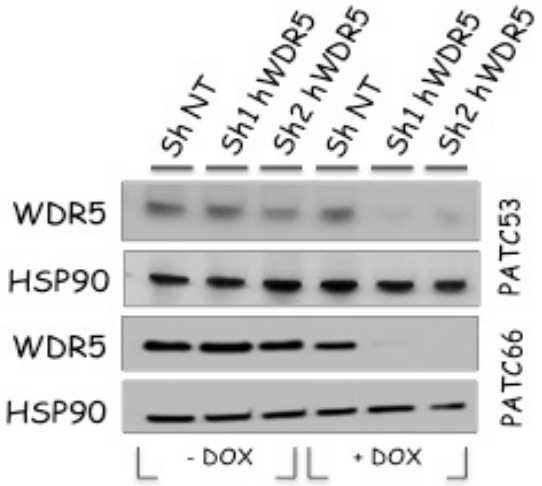
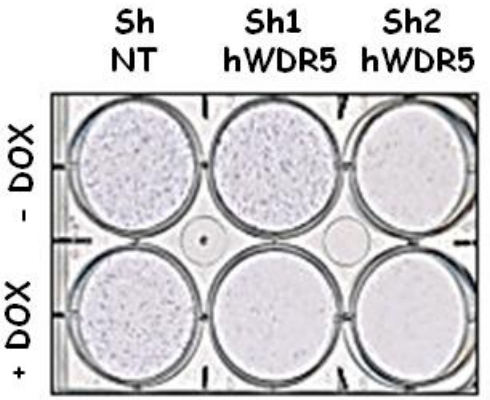
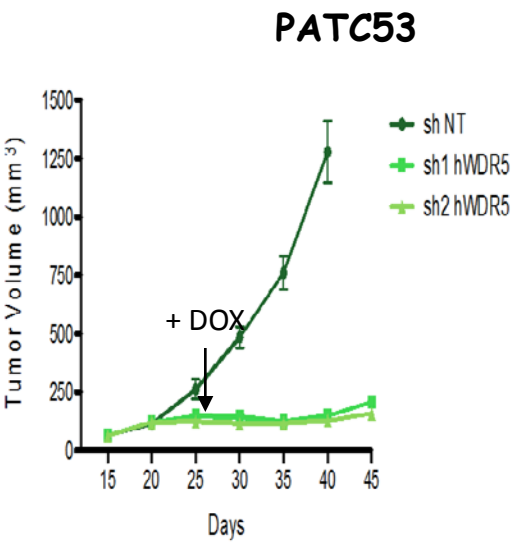
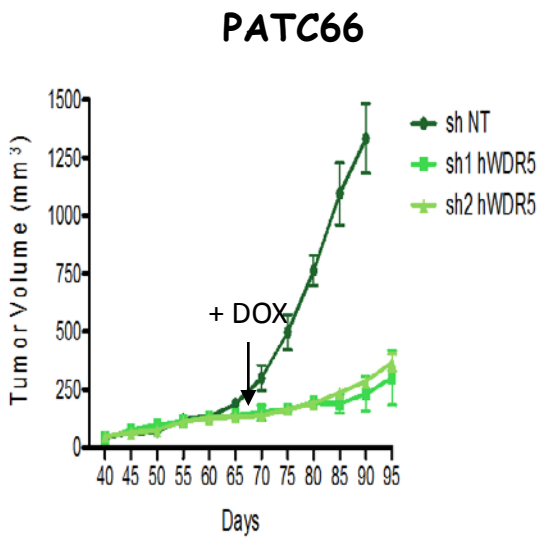
WDR5 is required to maintain growth of established tumors.



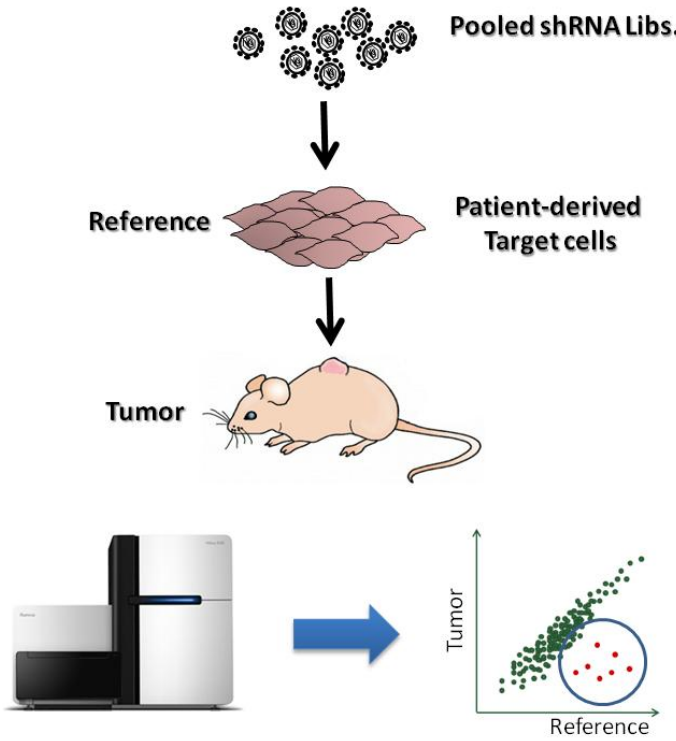




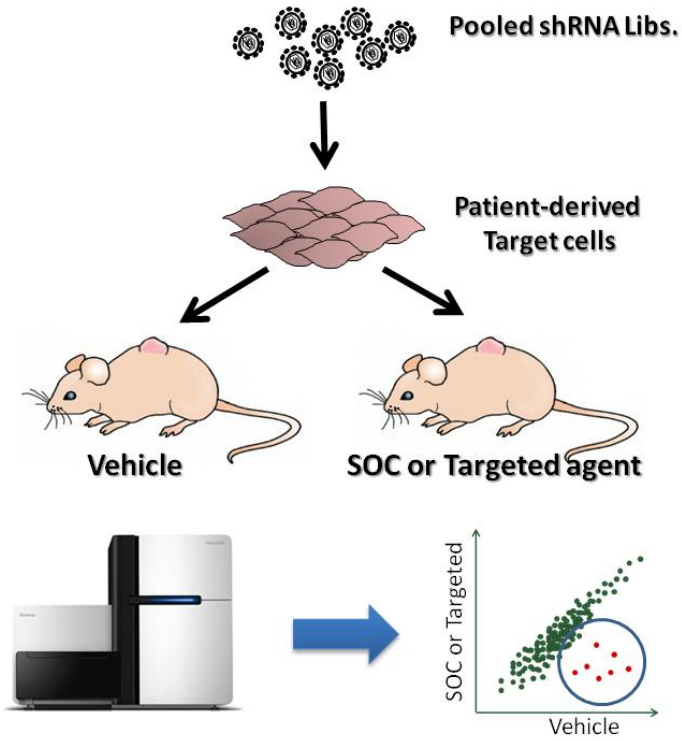


IACS Discovery Platform:
Opportunity to industrialize the approach

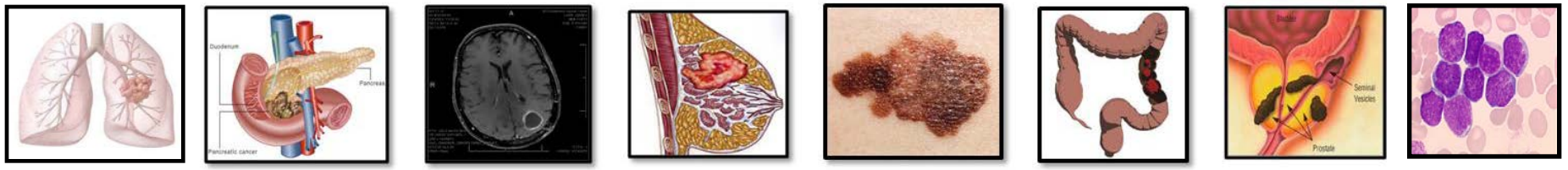
Simple lethality to inform novel therapeutic targets



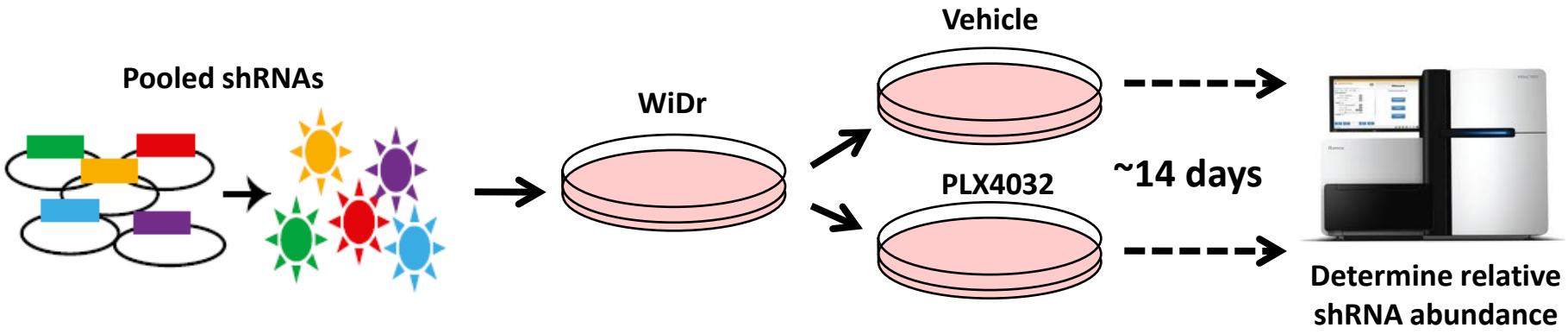
Synthetic lethality to inform novel co-extinction targets



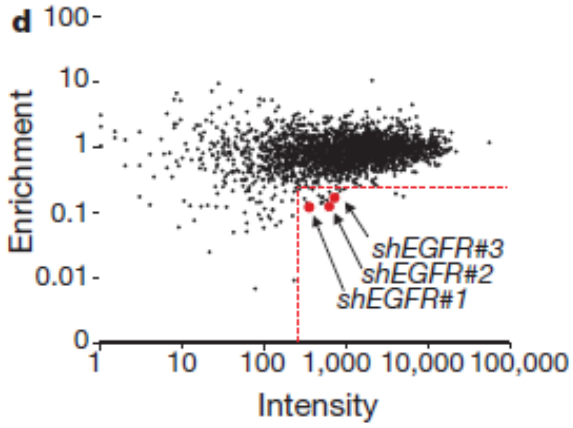
NSCLC **PDAC** **GBM** **TNBC** **Melanoma** **CRC** **Prostate** **AML**

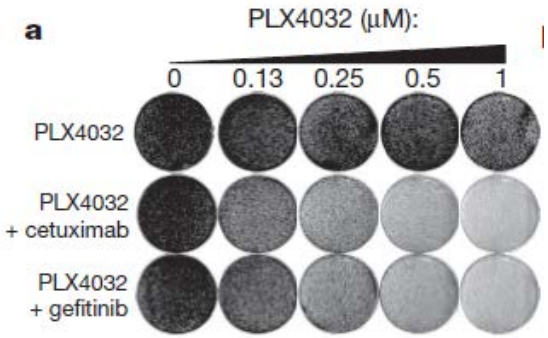


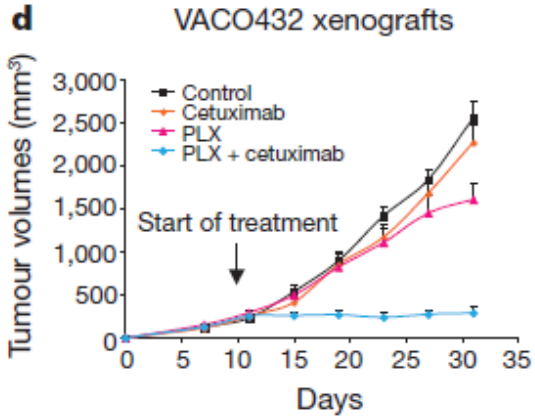
Synthetic lethality screen informs on combination strategy to treat BRAF* CRC



EGFR inhibition enhances the activity of PLX4032 in BRAF* CRC







Prahallad et al Nature 2012

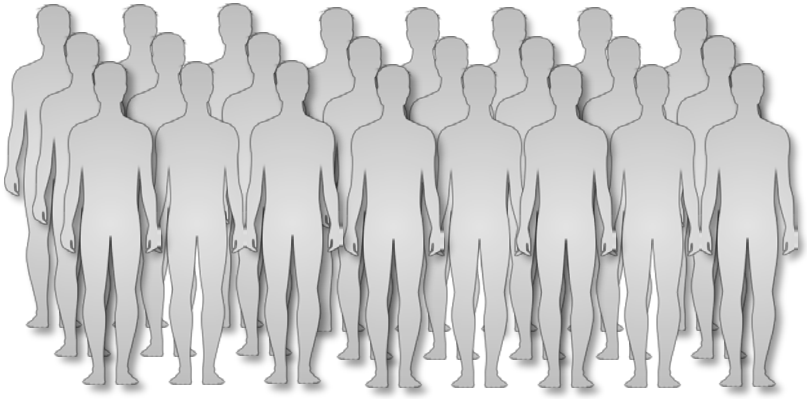
Multiple clinical trials ongoing to test efficacy of EGFRi + BRAFi combination in CRC

Barriers to progress

- Elemental knowledge of cancer omics.
  - Thinking beyond the genome.
- Limited insights into factors driving cancer.
  - Genetic and functional weight of evidence.
- Poor understanding of the target's "biology"
  - In what context (cellular/genetic) is the target rate-limiting?
- Lack of insight on appropriate combination
  - Tumor will find a way to bypass a single-point intervention
  - Co-extinction is required to shut down a complex highly-redundant network

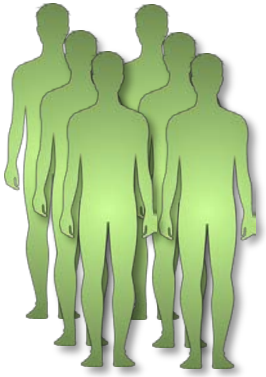
Target ID through functional genomics

Systematic approach with patient-centric focus

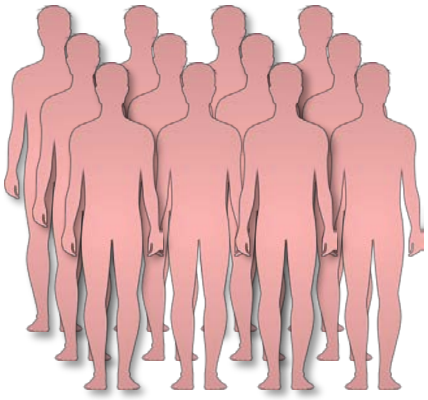


Identifying the context in which a target is rate limiting

Target A



Target B



Target C

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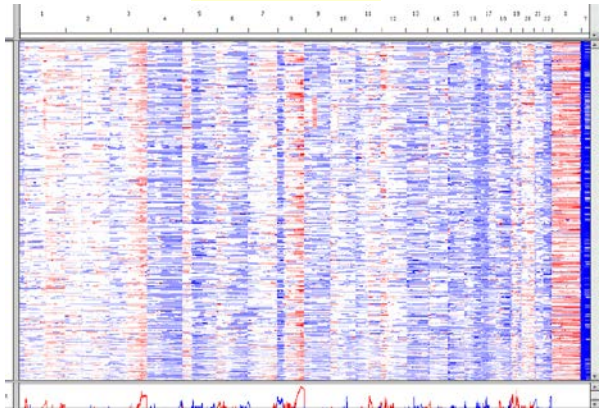
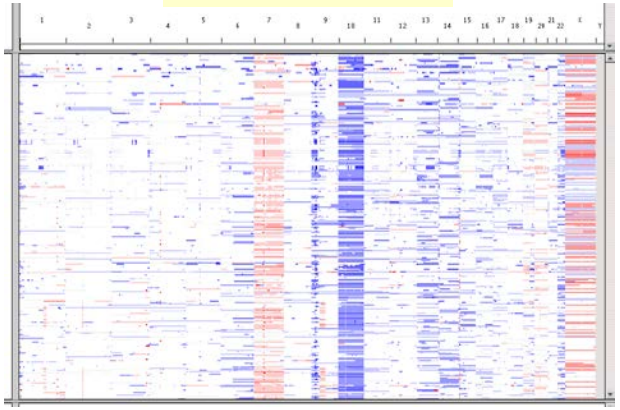
Cancer genomes are different – context is important for developing novel molecularly targeted therapies

Ovarian



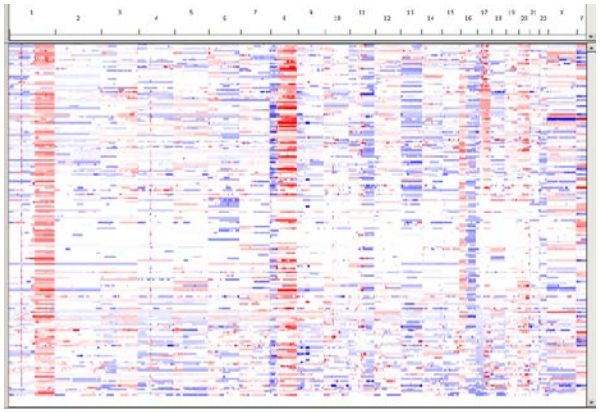
3q gain 8q gain

Glioblastoma



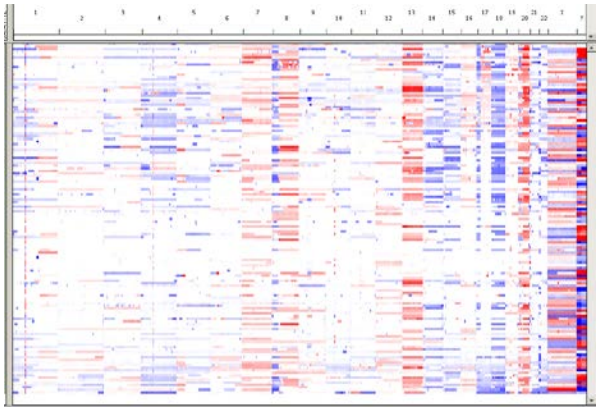
7 gain 10 loss

Breast



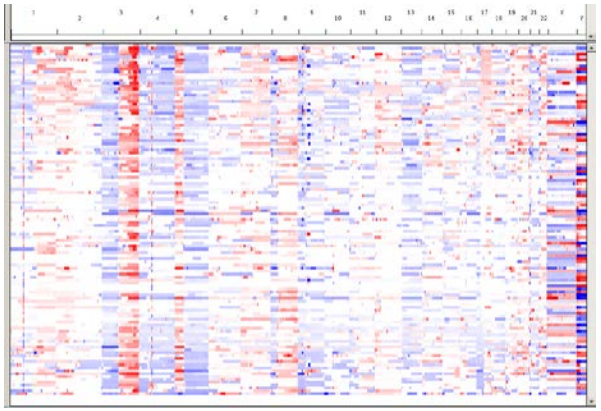
1q gain 7 gain

Colon



7 gain 8 gain 13 gain

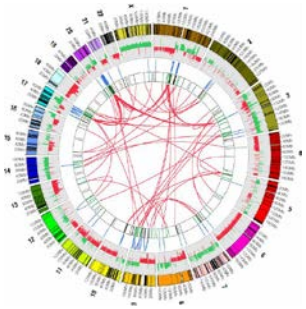
Lung squamous



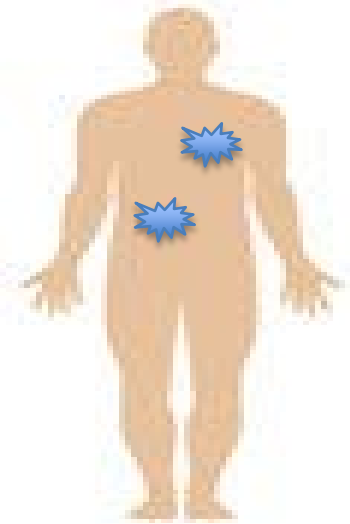
3q gain

Context is important!

- Genetic Context:
  - BRAF vs. NRAS melanoma
  - EGFR vs. KRAS NSCLC
  - NOTCH is T-ALL vs. H/N

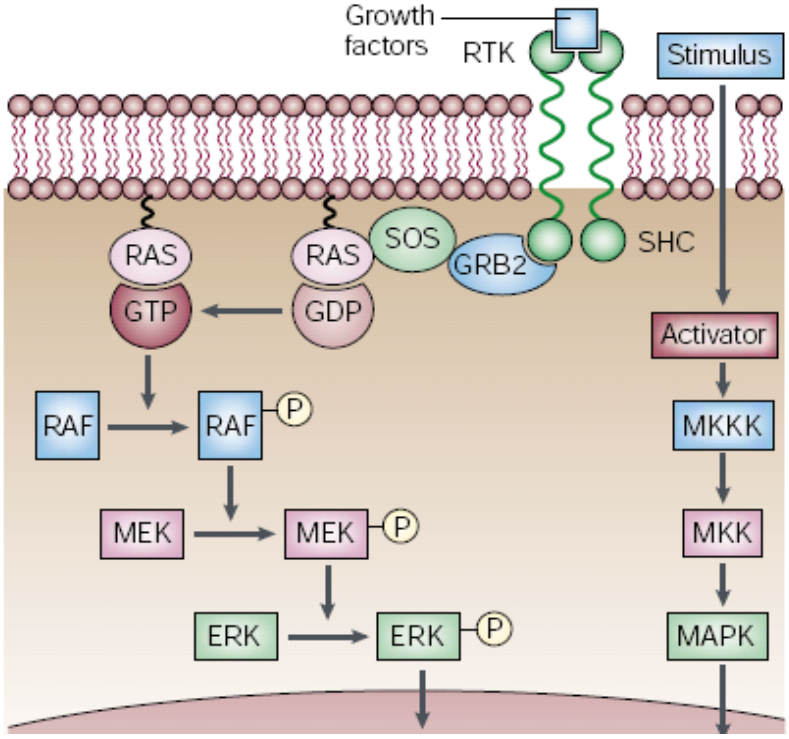


- Cellular Context:
  - EGFR inhibition in NSCLC vs. GBM
  - BRAF inhibition in melanoma vs. CRC

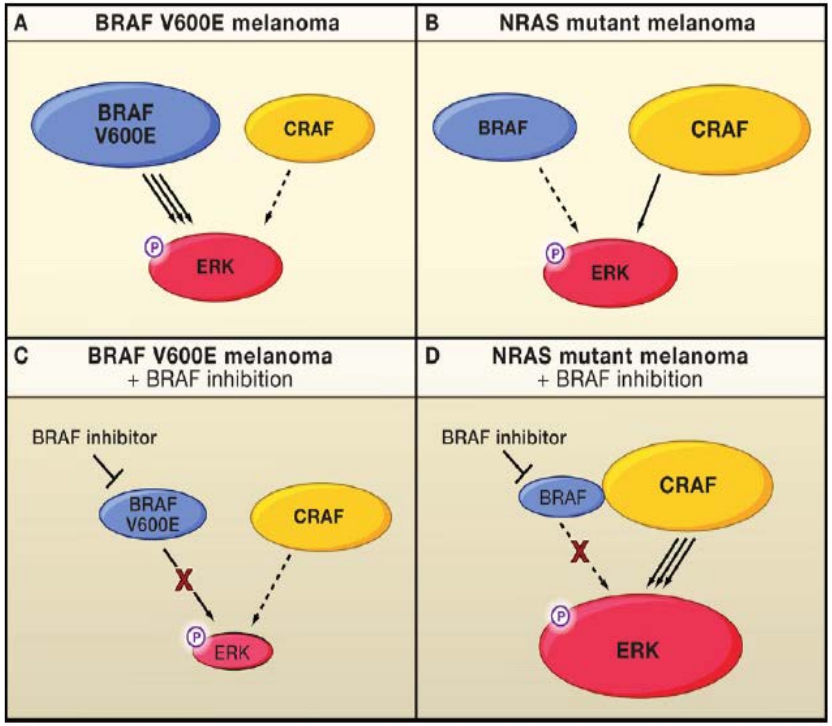


- Microenvironmental Context:
  - Stromal barrier in PDAC

Cancer signaling pathway is not linear…



L Chin, *NRC* 2003



Kwong & Chin, *Cell* 2010

- **Inhibiting RAF is not the same as inhibiting MEK**
- **RAS mutant tumors do not respond to BRAF inhibition as RAF mutant tumors**

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Biomarkers predictive of non-response to EGFR-targeted therapy

KRAS vs. EGFR

Table 1 Impact of KRAS mutations on response to EGFR-targeted therapies[11–13]

Therapy	Treatment response rate		Median patient survival	
	KRAS mutation positive	*KRAS* mutation negative	*KRAS* mutation positive	*KRAS* mutation negative
Colorectal cancer				
Cetuximab	0% (0/36)	44% (34/78)	9 weeks (PFS)	32 weeks (PFS)
Panitumumab	0% (0/84)	17% (21/124)	7 weeks (PFS)	12 weeks (PFS)
NSCLC				
Erlotinib	8% (2/25)	26% (27/104)	4.4 months (OS)	12.1 months (OS)

PFS (progression-free survival); OS (overall survival).

Chin L, Andersen JN, Futreal PA. Nat Med. 2011 Mar;17(3):297-303.

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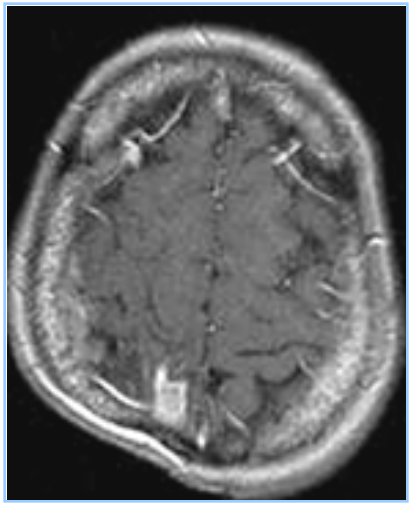
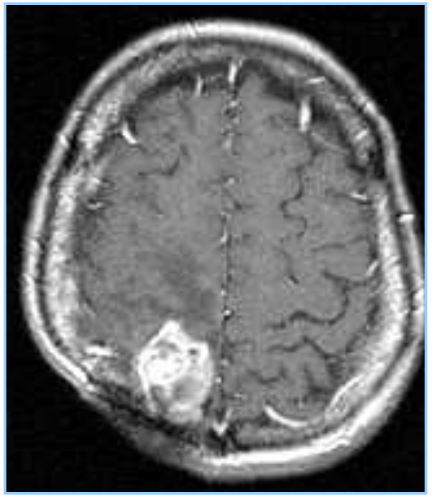
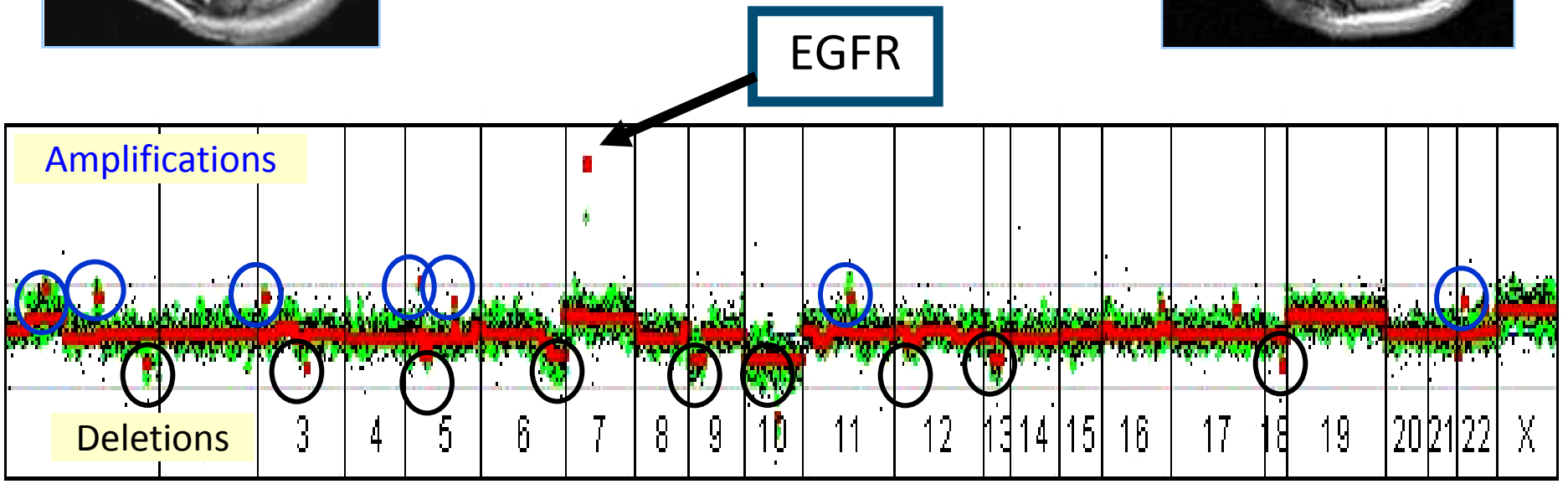
Failure of single targeted therapies in GBM is likely due to modulation of a single node in a network



EGFR inhibitor x 2 months





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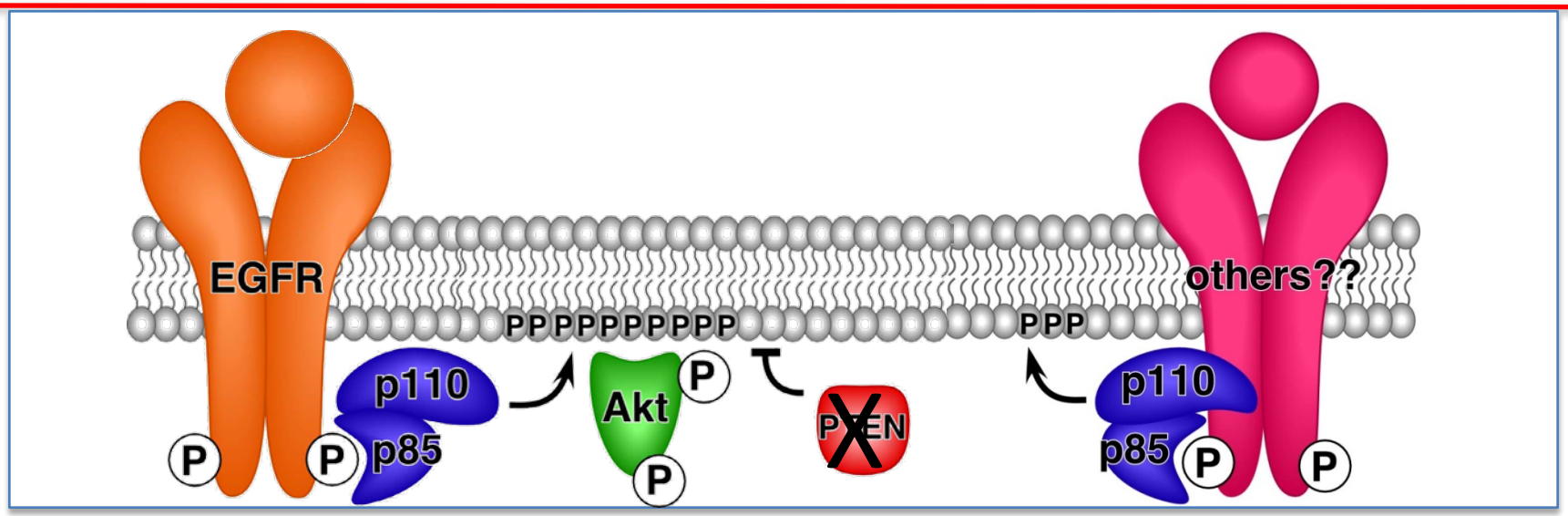
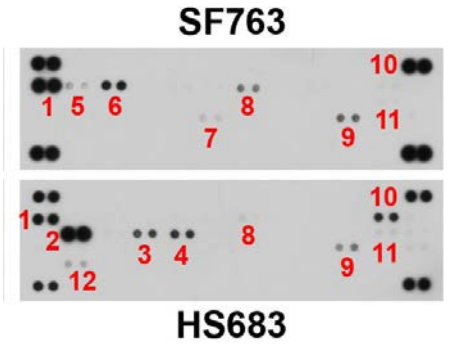
Co-activation drives disease, co-extinction overcomes it



Multiple RTKs are activated simultaneously in glioma

Stommel (DePinho), Science 2007



RTK co-activation:

- Concomitant activation of 2-4 key targets that prevents exclusive dependence on any single target.
- Render a diseased cell refractory to single-target inhibition.

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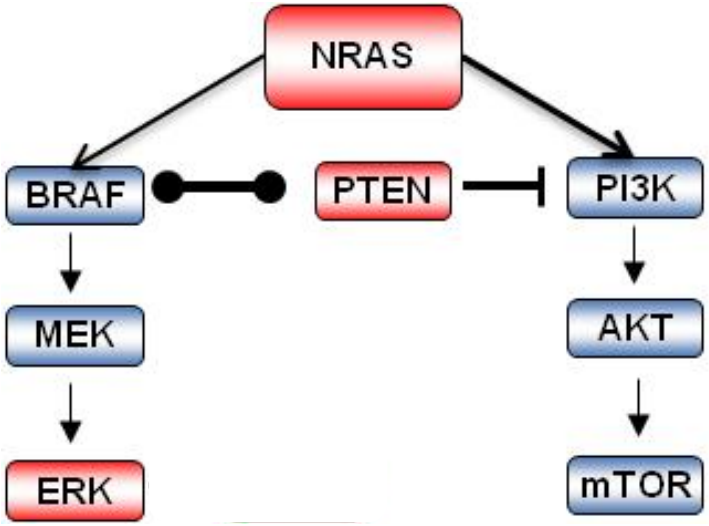
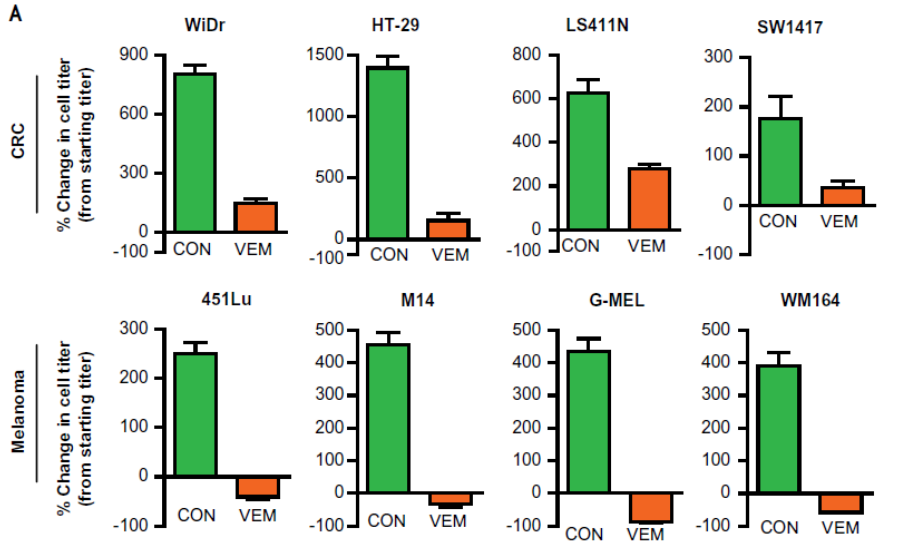
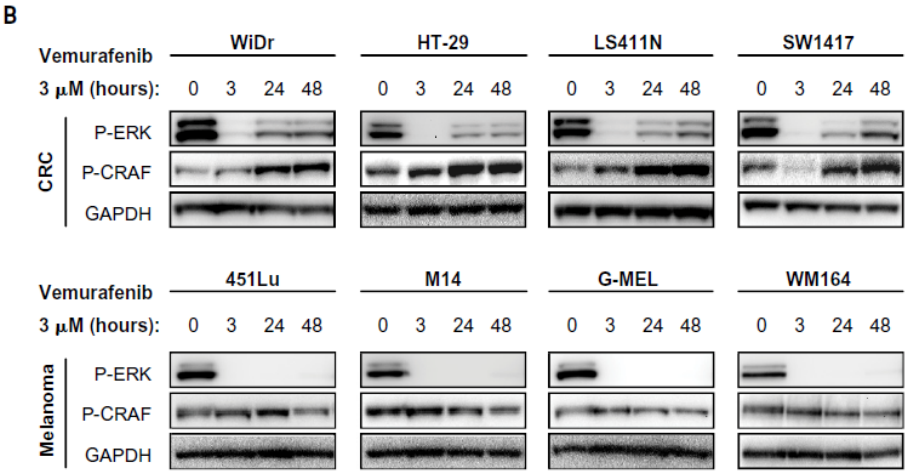
Context Dependent Response to BRAF Inhibition







BRAF mutant CRC and melanoma respond differently to BRAF inhibitors

Corcoran et al. Cancer Dis. 2012

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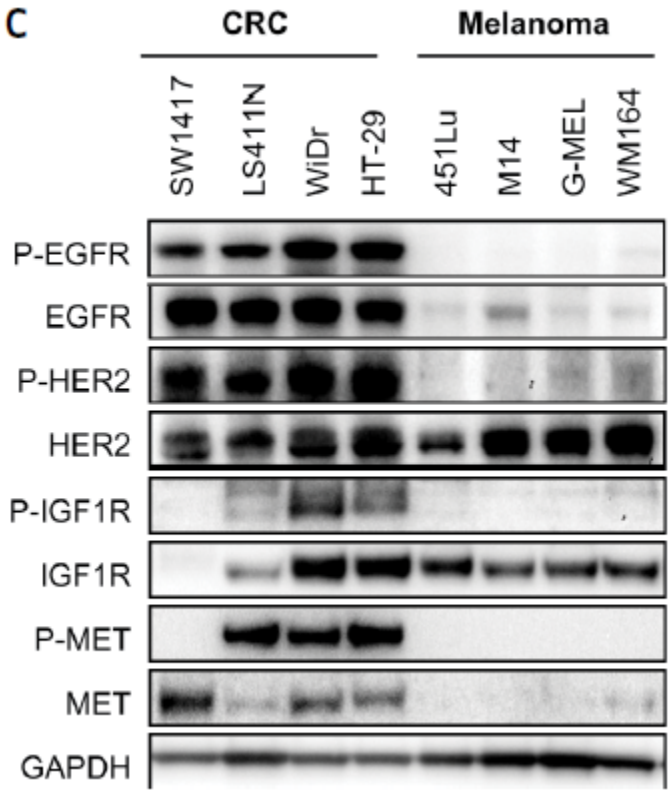
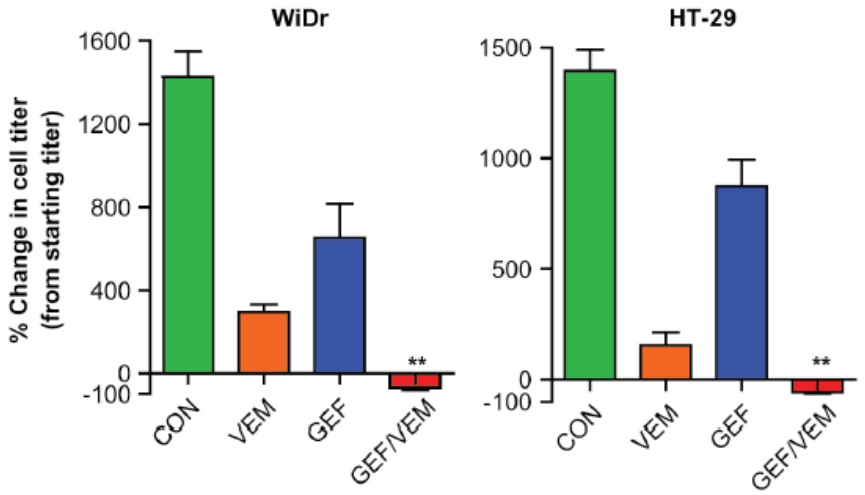
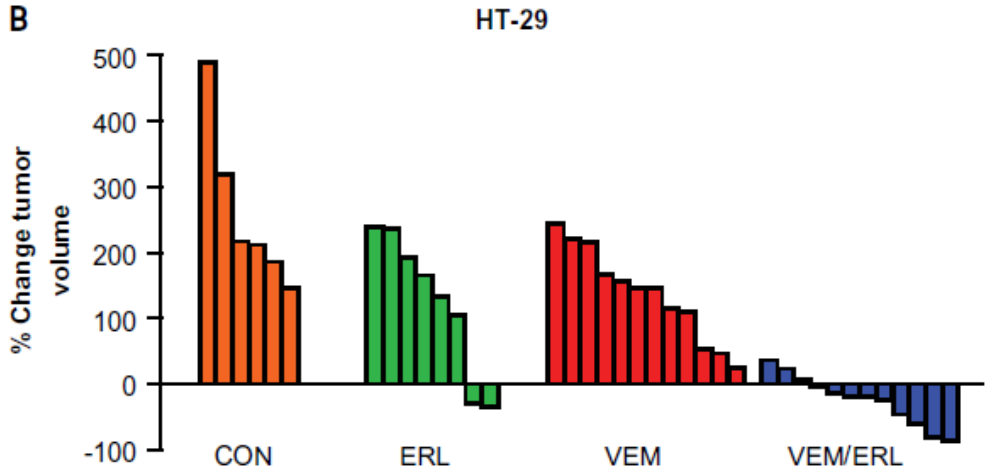
Context Dependent Hyperactivation of RTKs Defines Response in CRC







Corcoran et al. Cancer Dis. 2012

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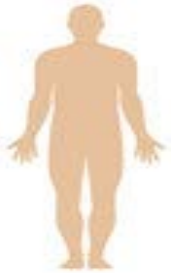
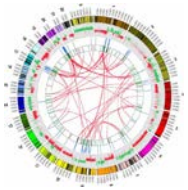
Functionalizing the Cancer Genome

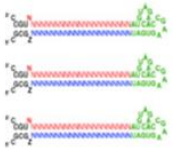
Omic Annotation

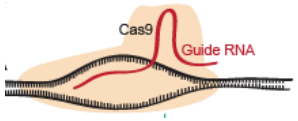
Genetic Elements of Interest

Proteome scale cDNA Libraries

Genome scale shRNA Libraries



CRISPR/CAS9



Context

Genetic:
KRAS vs. EGFR vs. PI3K

Pharmacogenomic:
Resistant vs. sensitive

Phenotype

In vivo Tumorigenicity

Drug Sensitization

Functional genomics will identify context specific targets and inform on rationale drug-drug combinations.

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Agenda

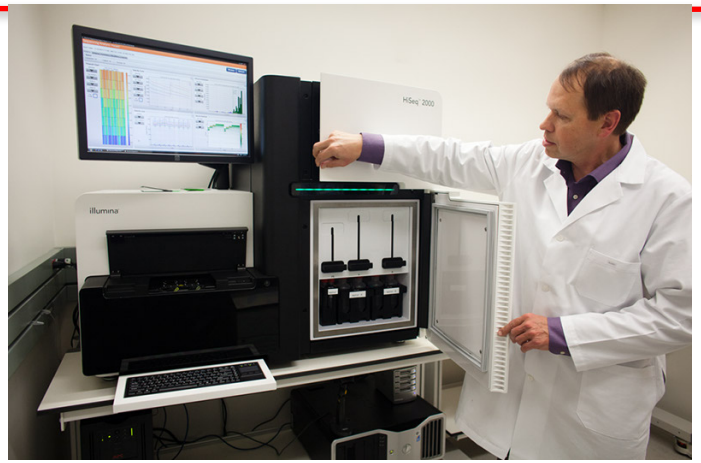
- Barriers to progress in the fight against cancer.
  - Complexity
  - Few successes but many failures
  - Focus on personalized medicine

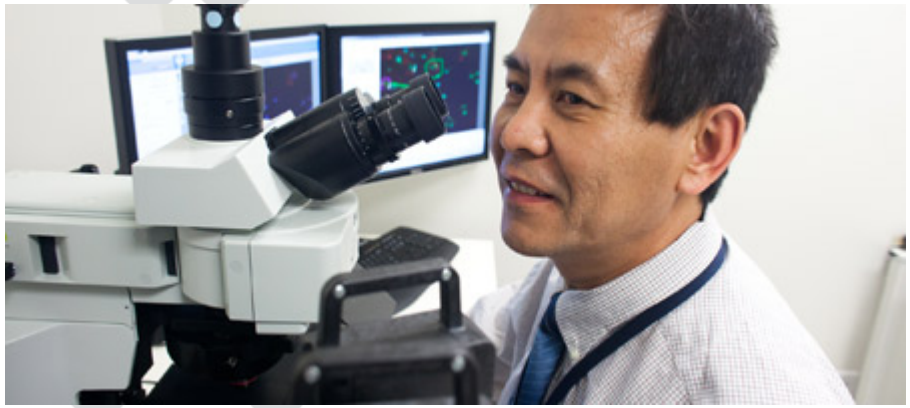
- Functional Genomics to identify genetic dependencies.
  - Prioritization must be based on both genomic and biological weight of evidence.

- Introduction to the Institute for Applied Cancer Science.
  - Drug discovery in an academic setting.

- Question and Answer Session

An introduction to the Institute for Applied Cancer Science (IACS)





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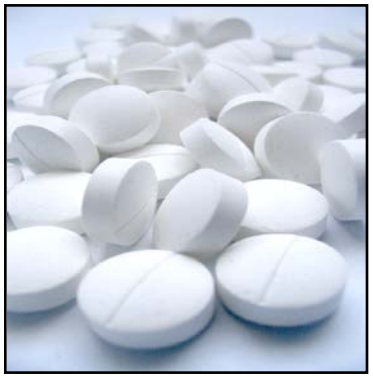
Valley of Death: targets to drugs

~5% Success to Market

ACADEMIA:
New Discoveries

BIO-PHARMA:
Drug Discovery
Diagnostics
Devices

ACADEMIA:
Clinical
Research



- Conceptual:
  - Knowledge gap
  - Lack of clear line-of-sight for clinical development
- Organizational:
  - Biology is divorced from drug discovery
  - Poor integration and hand-off between stages

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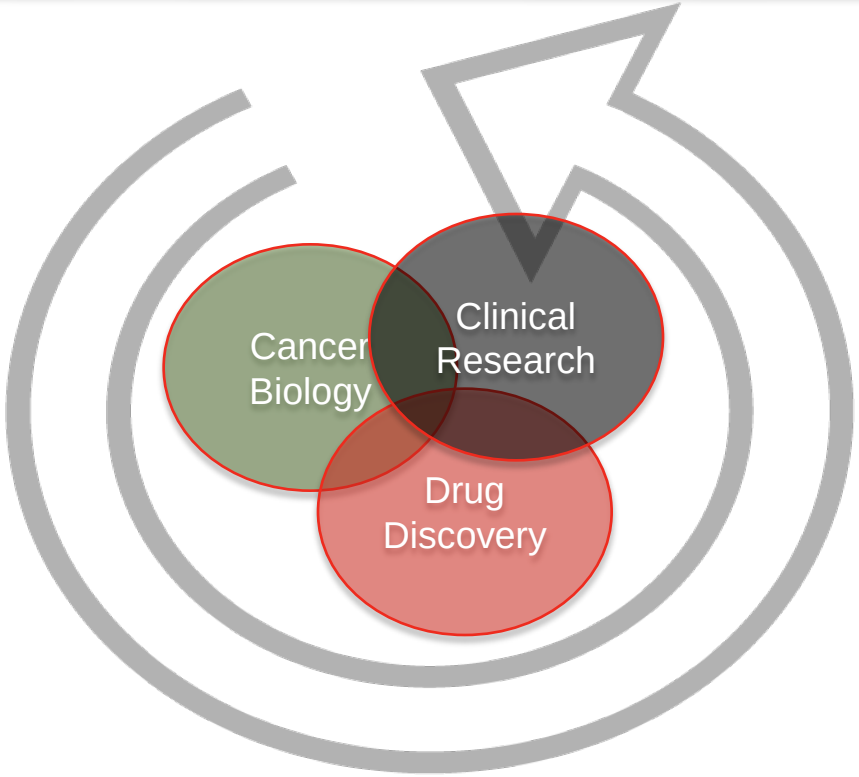
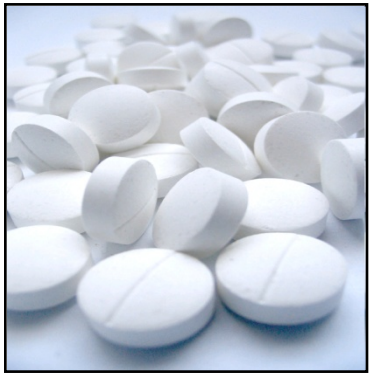
Drug Discovery at MDACC
The Bench-at-Bedside Approach





- Applied Cancer Science
  - Cross-functional teams
  - Milestone-driven, goal-oriented
  - Fast kill and prioritization
  - Singular Focus to develop new drugs

- Integration with MDACC Clinic
  - Daily interaction with leading clinicians
  - Unparalleled access to clinical material
  - Accelerated translation of pre-clinical hypotheses into POC clinical trials

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Driving a Comprehensive Plan of Attack

- **Prevention**
- **Early detection: imaging, tissue markers**
- **Diagnostics: integrate genomic profiling into clinical practice**
- **Drug discovery expertise**
  - ***Internal effort:*** provide internal expertise to better ***integrate with the external world*** – importance of scouting and triaging
- **Clinical development**
  - Evaluating therapies of true potential: Early access to new, high quality treatments
  - Streamlining regulatory reviews and operations
  - Imaging and other modalities to monitor response
  - Immuno-monitoring

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MDACC Translational Continuum: Institutional platforms support moonshot initiative *and beyond*

- APOLLO
- Big Data
- Cancer Prevention and Control
- Center for Co-Clinical Trials
- Clinical Genomics
- Molecular Diagnostics
- Immunotherapy
- Institute for Applied Cancer Science
- Institute for Personalized Cancer Therapy
- Proteomics
- Research Genomics

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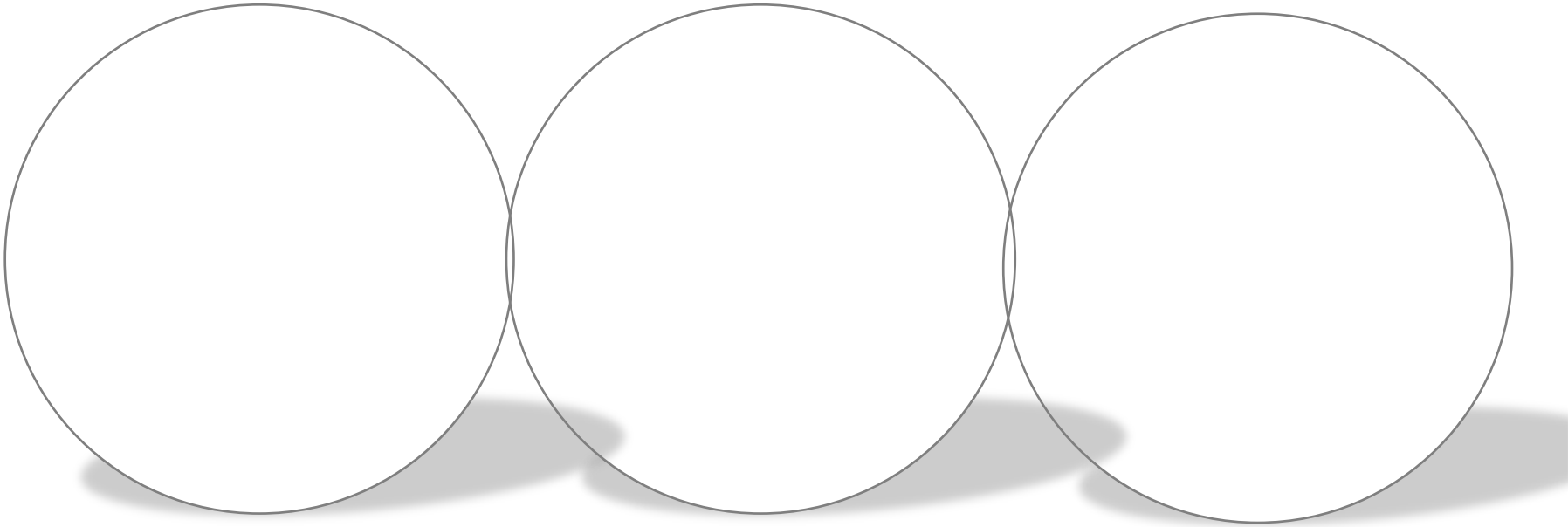
Where will improvements come from?



Pharmacokinetics
Biodistribution
Adequate safety

Tumor fingerprinting
Patient stratification
Tailored combination strategies

Focused phase 1b/2a
PoC trials
Early response biomarkers

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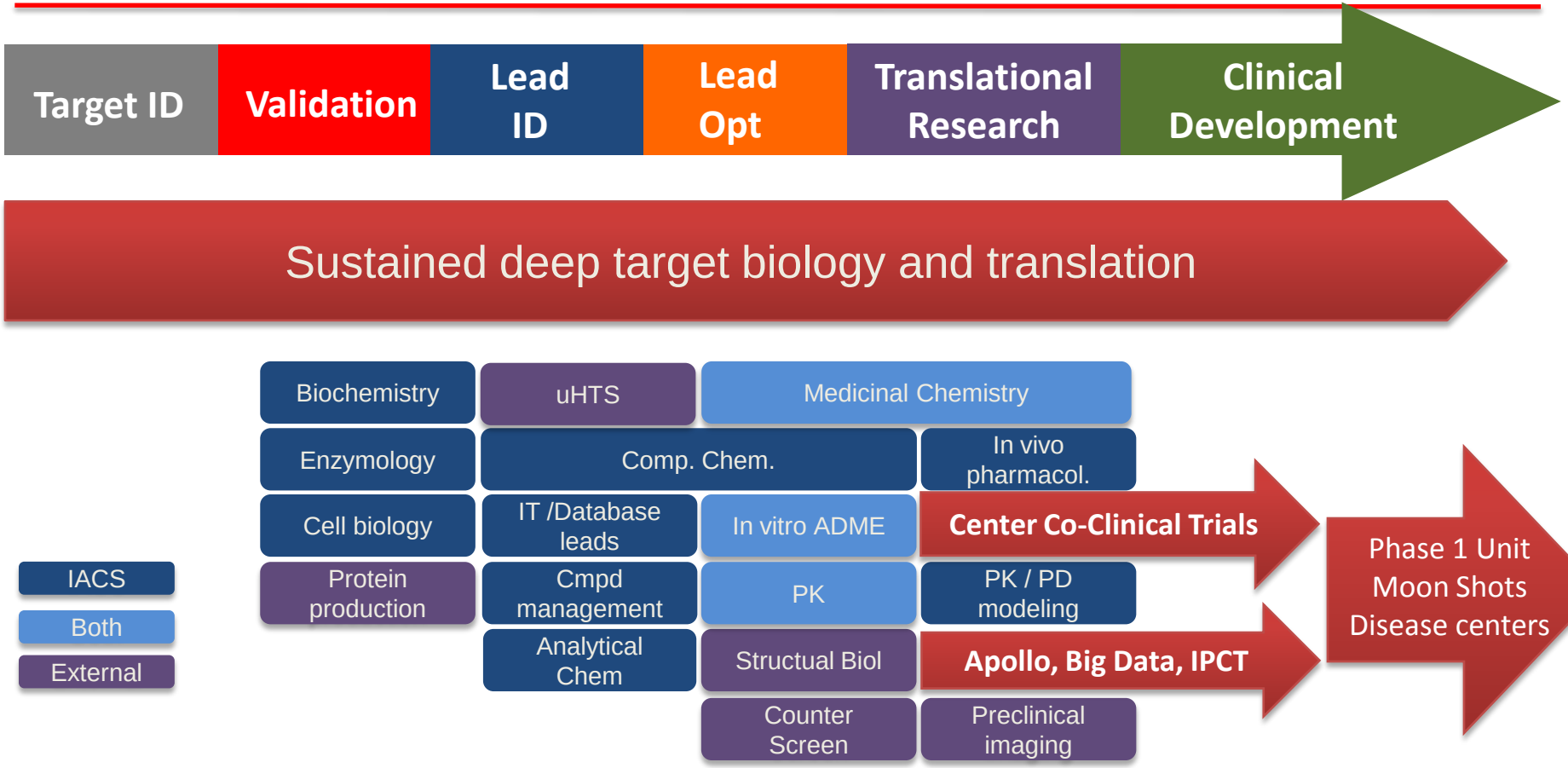
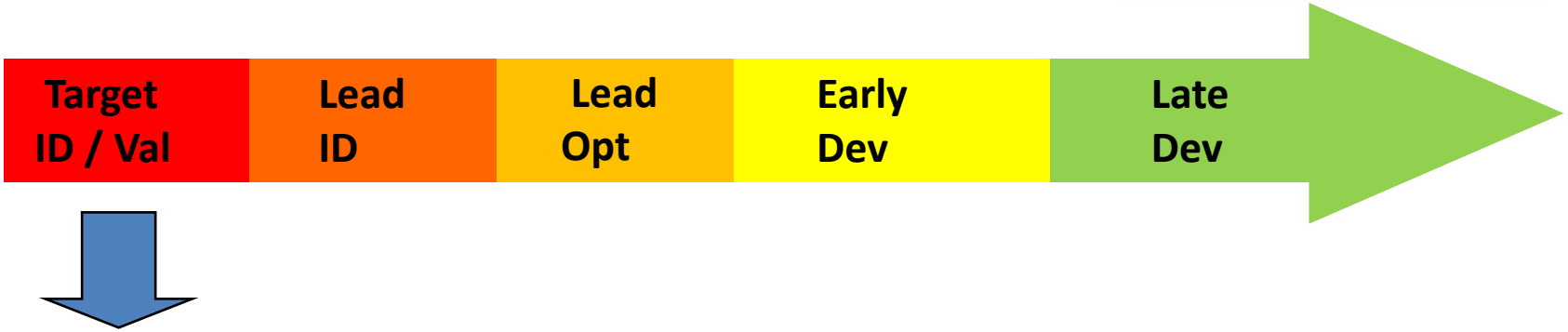
Institute for Applied Cancer Science:
Discovering new drugs



- Rigorous evaluation of targets, focus on defining the clinical path hypothesis.
  - Disease relevance
  - Ease of therapeutic attack
  - Clinical need

IACS drug discovery pipeline - Target Identification and Validation



- *Target identification*
  - proteins & signaling molecules which are believed to be associated with disease pathogenesis.
- *Target validation*
  - confirm that interactions with the drug target are associated with behavior of diseased cells
  - manipulation (genetic or pharmacological) restores function

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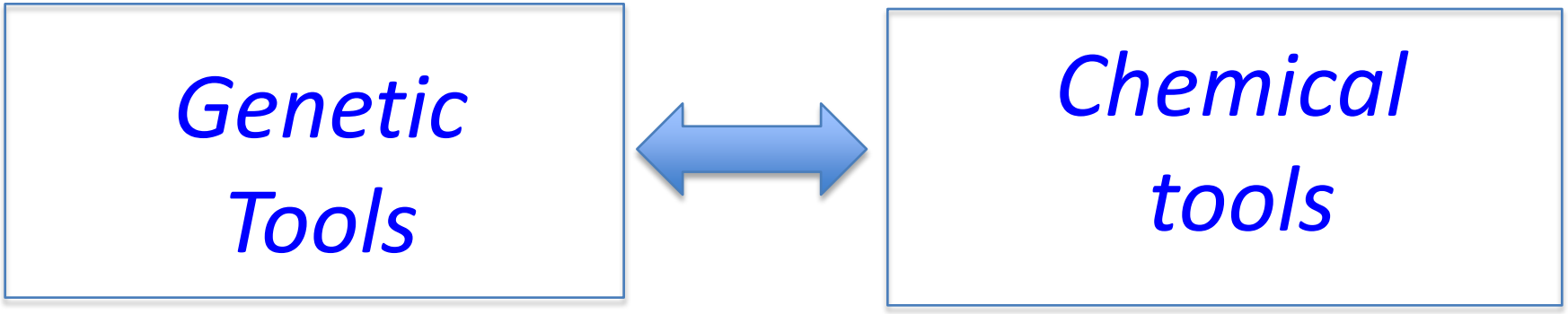
IACS Target Validation Strategy

Parallel use of genetics and tool compounds to define **mechanism of action** & **clinical path**



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Drug target Assessment Profile

Biological Function	Biological function – evidence connecting target to essential tumor biology or host response
Rationale , including Cancer Genomics	Cancer relevance – evidence that target is functional in cancer cells or regulates host response Oncogenomic – *mutations, amplifications, translocations, epigenetic, expression…*
POC (preclinical / clinical)	What evidence is there to show mechanism is essential? Tool biologic/molecule >> shRNA. Clinical >> In vivo >> in vitro
Status of antibodies/vaccines	Conceptual? Mono/Polyconal Ab? Mouse or human? Cross-Reactive? Humanized? Optimized?
Feasibility of screening funnel	(1) Affinity, (2) cellular target engagement – internalization/(ant)agonism, (3) phenotypical – Proliferation/colonogenicity/immunomodulation
Preclinical models *in vivo*	What models has the asset been evaluated in? What models are available?
Responder ID hypothesis	What is the sub-population you would target?
PD readout, suitable for clinic	Biomarkers (Target engagement, pathway modulation, Responder ID)
Predicted tolerability	Any potential side effects? From primary target, or related family members
Monotherapy activity (Y/N/unlikely)	Is this going to be effective as a monotherapy? What would a clinical combo strategy look like?
Tumor type indication; Moonshot: Y/N	Primary indications/combinations
Intellectual Property	Status of disclosures and filings? Any known encumbrances or MTAs? Any known relevant third party IP (we can help with deeper dive down the line).
Competition (small mol + biologic)	Any and all levels known – industry/academia. Same target, pathway, modality, indication?
Key Issues	What are the key questions today?
Go/NoGo experiments	What are the decision points? – what are the key studies that need to be done to show that this is a high priority target? What are the go/no-go experiments? – what expt would stop you from doing further work on target or antibody X?

IACS drug discovery pipeline - Lead identification

- *Lead identification*
  - develop suitable screening platform to identify novel chemical matter
  - identify chemical matter which binds to target & modulates the signaling pathway/function
  - optimized for potency, cellular activity & activity
  - fail poor chemical series early

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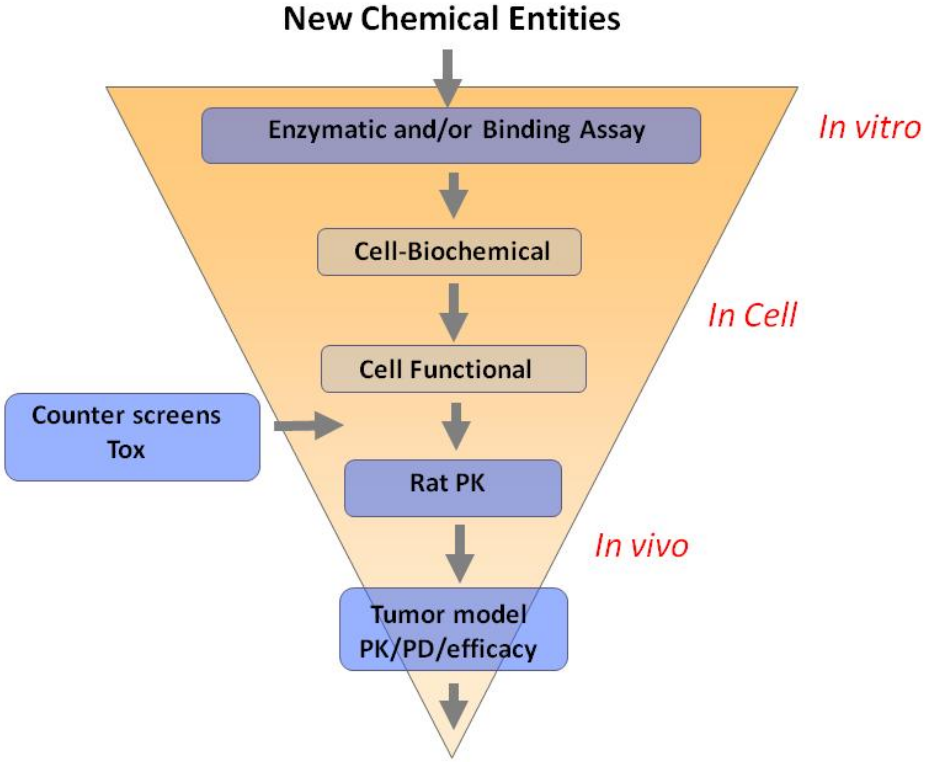
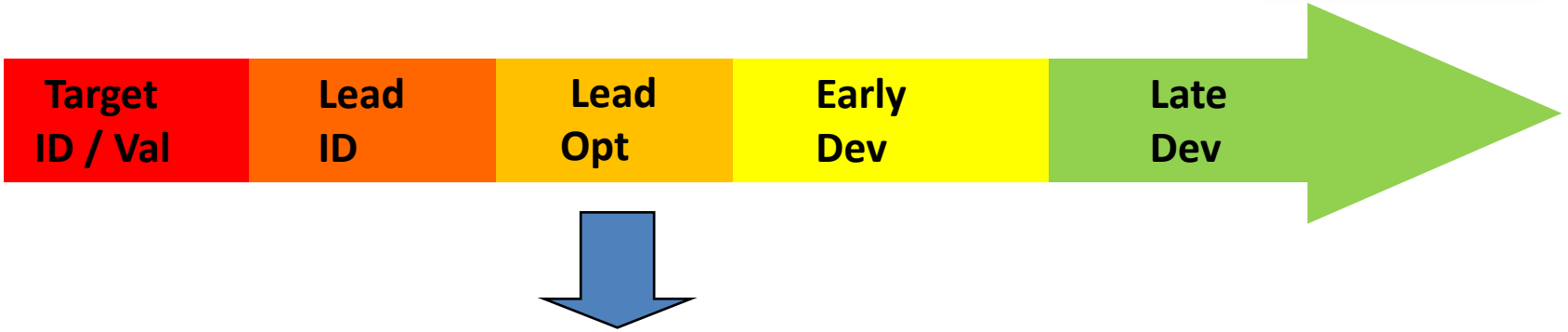
IACS drug discovery pipeline
Disease relevant screening funnel implemented

- Three key components
  - *In vitro* biochemical /binding
  - cellular target engagement assay
  - phenotypical assays



Research stages in drug discovery - Lead optimization



- *Lead optimization*
  - install all of the desired properties of a drug into a single compound …

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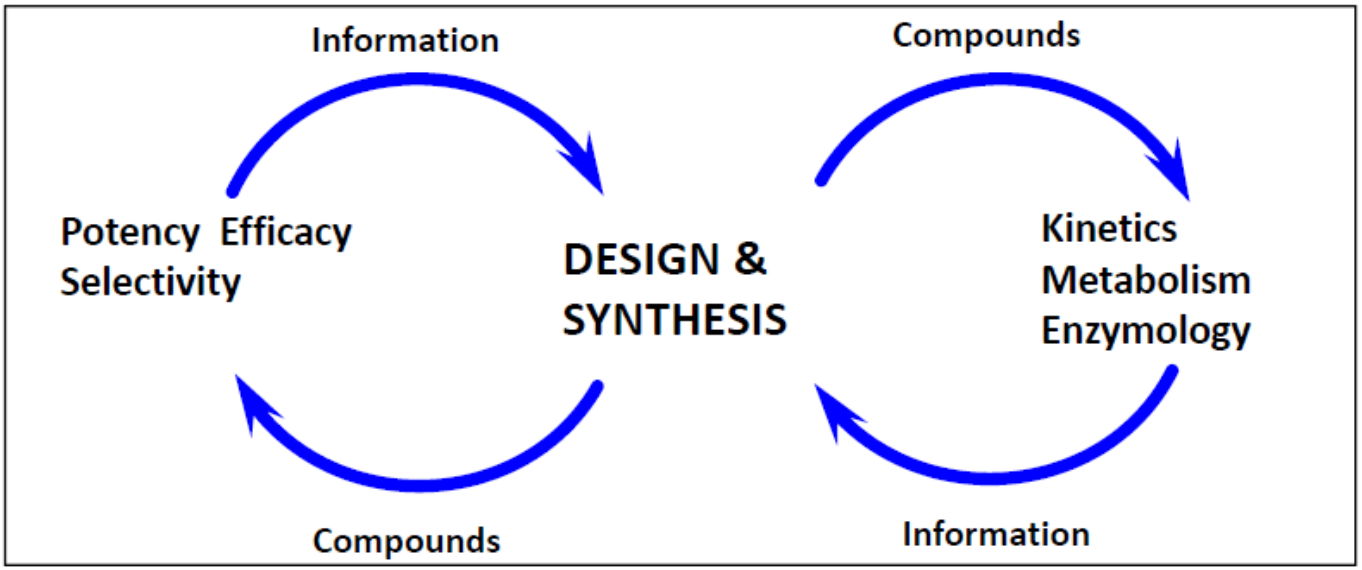
Rapid optimization of chemical matter: generate *in vivo* tool compound

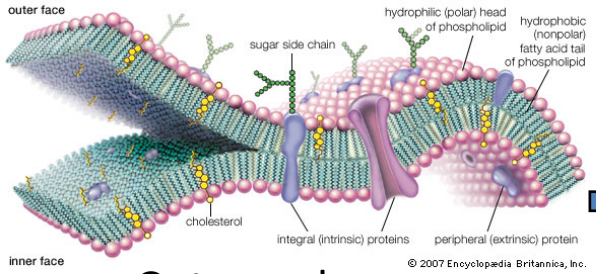
- Multiple rounds of SAR rapidly improve potency, & cellular activity
- Close cooperation of medicinal chem, screening, computational chem, drug metabolism, in vivo, and program biology



Need to adjust overall properties to ensure that compound is safe and effective in humans

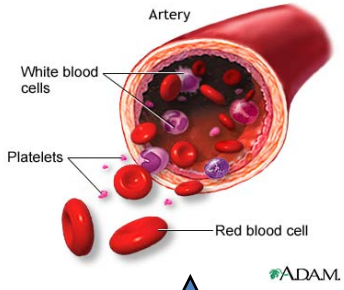
- Drug's journey from the gut to target includes interactions with water, membranes and proteins, ...very different environments!
- Body is extremely efficient at eliminating foreign substances!

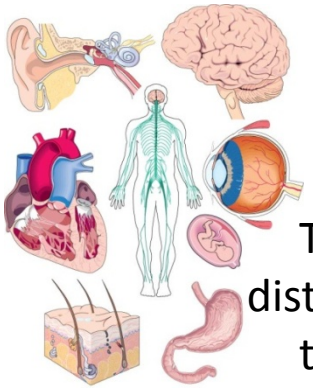
Solubility



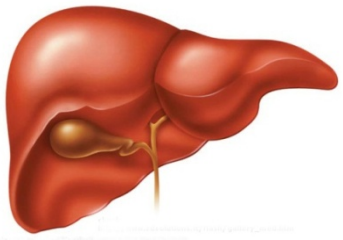
Gut membrane permeation

Plasma protein binding

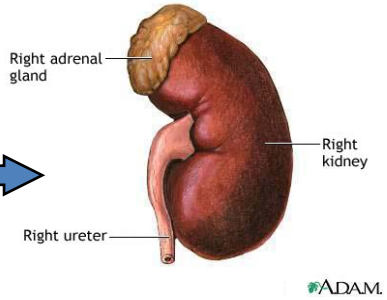




Tissue distribution tumor penetration



Hepatic clearance *via* metabolism



Renal clearance *via* excretion

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IACS drug discovery pipeline - Translation research/early development

- *Early development/translation*
  - generate testable hypotheses for early clinical trials – *"proof of biology"*
    - robust translational strategies needed to reduce failure rate in clinic
    - shorten time to get effective agent to patients likely to benefit
    - reduce cost of failure
      - keep ineffective drugs away from patients
      - reduce cost ($$$) to Pharma/Biotech community
  - **Closely working with MDACC clinicians to enable translation**

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TRIM24: Candidate breast cancer target discovered at MDACC. *Opportunity to seed multiple programs*

2011 Q4 | 2012 Q1 | Q2 | Q3 | Q4 | 2013 Q1

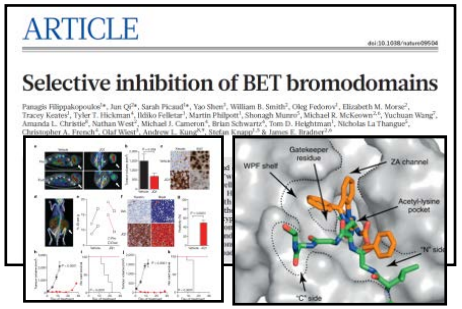
TRIM24

Bromo X

Bromo Y

Bromo X

Excitement in field

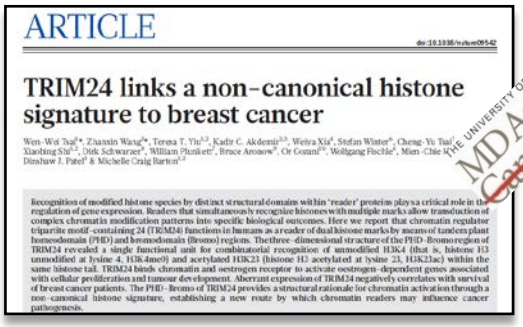

ARTICLE

Selective inhibition of BET bromodomains

Panagis Filippakopoulos*, Jun Qi*, Sarah Picaud*, Yao Shen, William B. Smith, Oleg Fedorov, Elizabeth M. Morse, Tracey Keates, Tyler T. Hickman, Ildiko Felletar, Martin Philpott, Shonagh Munro, Michael R. McKeown, Yuchuan Wang, Amanda L. Christie, Nathan West, Michael J. Cameron, Brian Schwartz, Tom D. Heightman, Nicholas La Thangue, Christopher A. French, Olaf Wiest, Andrew L. Kung, Stefan Knapp & James E. Bradner

Gatekeeper residue
WPF shelf
ZA channel
Acetyl-lysine pocket
"N" side
"C" side

Synergy with MDACC


ARTICLE

TRIM24 links a non-canonical histone signature to breast cancer

Wen-Wei Tsai*, Zhaoxin Wang*, Teresa T. Yiu, Kadir C. Akdemir, Weiya Xia, Stefan Winter, Cheng-Yu Tsai, Xiaobing Shi, Dirk Schwarzer, William Plunkett, Bruce Aronow, Or Gozani, Wolfgang Fischle, Mien-Chie Hung, Dinshaw J. Patel & Michelle Craig Barton

Recognition of modified histone species by distinct structural domains within 'reader' proteins plays a critical role in the regulation of gene expression. Readers that simultaneously recognize histones with multiple marks allow transduction of complex chromatin modification patterns into specific biological outcomes. Here we report that chromatin regulator tripartite motif-containing 24 (TRIM24) functions in humans as a reader of dual histone marks by means of tandem plant homeodomain (PHD) and bromodomain (Bromo) regions. The three-dimensional structure of the PHD–Bromo region of TRIM24 revealed a single functional unit for combinatorial recognition of unmodified H3K4 (that is, histone H3 unmodified at lysine 4, H3K4me0) and acetylated H3K23 (histone H3 acetylated at lysine 23, H3K23ac) within the same histone tail. TRIM24 binds chromatin and oestrogen receptor to activate oestrogen-dependent genes associated with cellular proliferation and tumour development. Aberrant expression of TRIM24 negatively correlates with survival of breast cancer patients. The PHD–Bromo of TRIM24 provides a structural rationale for chromatin activation through a non-canonical histone signature, establishing a new route by which chromatin readers may influence cancer pathogenesis.

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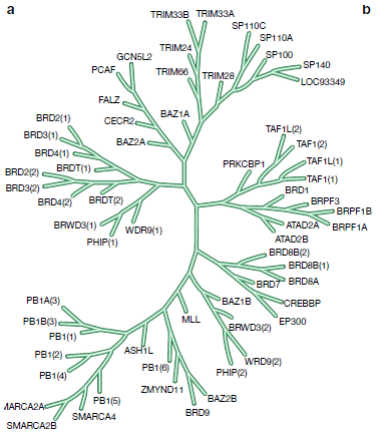
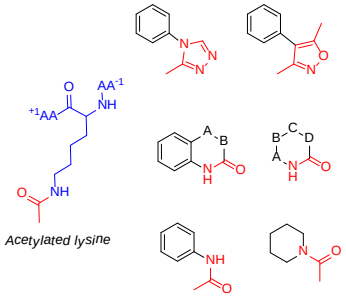
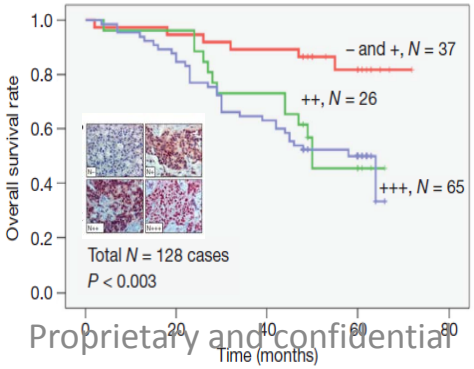
Opportunity to cross-fertilize



Tractable class



Clinical Relevance



Proprietary and confidential

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Rapidly developed fully enabled screening funnel…

New Chemical Entities

Dr. Mark Bedford

Primary AlphaScreen and FP Assays
Multiple Bromodomains

Selectivity panel

Orthogonal assays & X-ray

Proprietary Cell Binding

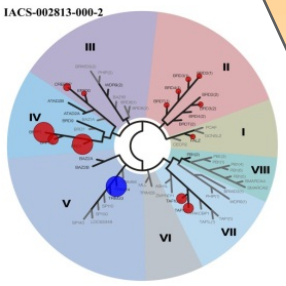
Cell Functional

ADME/Tox

Mouse/Rat PK

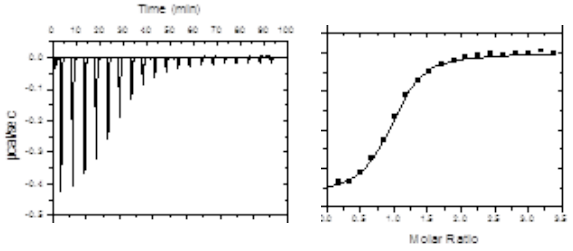
PK/PD/efficacy

Clinical candidate



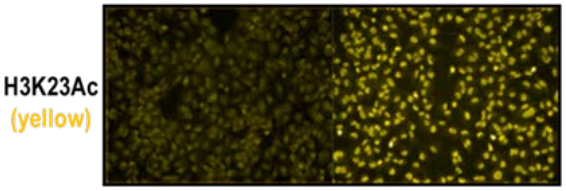
Biochemistry & Structural Biology

Dr. John Ladbury



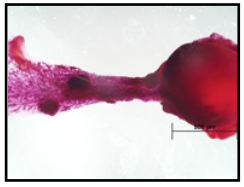
Chromatin assays & protocols

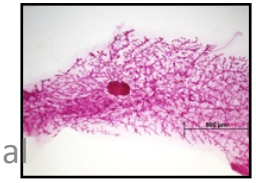
Dr. Jessica Tyler

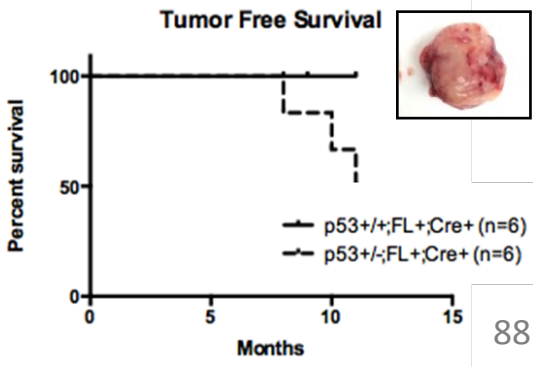


TRIM24 knock-out & Tumor mouse models

Dr. Michelle Barton







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…and proprietary chemical matter…

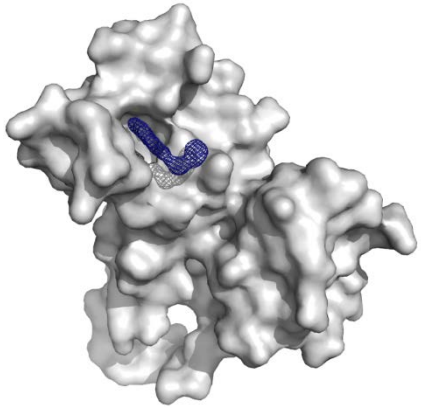
VANDERBILT UNIVERSITY MEDICAL CENTER

Focused library
- Built in house library of acetyl-lysine mimetics

Virtual screen
- Used bromo-1 &-2 structures
- ~600 selected for *in vitro* testing

HTS
- Screen completed at TxSACT
- Novel chemotypes identified

Fragment Library
- Vanderbilt/Fesik ~20,000 fragments
- Second site suppressor screen



- ✓ Multiple scaffolds -Novel IP
- ✓ Tractable SAR
- ✓ X-ray co-crystal structures on multiple proteins
- ✓ Distinct selectivity profiled achievable across family
- ✓ Cell potent

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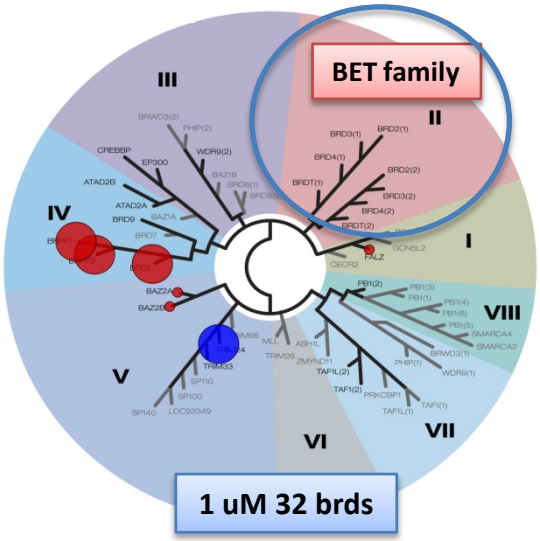
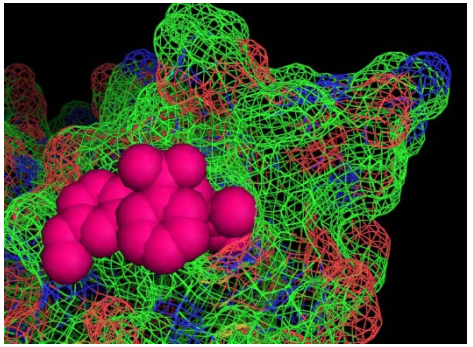
… to give potent, selective, cell-active TRIM24 inhibitors

TRIM24 inhibitor - IACS-9571

- TRIM24 IC_{50} = 13 nM (n=13)
- H3 AlphaLisa EC_{50} =45 nM (n=10)
- IF OV90 EC_{50} = 16 nM (n=3)
- IF Hela EC_{50} = 36 nM (n=2)
- Favorable physiochemical properties
- Selective (1 uM 32 bromdomains)



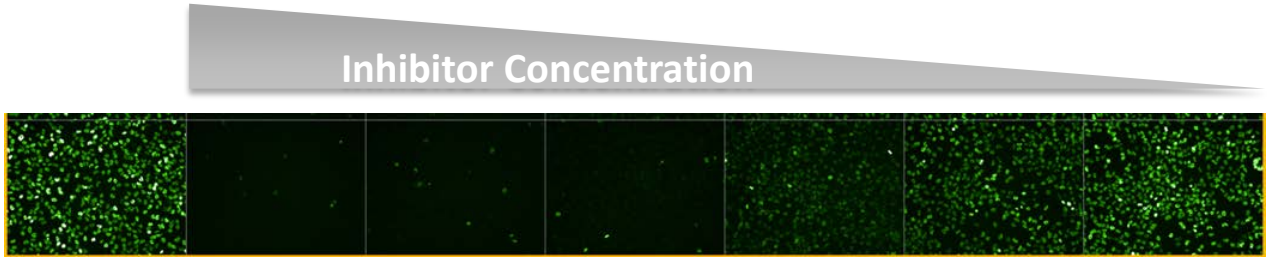
Target two binding pockets



Dr. John Ladbury Collaboration
(>80 bromodomain x-ray structures to date)

Catalogue of cell-based assays inform on binding activity

- IACS inhibitors displace TRIM24 from Histone H3 (Alpha-Lisa) and chromatin in cells (IF assay)



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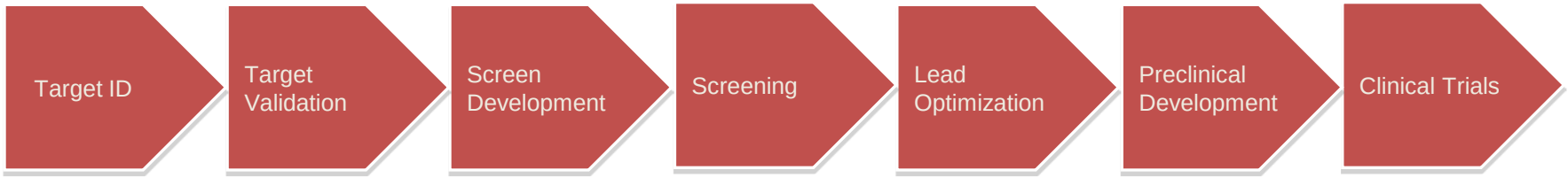
Current IACS Pipeline:



Program #1 –Oxidative Phosphorylation Inhibitor	***IND-enabling studies***
Program #2 – Metabolic Target	*Optimizing proprietary inhibitors* *Candidate selection 4Q14*
Program #3 – Metabolic Target	*Identifying proprietary inhibitors*
Program TV #1 – Metabolic Target	*Hit triage underway*
Program TV #2 – Epigenetic Target	*Multiple chemotypes being explored*
Program TV #3 – Sig. Target	*Risk sharing collaborations*
Program TV #4 – Met. Target	*HTS assay being established*
Program TV #5 – SHP2 inhibitor	STOP *Lack of tractable chemical matter*

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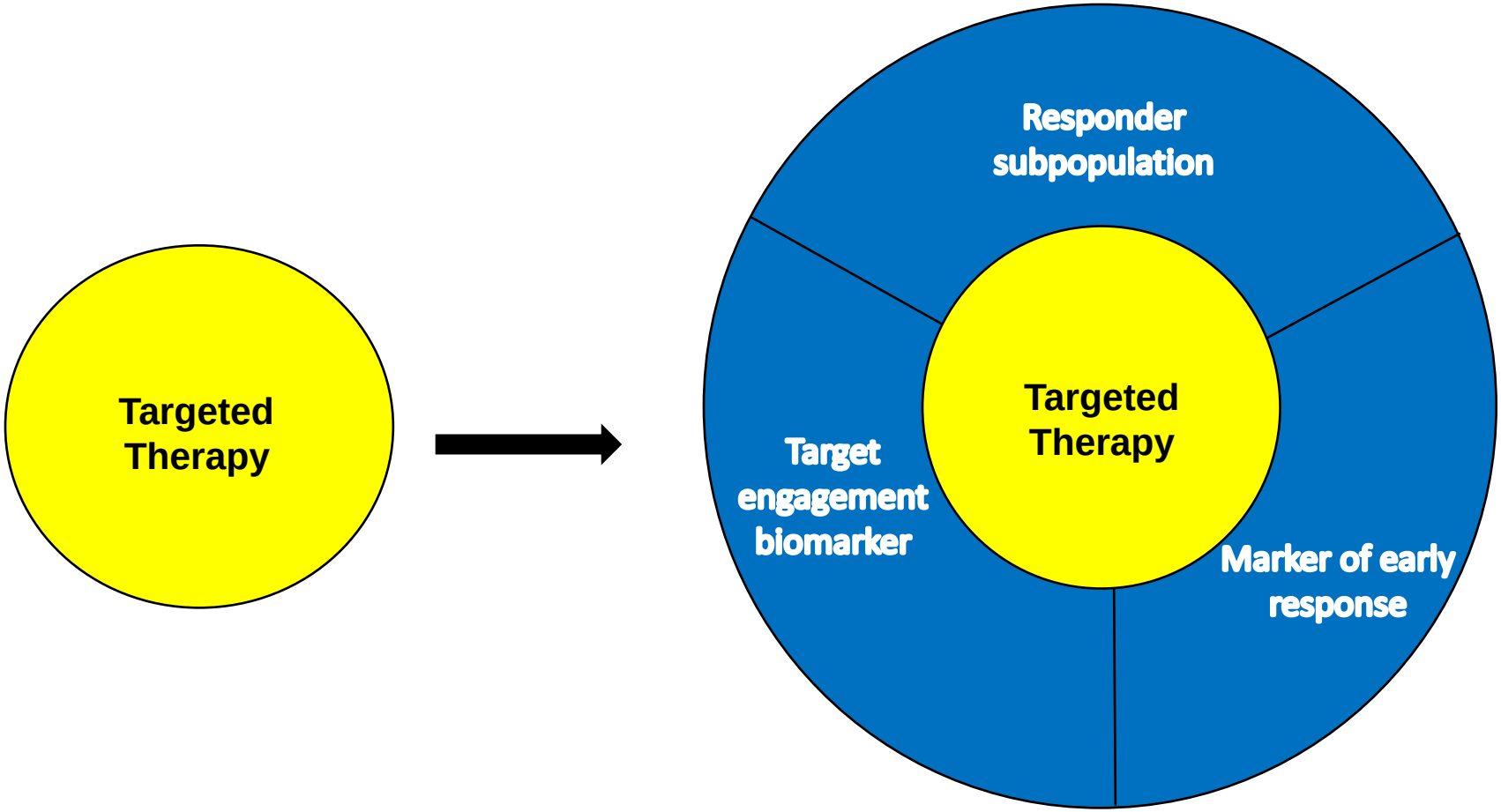
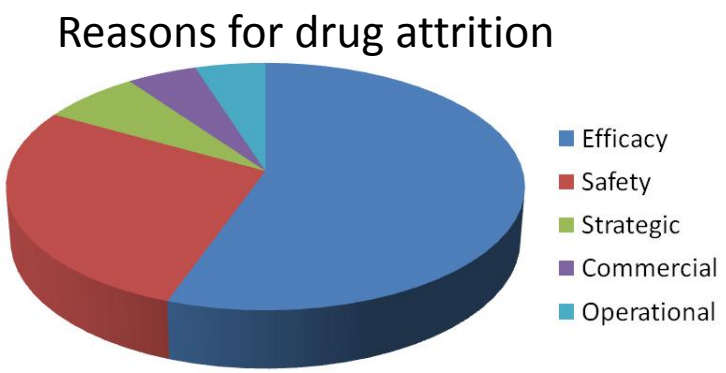
Targeted Cancer Therapeutics: not just about the drug



The problem: The Valley of Death and Drug Attrition



- **Process:** Biology divorced from drug discovery.
- **Mentality:** Candidate drugs directed against the same targets.
- **Biomarkers:** Lack of clinically validated BMx to support clinical translation.
- **Models:** Fail to predict response in the clinic.
- **Patient selection:** Target dependency often ill-defined.

Center for Co-Clinical Trials: Capabilities

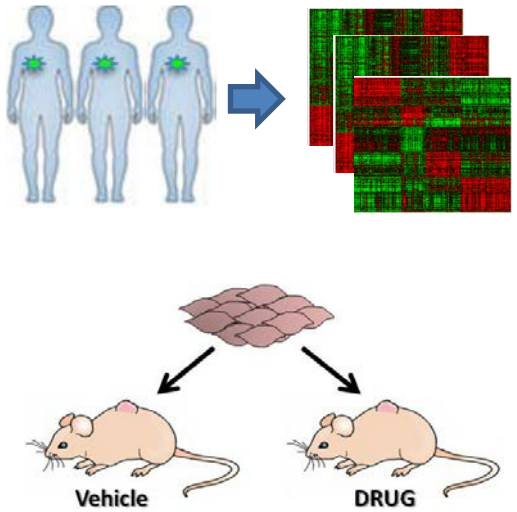
Accelerating the Development & Preclinical Evaluation of Novel Therapeutics

CCCT Capabilities

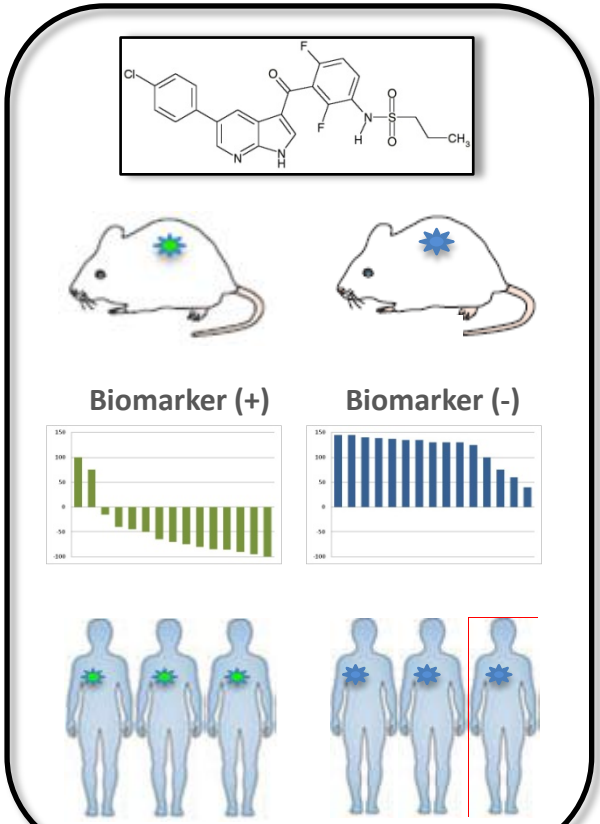
- Comprehensive target biology to inform on the cellular and genetic **context in which a drug target is rate limiting.**
- **Evaluation of in vivo efficacy** of single agents or combinations in appropriate pre-clinical models.
- Predictive and target engagement **biomarker development and validation.**
- **Systems pharmacology and functional genomics** to inform on mechanisms of drug resistance and co-extinction strategies.
- **Preclinical modeling** to capture cellular and genetic context of each cancer subtype.

CCCT: Areas of Focus

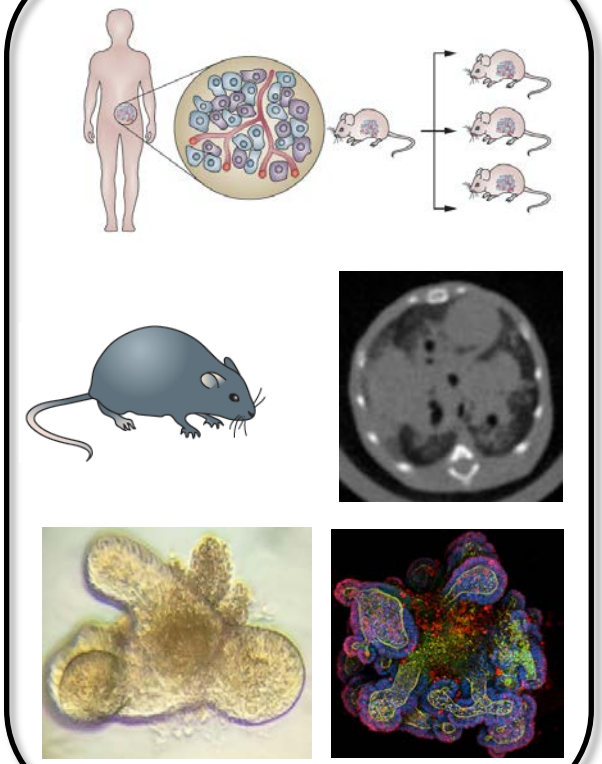
Systems Pharmacology Functional Genomics



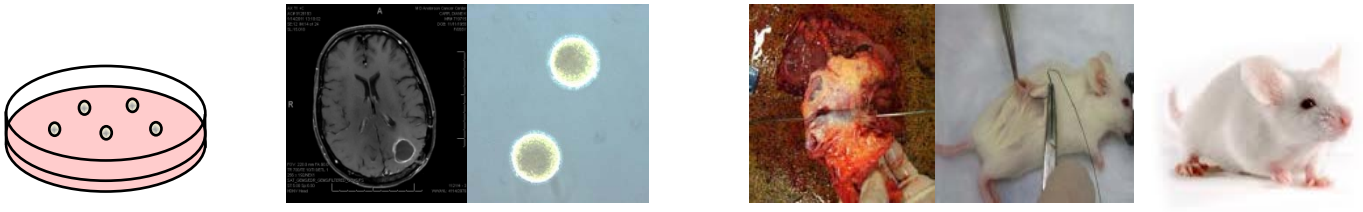
Translational Biology



Model/Technology Development



Disease modeling and drug development:
Leveraging the most predictive model systems



In vitro | In vivo

Cell Line Panels
3-D Cell Line Models
Cell Line Xenograft
GEMM
Ph 0-1 Trial
Matched Pair Cell lines
GEMM and Human Tumor Explants
Human Tumor Xenograft
Genetically-defined human cells

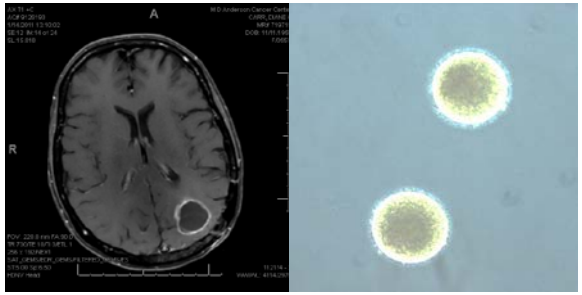
High Information Content & Clinical Relevance
Organism / Disease Focus
Complexity

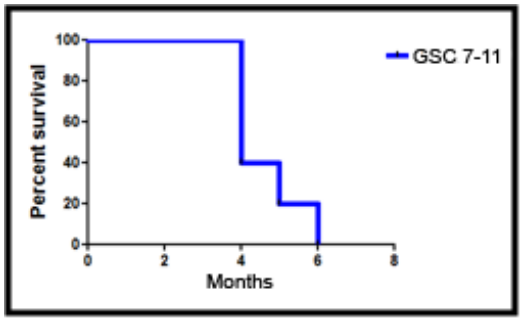
Simplicity
High Throughput & Statistical Power
Biochemical / Cellular Focus

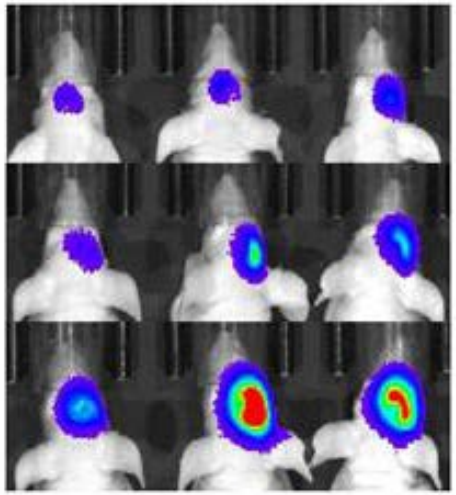
Fast (days - weeks)
Slow (month - years)

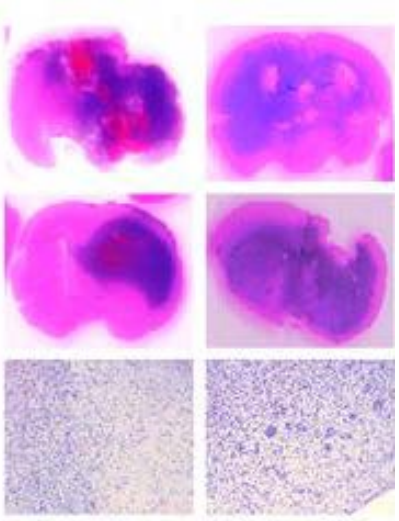
Modeling GBM with unique patient-derived glioma stem cells (GSC)

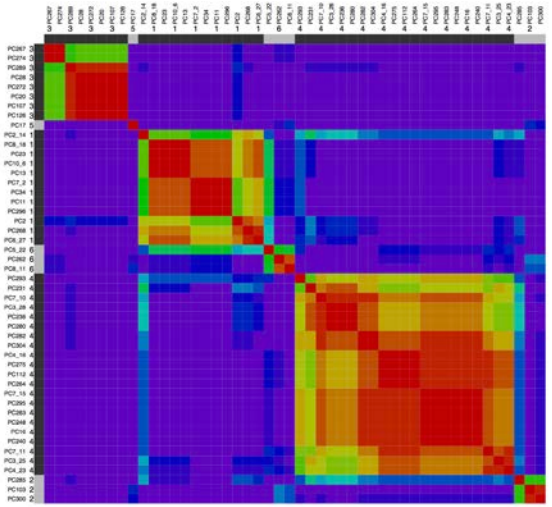
Annotated collection ~45 GSC lines available for functional studies







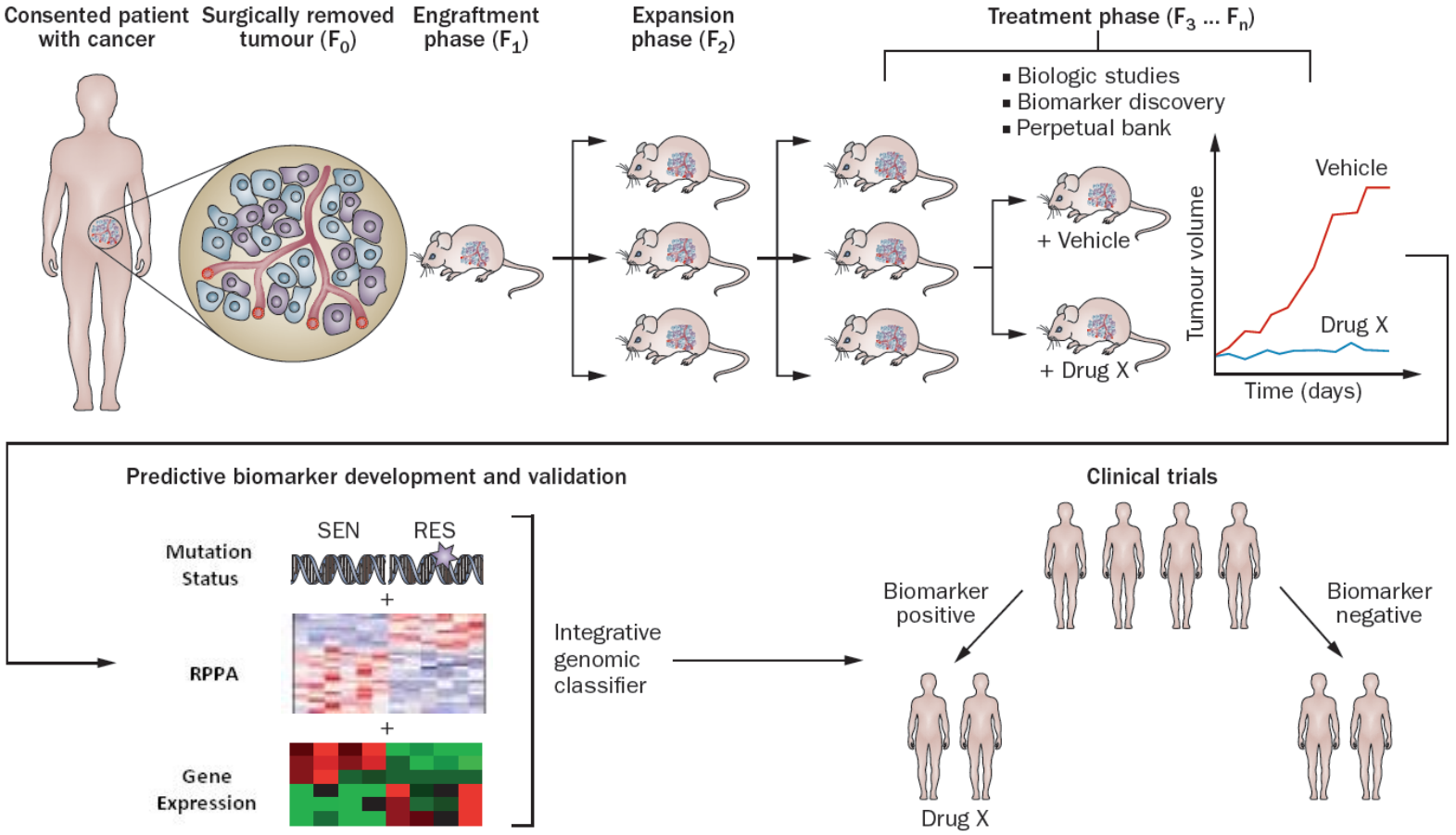




Fred Lang and Erik Sulman

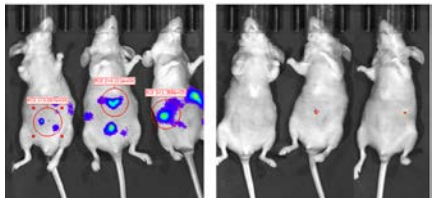
Patient-derived xenografts:

From in vivo efficacy to clinical translation



Comprehensive genomic annotation to prioritize models and inform on responder ID

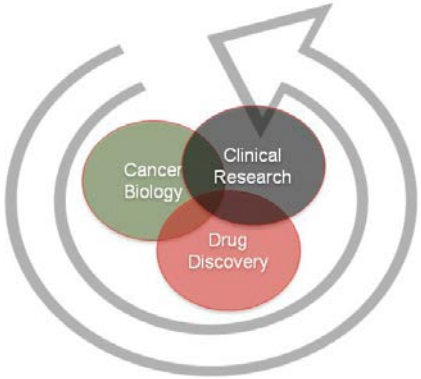
Center for Co-Clinical Trials: The bridge to the MDACC clinic (and back)

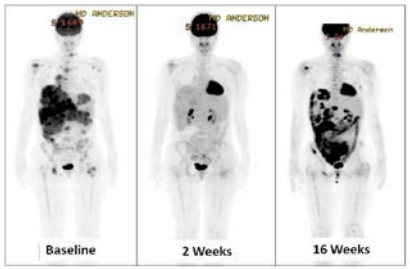


Translational Biology

Model/Tech Develop.
- Heterogen.
- Resistance

Systems Pharm Func. Genomics





BMx informed trials

Patient response resistance

Novel treatment strategies

Clinical integration is the competitive advantage to attract BioPharma collaborators.

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Bed-at-Bedside approach to drug discovery and translational research