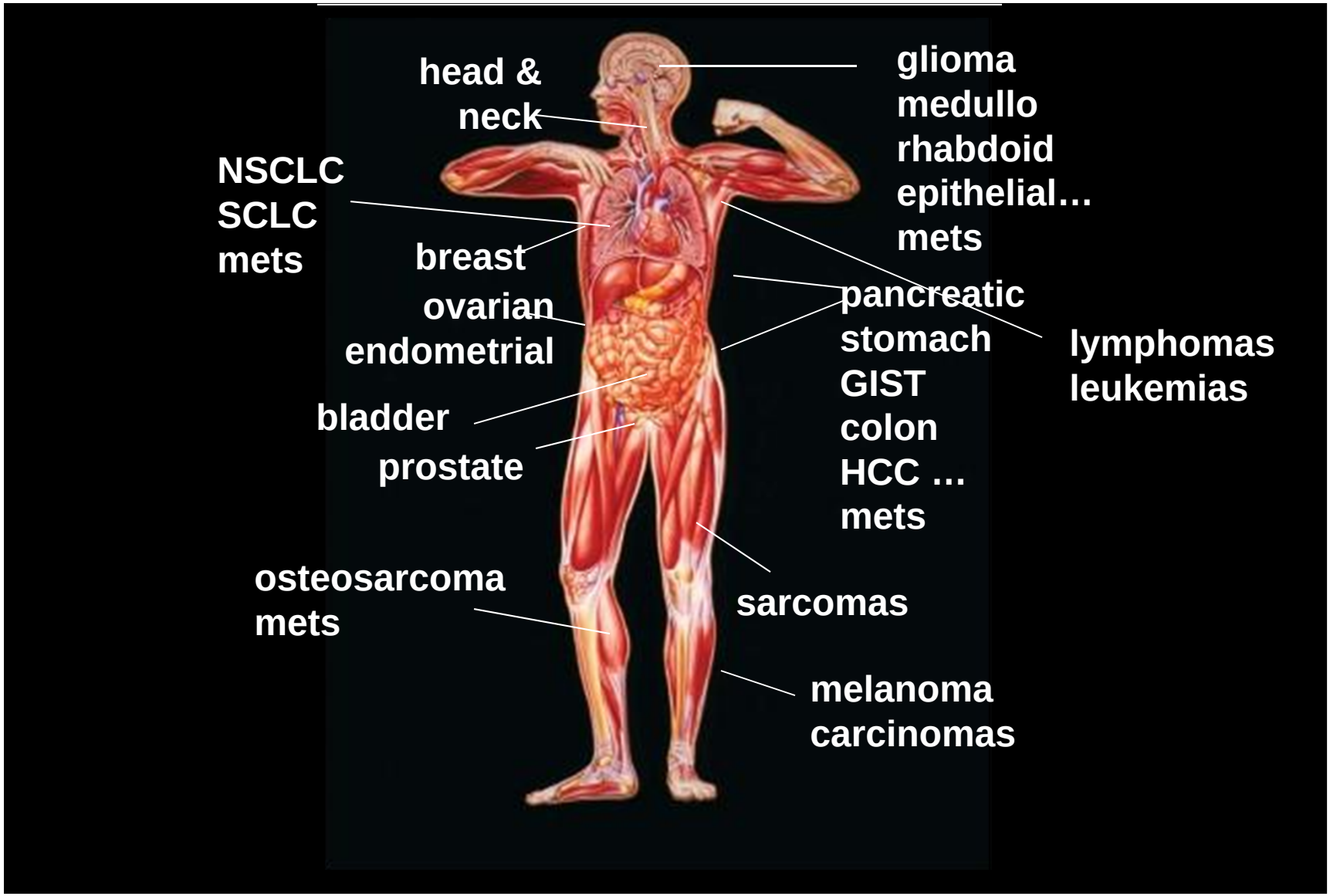
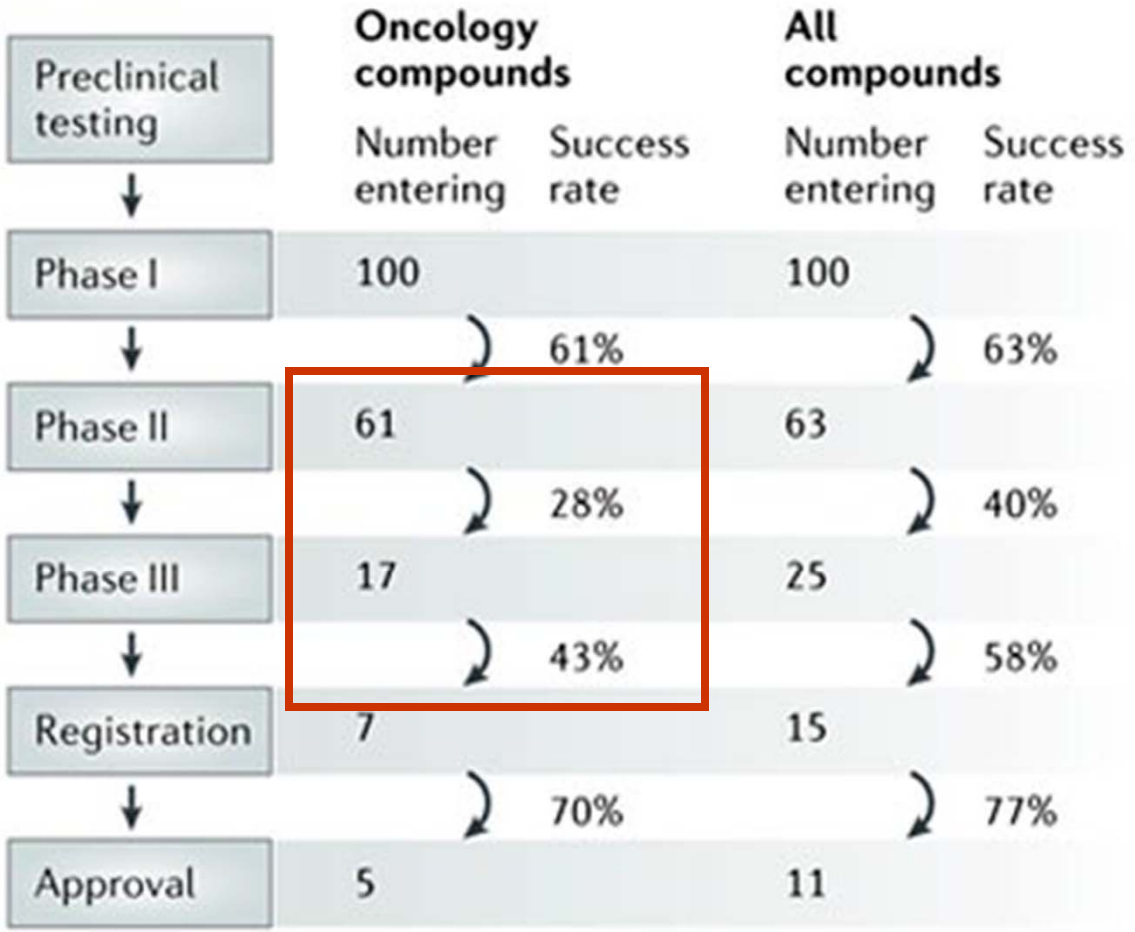
Over 100 Cell Types Susceptible to Cancer, Each With Multiple Molecular Etiologies



Current Cancer Drug Development



……at an average cost of $1B per drug

adapted from: Sharpless and DePinho; Nature Reviews Drug Discovery '06

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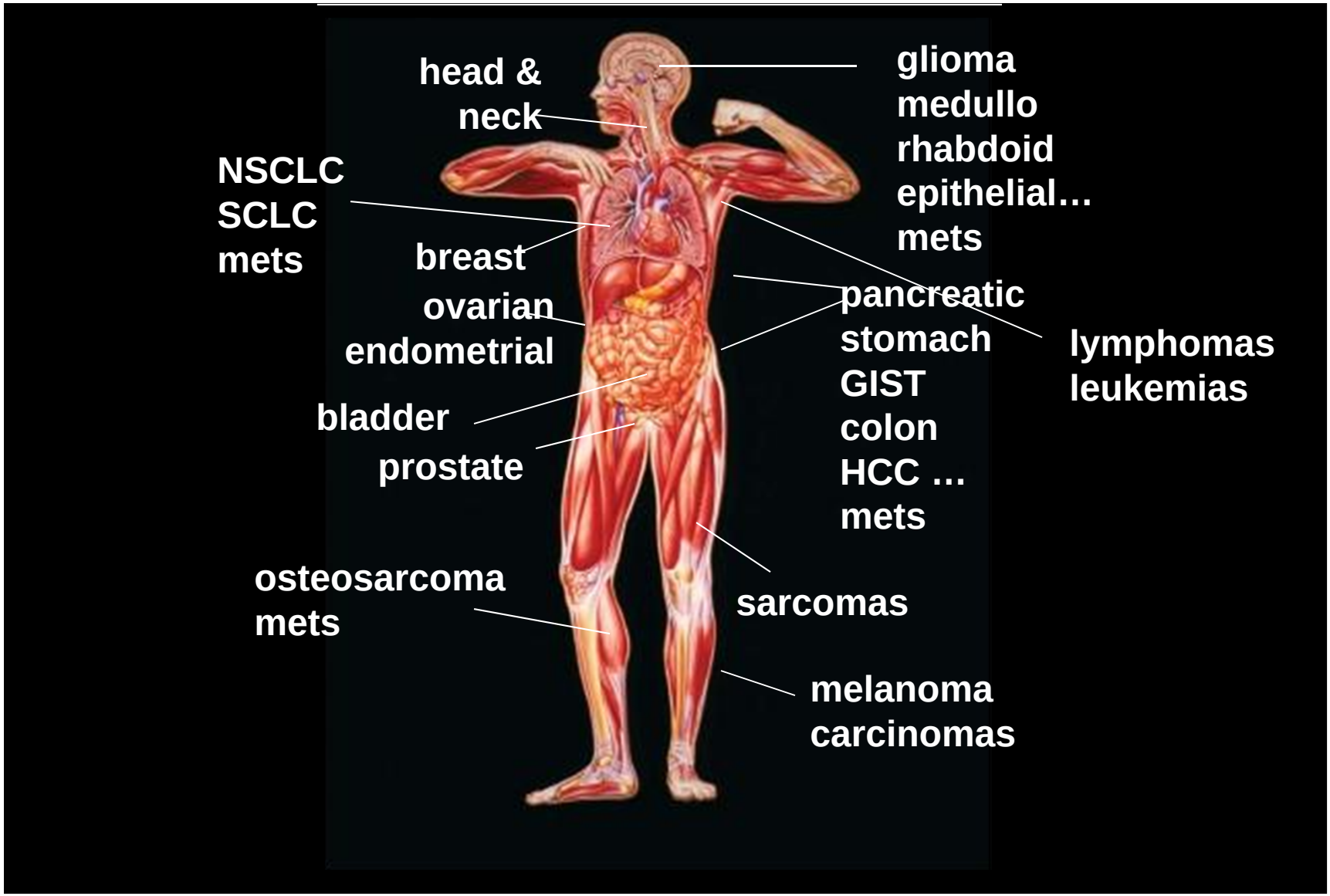

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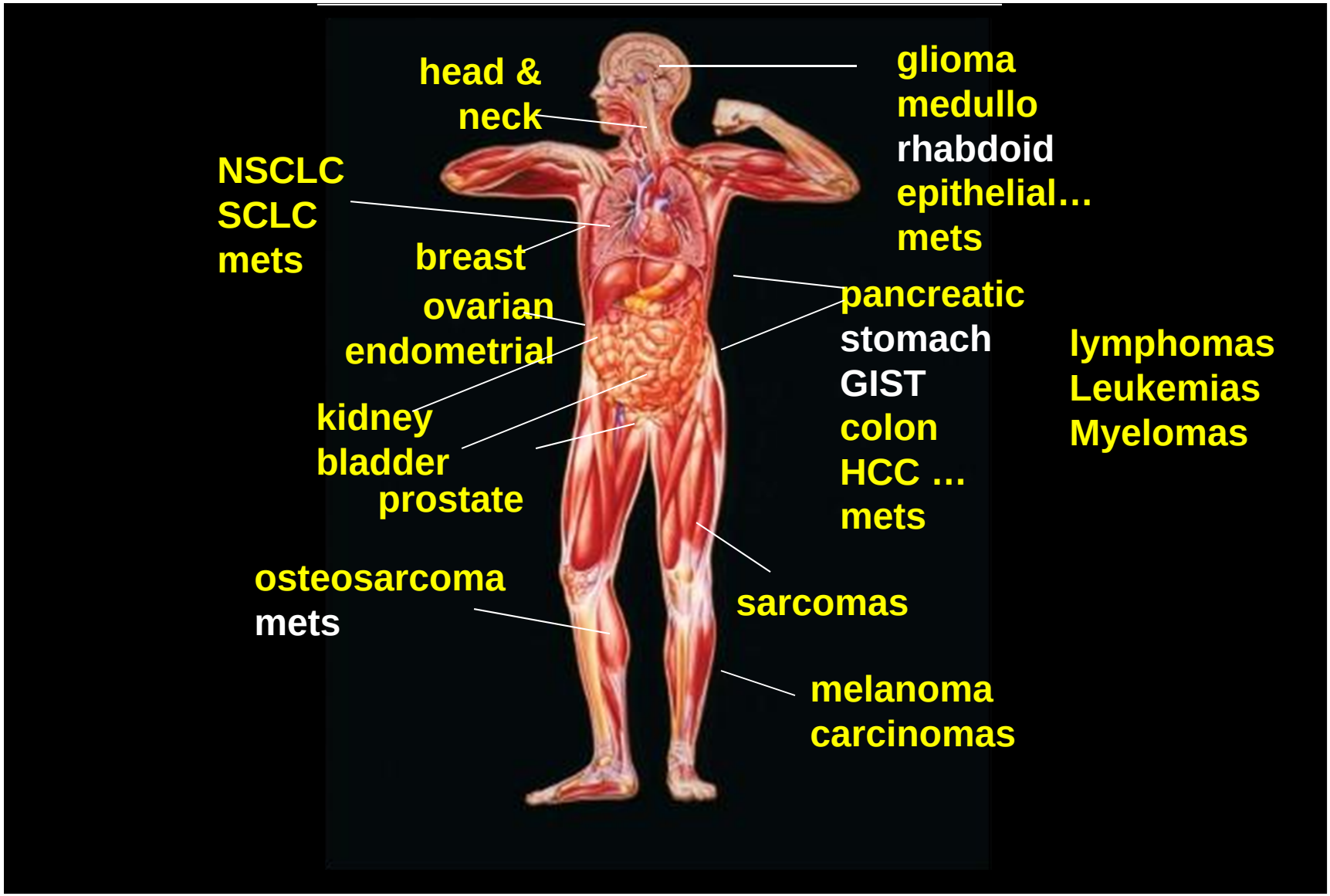
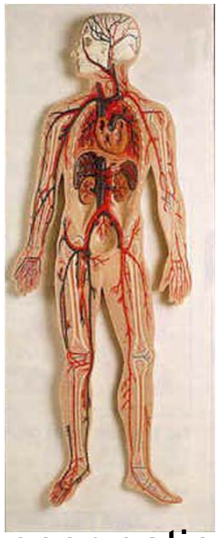
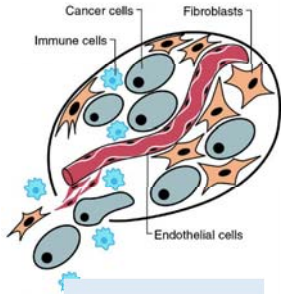


GEM in Clinical Translation



cancer patient



Cancer genome
Cancer transcriptome
Cancer proteome

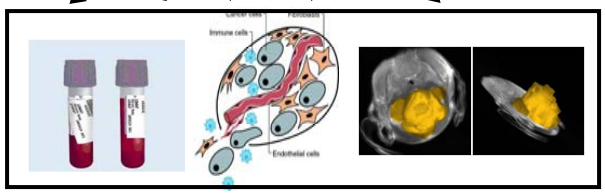
Serum proteome

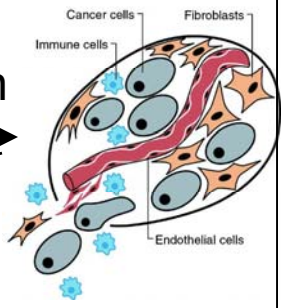
frequent aberrations

engineer programmed aberrations

GEM model

cancer initiation and progression



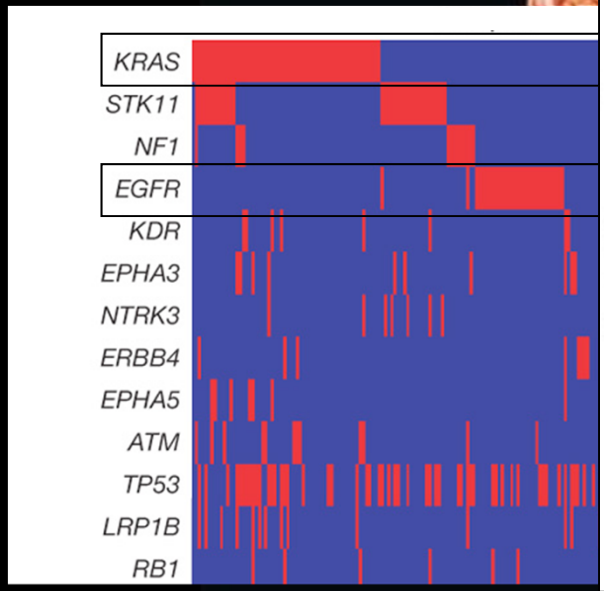


genome,transcriptome
proteome,metabolome
disease-relevant
"fingerprints"
biomarker discovery
target discovery
target validation
pre- + co-clinical trials

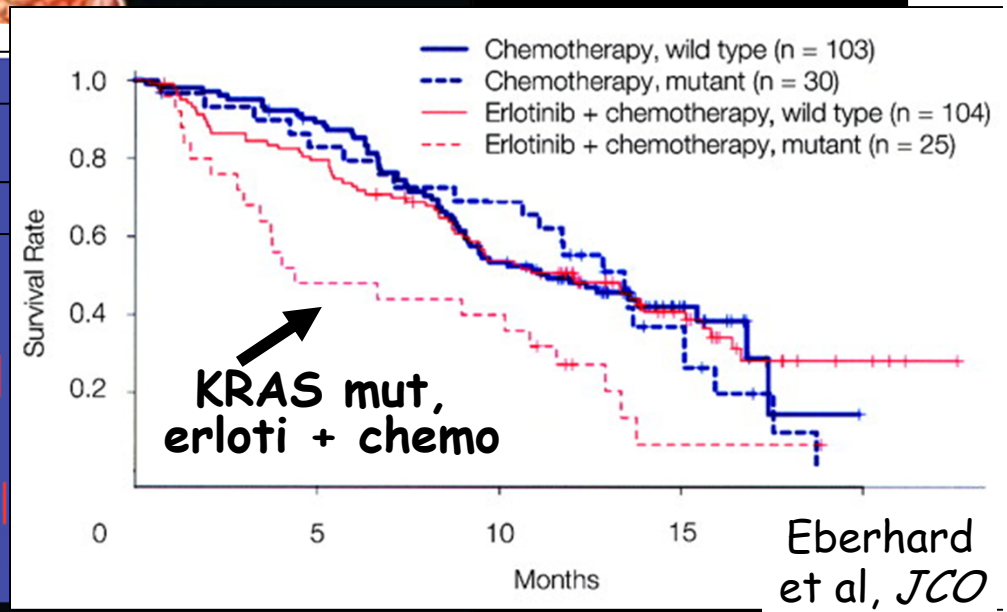
NSCLC: A Paradigm for Tailoring Cancer Management

Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non–Small-Cell Lung Cancer to Gefitinib. *Lynch, et al (Haber) NEJM 2004*

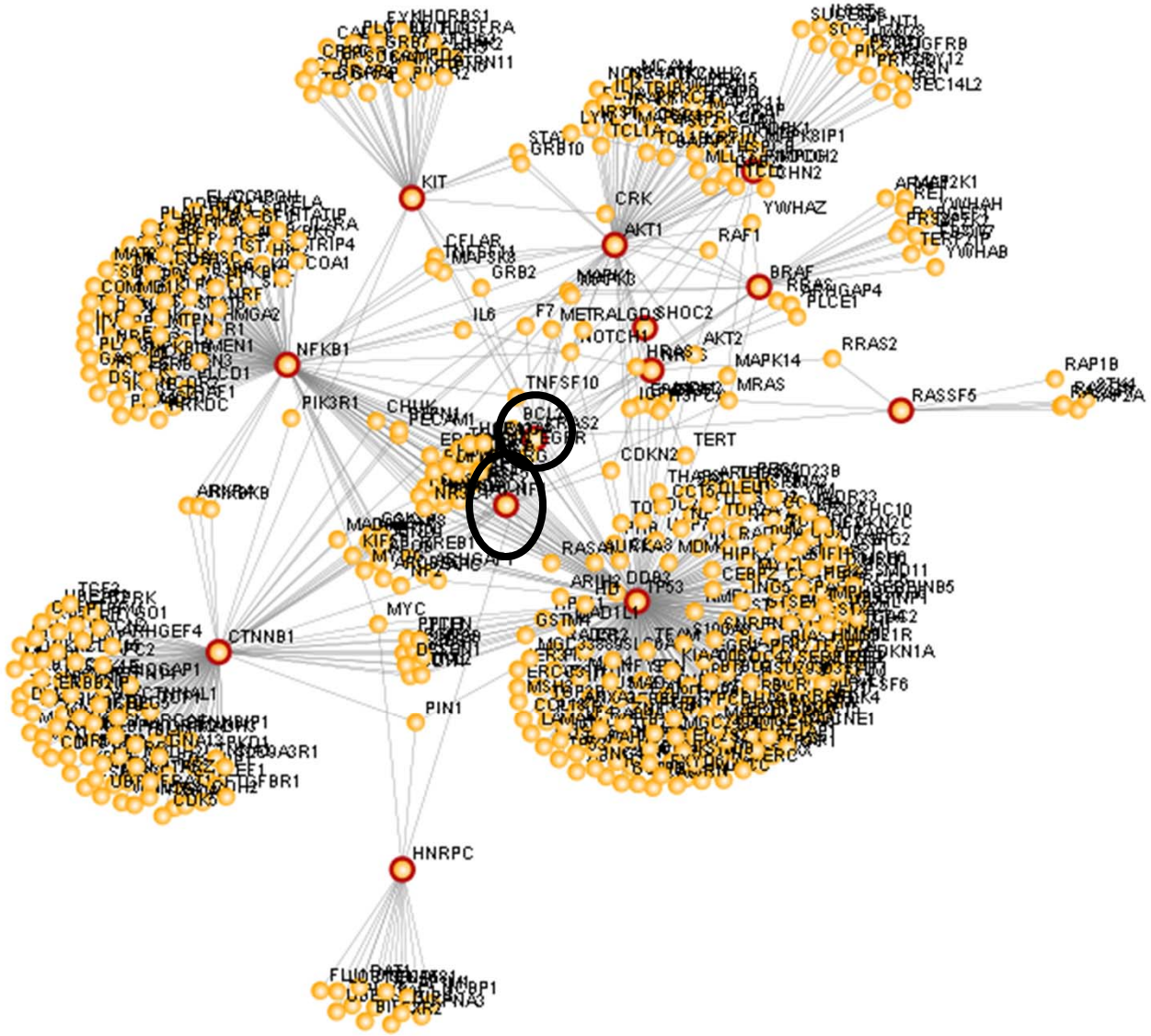
***EGFR* Mutations in Lung Cancer: Correlation with Clinical Response to Gefitinib Therapy.** *Guillermo , et al (Meyerson). Science 2004*



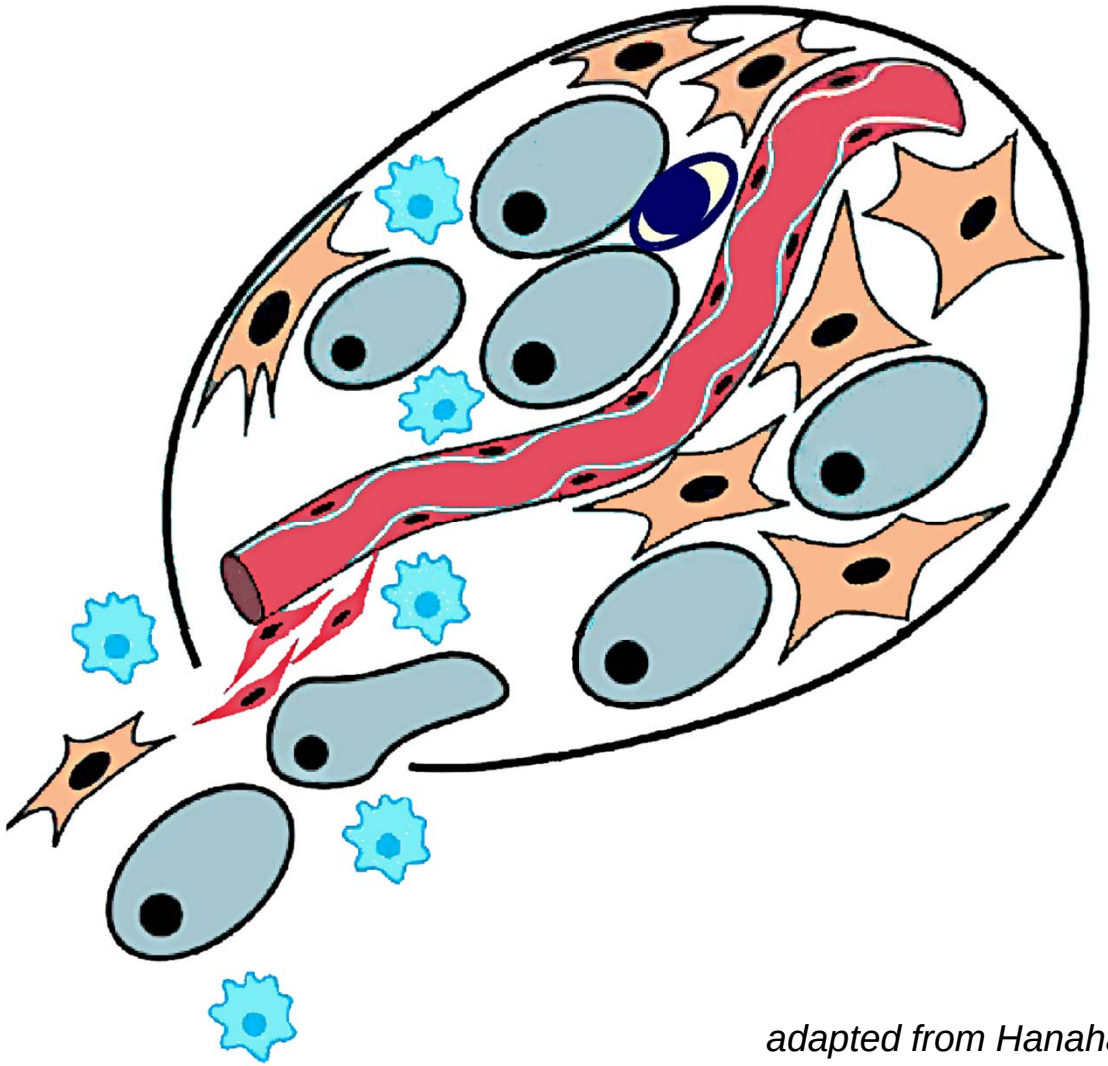
Ding et al., Nature 2008



Eberhard et al, *JCO* '05


KIT
CRK
AKT1
YWHAZ
RAF1
BRAF
GRB10
GRB2
IL6
F7
METRALGDS
SHOC2
NOTCH1
AKT2
MAPK14
MRAS
RRAS2
RAP1B
RASSF5
TNFSF10
NFKB1
PIK3R1
TERT
CDKN2
MYC
CTNNB1
PIN1
HNRPC
SEC14L2
YWHAB
COA1
TRIP4
CFLAR
MAPSK8
PLCE1
RASA1
MDM
TP53
DDB2
ARHGEF4
CDK5
FBR1
CDKN1A

Cancer is a Dynamic and Evolutionary Process



adapted from Hanahan and Weinberg, Cell 2000

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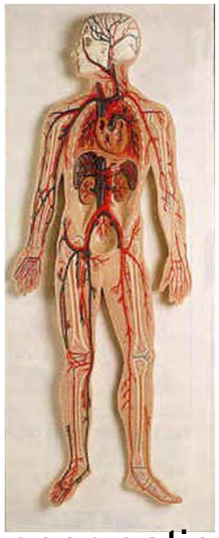

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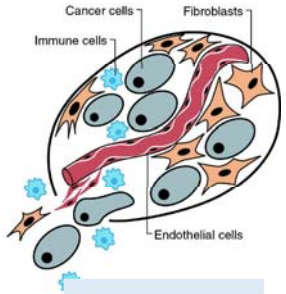

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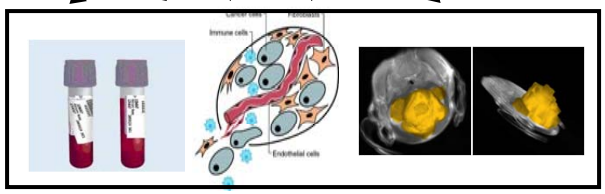

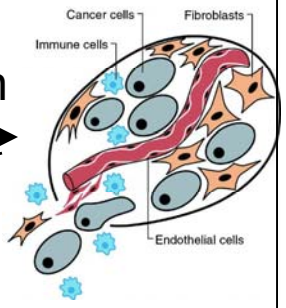

genome,transcriptome
proteome,metabolome
disease-relevant
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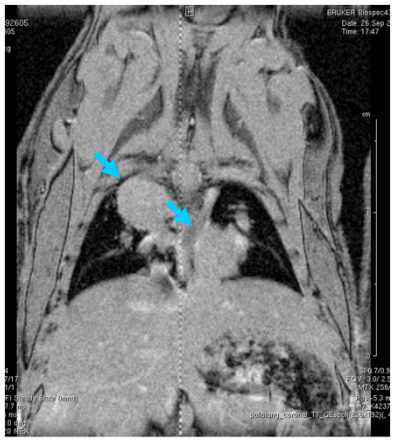
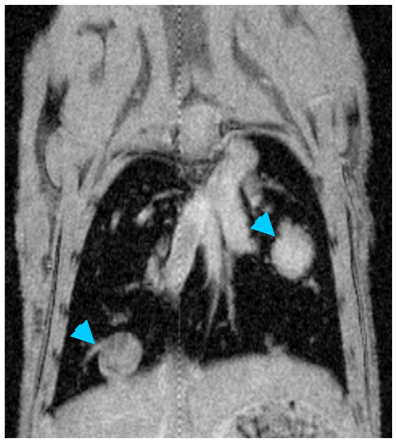
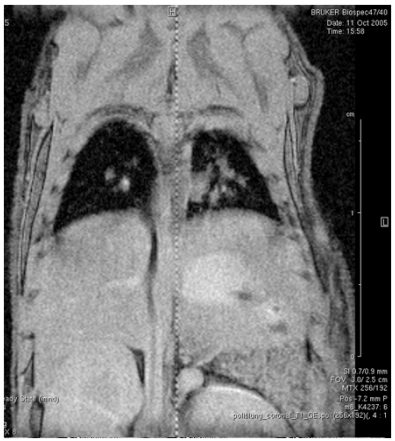
biomarker discovery
target discovery
target validation
pre- + co-clinical trials

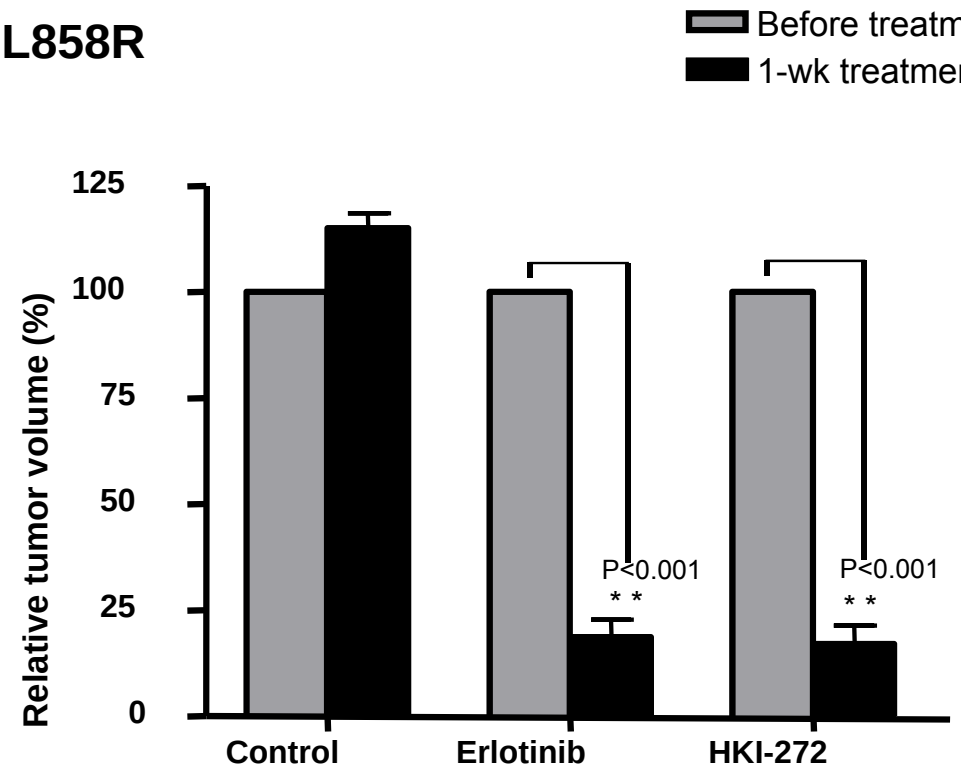
Inducible GEM NSCLC Reflects Human Treatment Response

$EGFR^{L858R}$	$EGFR^{\Delta L747\text{-}S752}$	$Kras^{G12D}$
		
6 days on Erlotinib	2 weeks on Erlotinib	4 weeks on Erlotinib
		

Politi et al (Varmus) G&D 2005

Preclinical Assessment Guides Clinical Trial

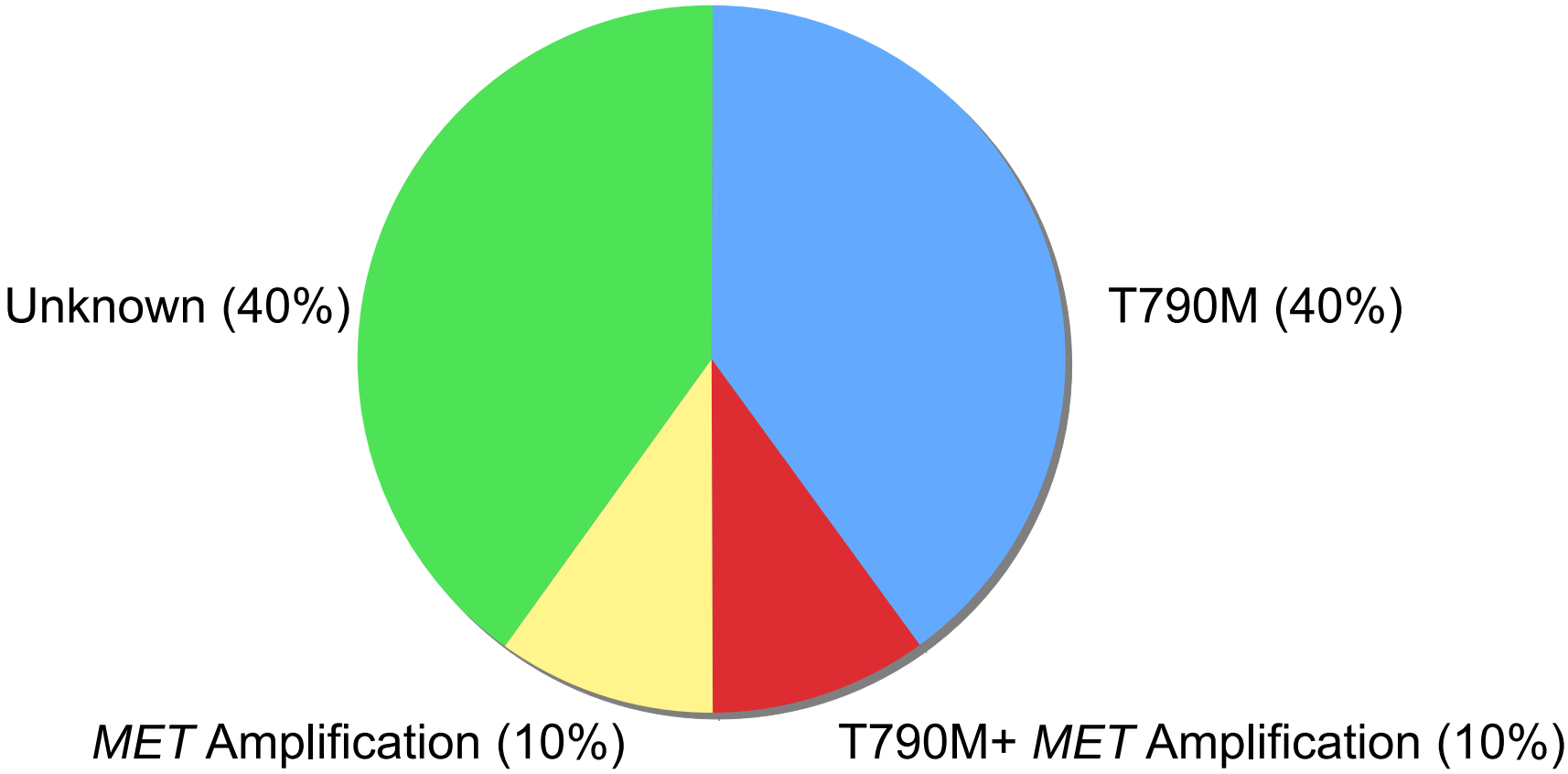
L858R



→ Clinical trial HKI272

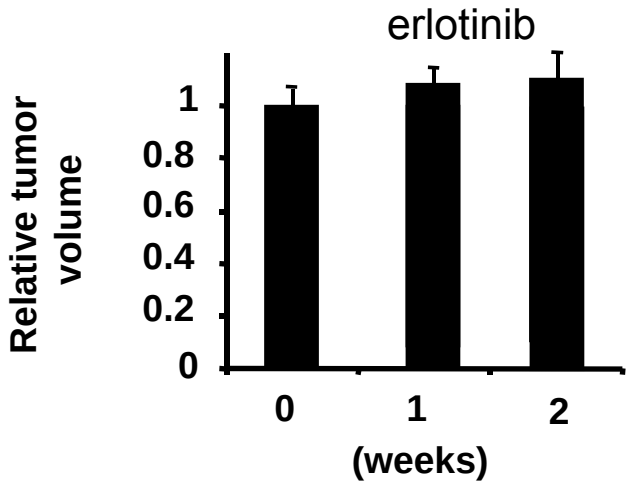
Ji et al, (Wong) Cancer Cell 2006

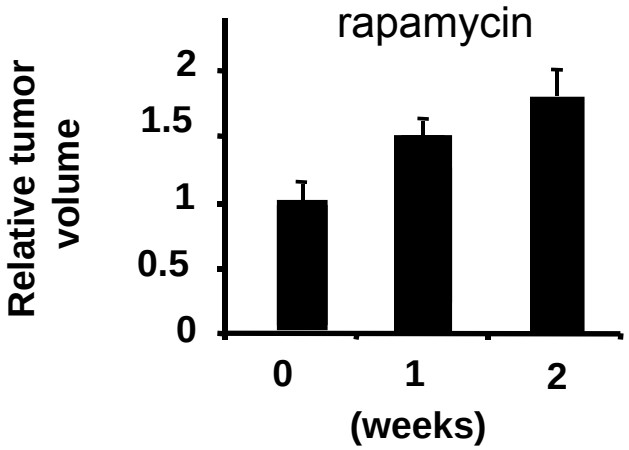
Acquired Resistance of Human EGFR-NSCLC to Inhibitors

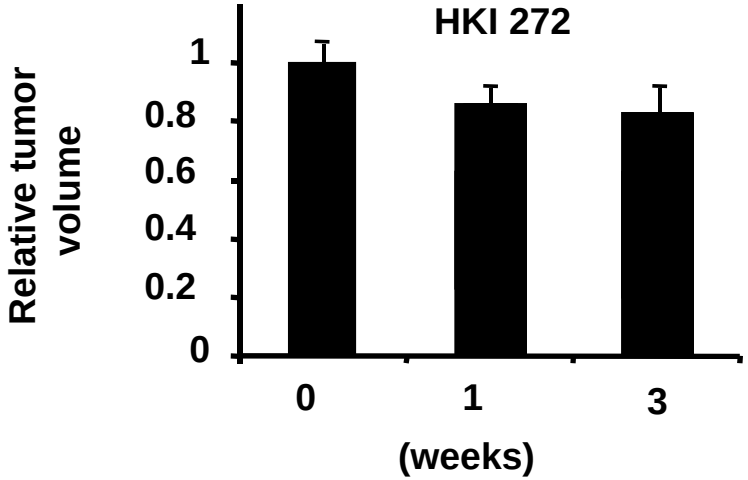


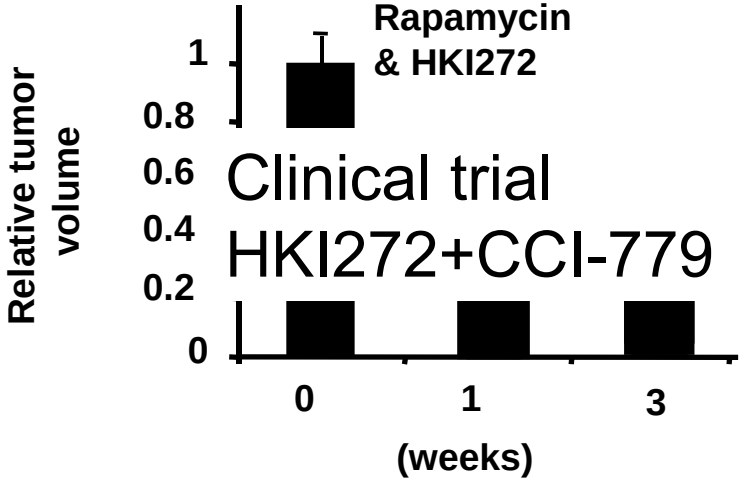
Preclinical Assessment Guides Combination Therapy Clinical Trial

Resistant Double EGFR Mutant

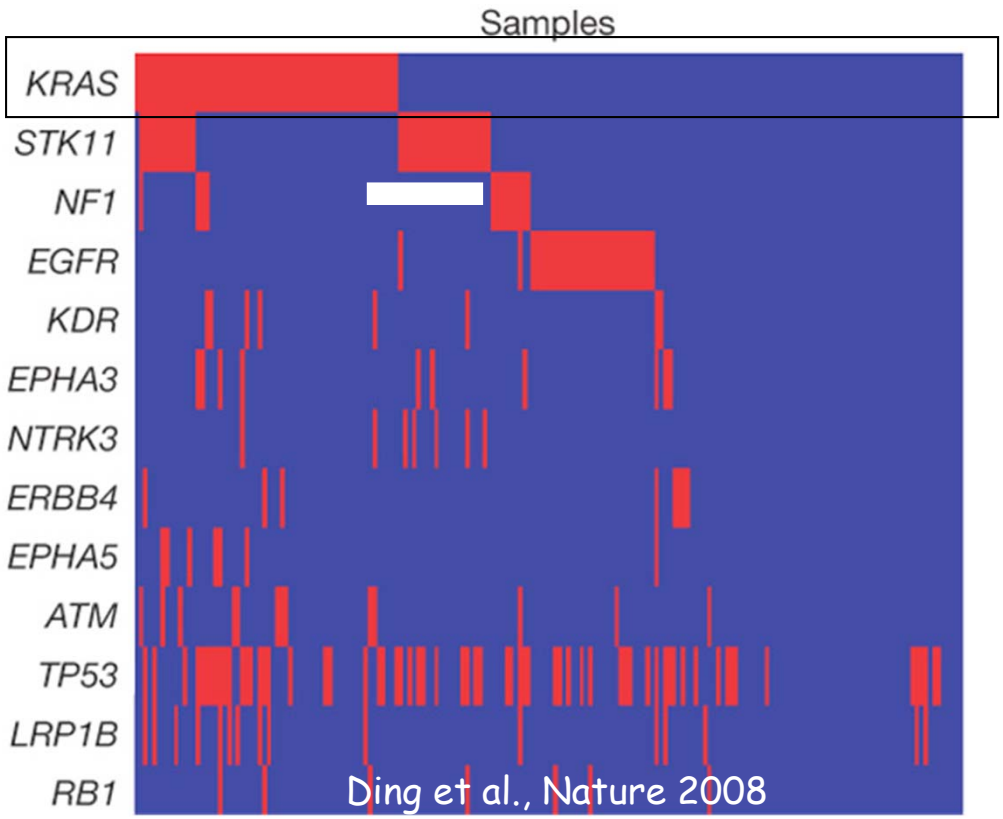




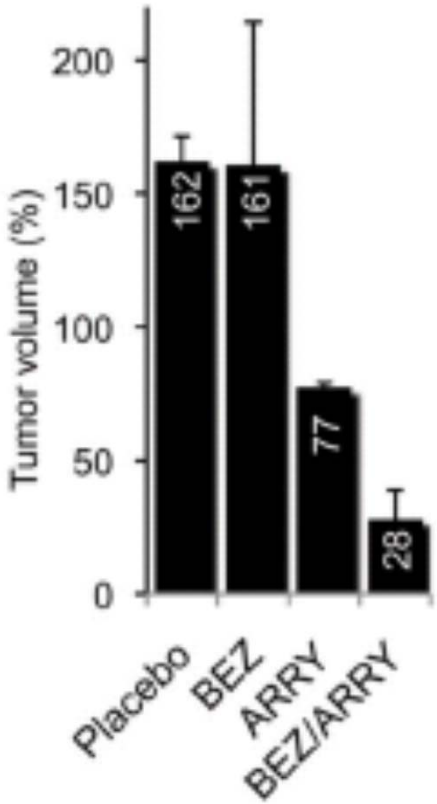




Preclinical Assessment Predicts Combination Therapy Effective in Ras-driven NSCLC



K-Ras driven NSCLC
MEK (ARRY) and/or
PI3K/mTor (BEZ) inhibitor



Engelman et al, (Wong)
Nature Medicine 2008

Multple GEM Modeled on Human Cancer Genetics/Biology

Inducible Mouse Lung Cancer Models

- KRAS G12D
- KRAS G12V
- KRAS G12C
- EGFR Del19
- EGFR L858R
- EGFR T790M
- EGFR wild type
- EGFR vIII
- HER2 exon 20 insertion
- HER2 wild type
- BRAF V600E
- ELM4-ALK

- IGF1R
- C-MET
- EGFR T790M-Del19/c-MET
- EGFR T790M-L858R/c-MET
- EGFR T790M-Del19
- EGFR T790M-L858R
- EGFR Del19/IGF1R
- EGFR L858R/IGF1R
- p110 exon 20 (H1047R)
- ROS1
- ELM4-ALK

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dullo
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lymphomas
Leukemias
Myelomas

mets

melanoma
carcinomas

Identification of novel genes involved in carcinogenesis	**Nedd9 involvement in metastatic progression of melanomas**	***Kim, et al., Cell 2006***
Determination of predictive molecular signatures for various cancer types	**Kras-associated expression signatures in lung carcinogenesis**	***Sweet-Cordero, et al., Nature Genetics, 2005***
Discovery of novel early tumor prognostic markers	**A compendium of circulating early markers for pancreatic cancer**	***Harsha, et al., PLoS Medicine, 2009***
Identification of modifier traits for cancer phenotypes	**Genetic modifiers of Aurora A associated carcinogenesis**	***Ewart-Toland, et al., Nature Genetics, 2003***
Evaluation of therapeutic compounds with clinical implications	**Description of EGFR blockade side-effects in brain tumorigenesis**	***Radiloff, et al., Drug Discov Today Dis Models, 2008***
Analysis of pathway dynamics in disease via systems biology approaches	**Analysis of prion disease progression through systems approach**	***Hwang, et al., Mol Syst Biology, 2009***

de novo Murine Glioma Models (circa 2009)

Genetics	Mechanism	Morph/grade	Incidence
Nf1+/−; p53+/−	KO	Astro/variable	92% by 6 months
Nf1+/−; p53+/−	KO;cond. KO (GFAP-Cre)	Astro/variable	100% by 5–10 months
Nf1+/−; p53+/−; Pten−/−	KO; cond. KO (GFAP-Cre)	Astro/HG	100% by 5–8 months
$GFAPT_{121}$	TG	Astro/LG	100% by 10–12 months
$GFAPT_{121}$*; Pten−/−*	TG; cond KO (MSCV-Cre)	Astro/HG	100% by 6 months
GFAP-V^{12}*Ras*	TG	Astro/HG	100% by 0.5–3 months
GFAP-V^{12}*Ras; EGFRvIII*	TG; adenovirus	Oligo/HG	100% by 3 months
GFAP-V^{12}*Ras; Pten−/−*	TG; KO	Astro/HG	100% by 6 weeks
S100-v-erbB	TG	Oligo/LG	60% by 12 months
S100-v-erbB; Ink4a/Arf−/−	TG; KO	Oligo/HG	100% by 12 months
S100-v-erbB; p53+/−	TG; KO	Oligo/variable	100% by 12 months
PDGF-B	MoMuLV	Oligo/variable	40% by 10 months
kRas; Akt	RCAS	Astro/variable	25% by 3 months
kRas; Pten−/−	RCAS; cond KO (RCAS-Cre)	Astro/variable	60% by 3 months
kRas; Akt; Ink4a/Arf−/−	RCAS; KO	Astro/variable	20%–50% by 3 months
PDGF-B	RCAS	Oligo/variable	60%–100% by 3

Adapted from Huse and Holland (2009) Br. Path.