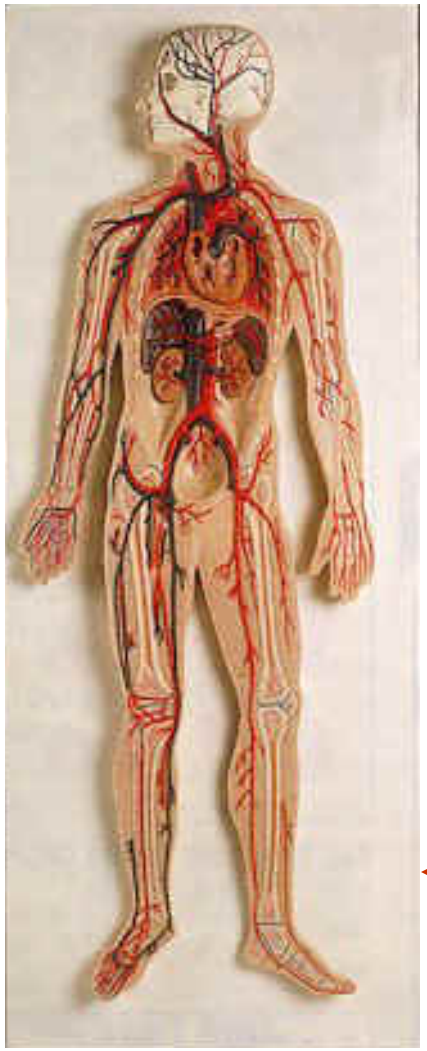
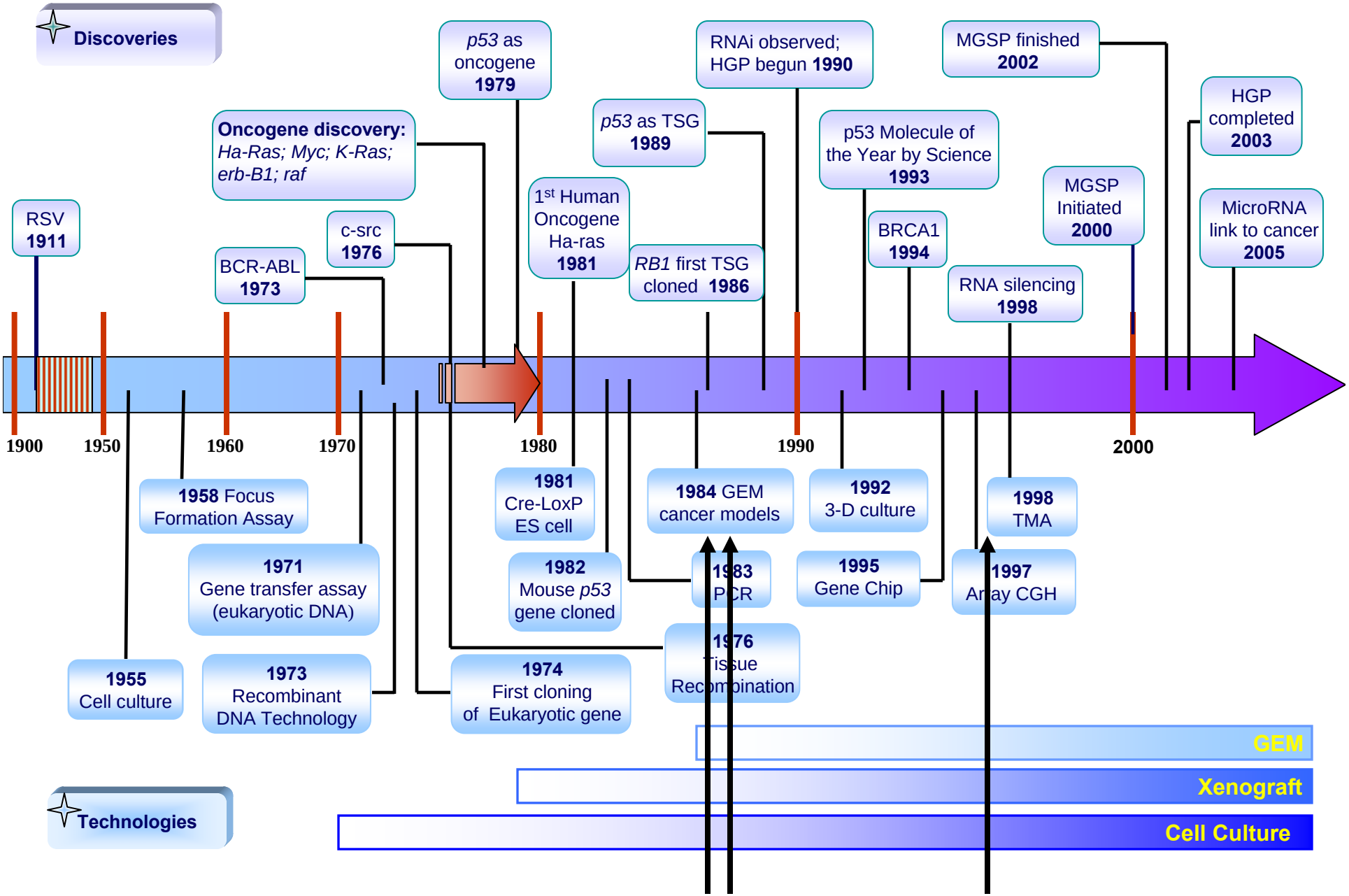
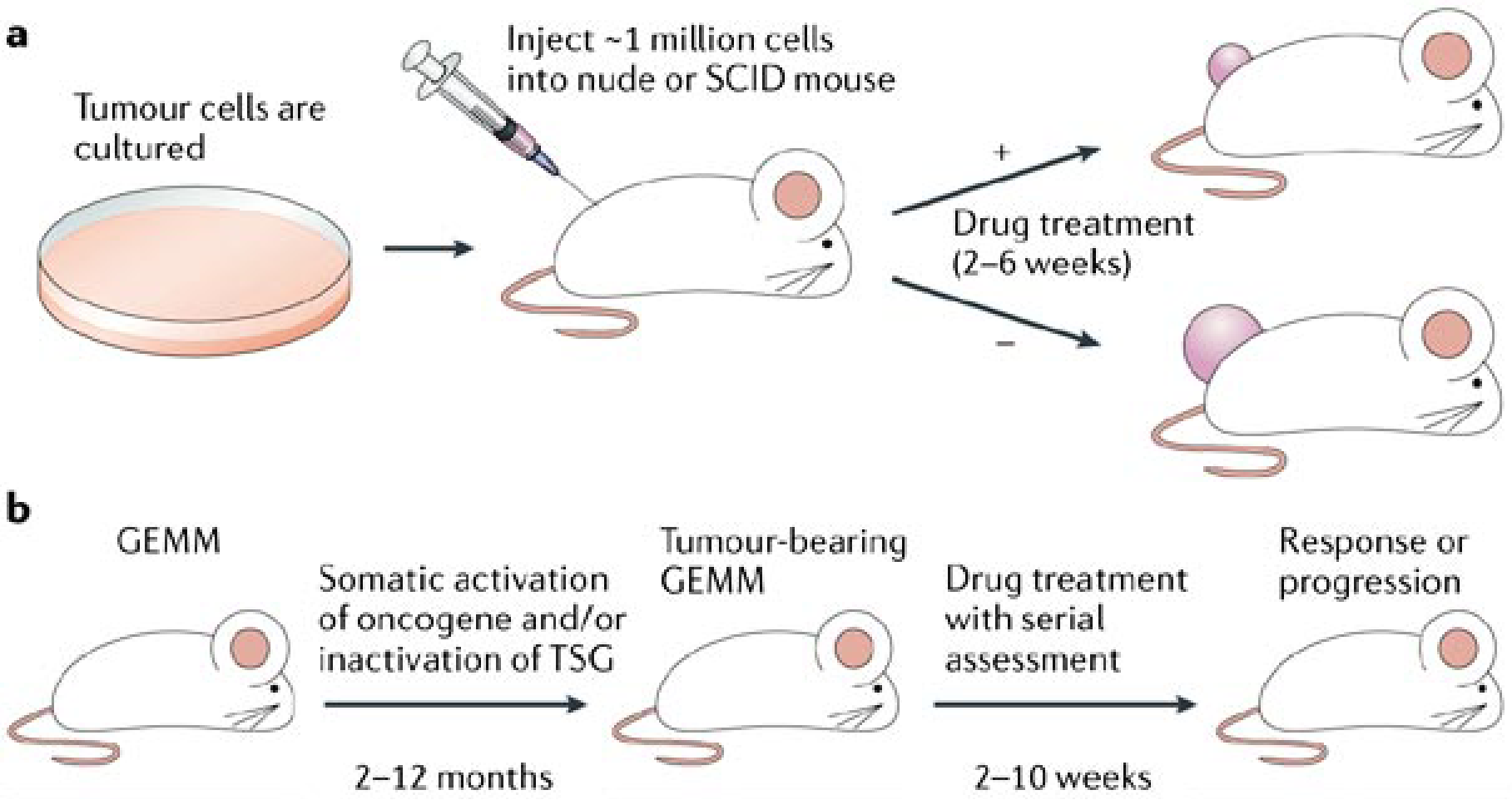


Acceleration of Improved Diagnosis and Treatment for Human Cancers

Essential Need for Accurate Preclinical Models

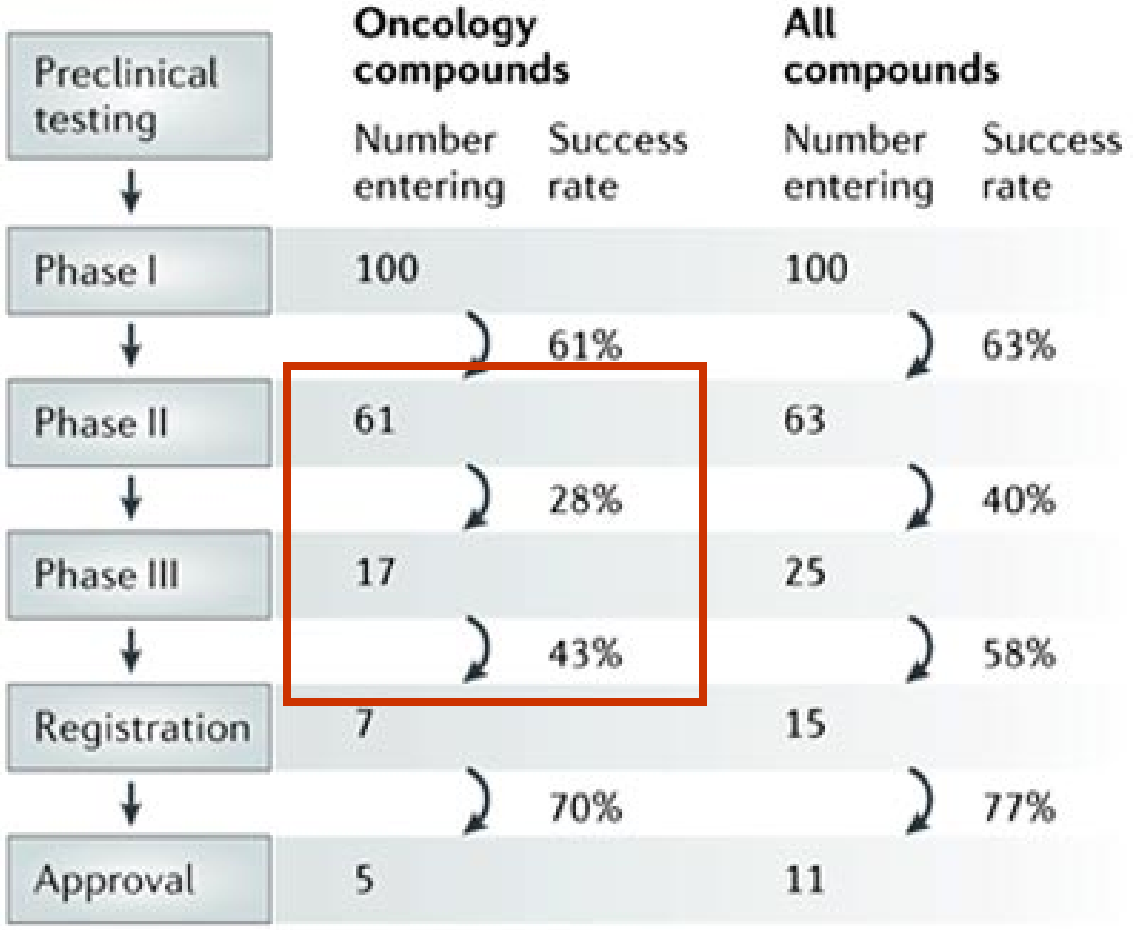

Discoveries
RSV 1911
Oncogene discovery: Ha-Ras; Myc; K-Ras; erb-B1; raf
BCR-ABL 1973
c-src 1976
p53 as oncogene 1979
1st Human Oncogene Ha-ras 1981
p53 as TSG 1989
RB1 first TSG cloned 1986
RNAi observed; HGP begun 1990
p53 Molecule of the Year by Science 1993
BRCA1 1994
RNA silencing 1998
MGSP finished 2002
MGSP Initiated 2000
HGP completed 2003
MicroRNA link to cancer 2005
1900
1950
1960
1970
1980
1990
2000
1955 Cell culture
1958 Focus Formation Assay
1971 Gene transfer assay (eukaryotic DNA)
1973 Recombinant DNA Technology
1974 First cloning of Eukaryotic gene
1976 Tissue Recombination
1981 Cre-LoxP ES cell
1982 Mouse p53 gene cloned
1983 PCR
1984 GEM cancer models
1992 3-D culture
1995 Gene Chip
1997 Array CGH
1998 TMA
Technologies
GEM
Xenograft
Cell Culture

Preclinical Cancer Models



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

Current Cancer Drug Development

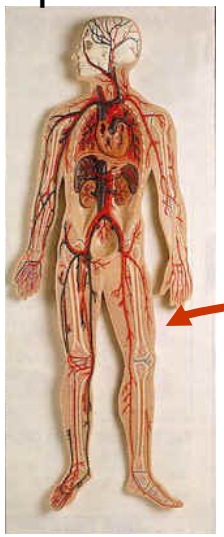


……at an average cost of $1B per drug

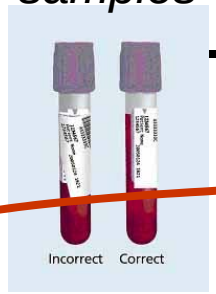
diagram from: Sharpless and DePinho; Nature Reviews Drug Discovery '06

Predictive Preclinical Models Revolutionize Clinical Development

patient



diseased samples

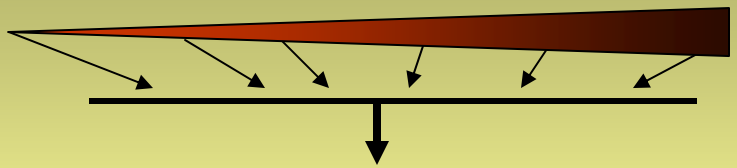


assess abnormalities

programmed disease in preclinical model

No disease

disease initiation and stages



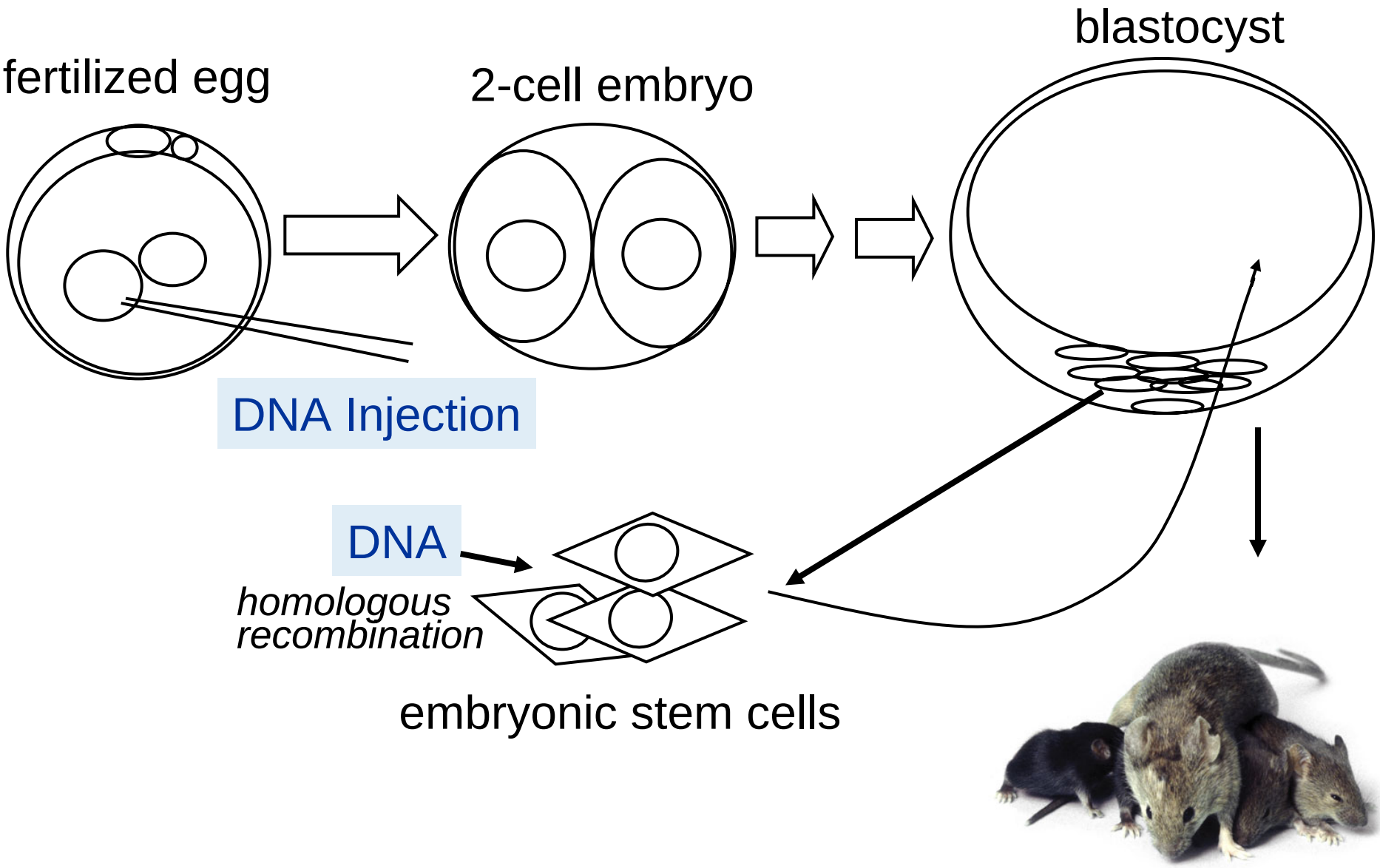
Full disease

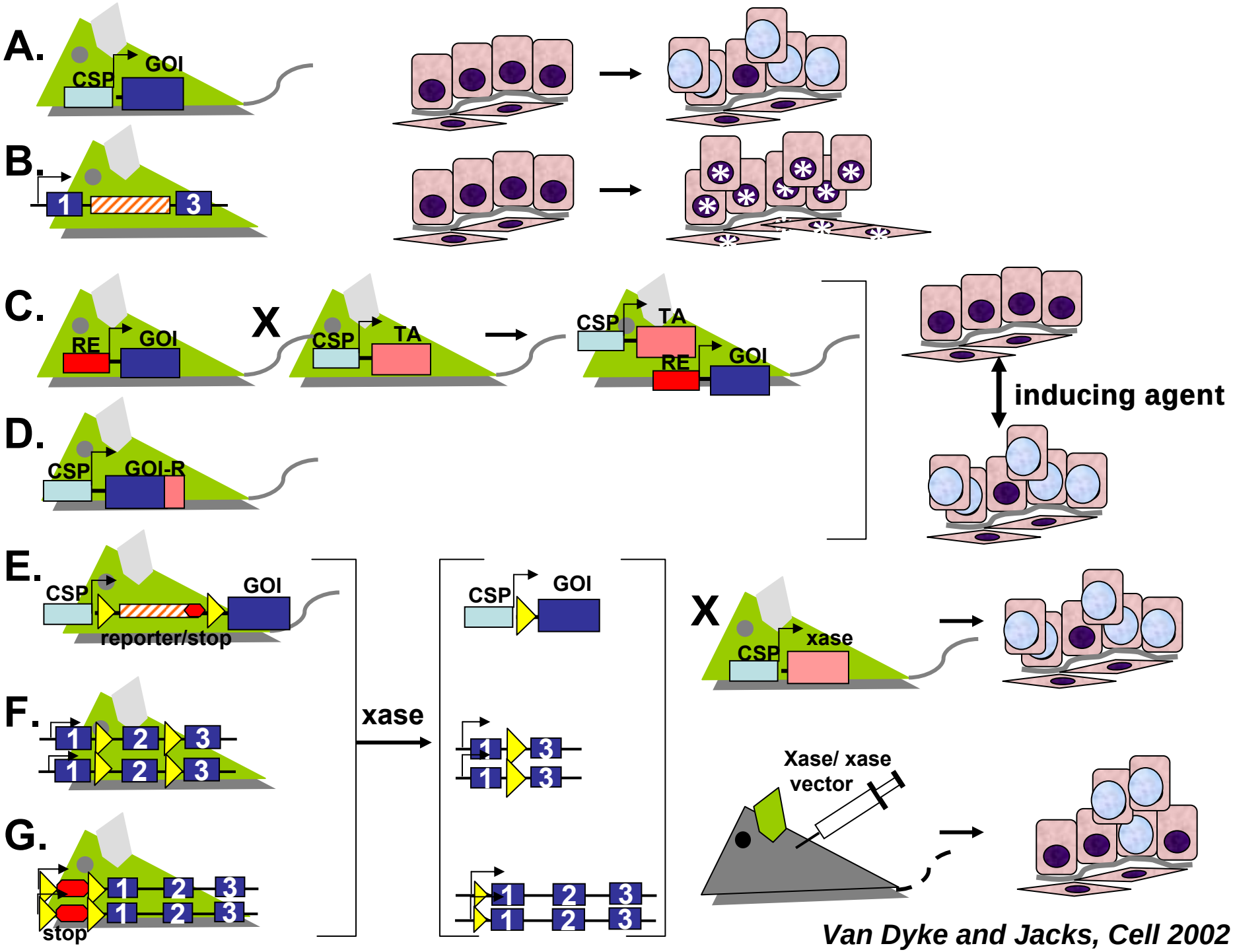
•Discover disease biomarkers (early detection, monitor treatment)

•Identify new drug targets

•Predict and evaluate drug efficacy

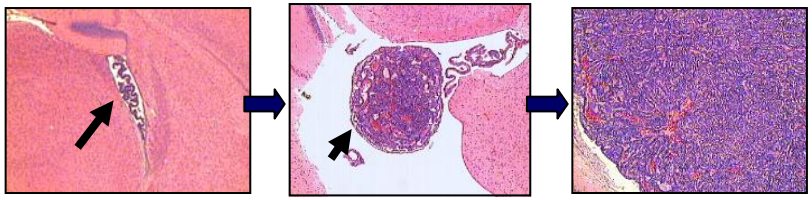
Genetic Engineering of Mice



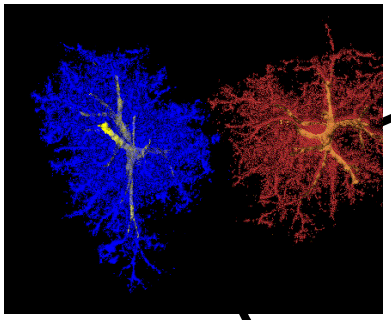


Van Dyke and Jacks, Cell 2002

An Integrated Approach to Disease Analyses, Diagnosis, Treatment Development

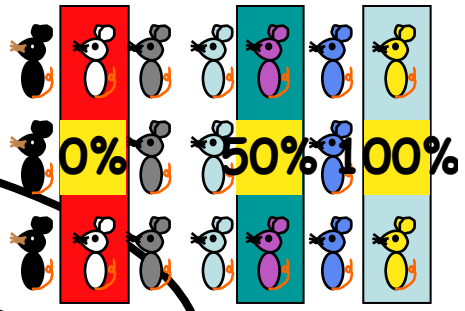


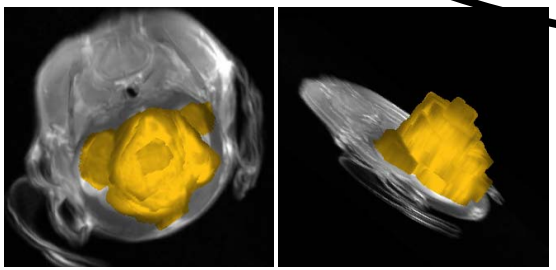
cell biology & imaging



histopathology, physiology

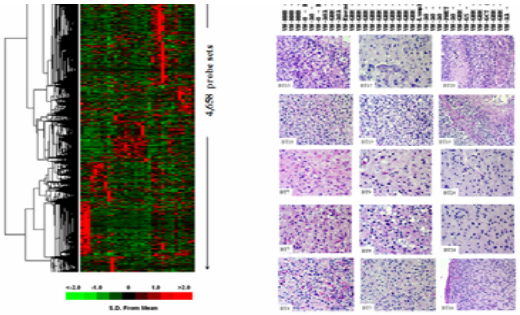
complex genetics

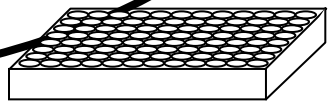




animal imaging

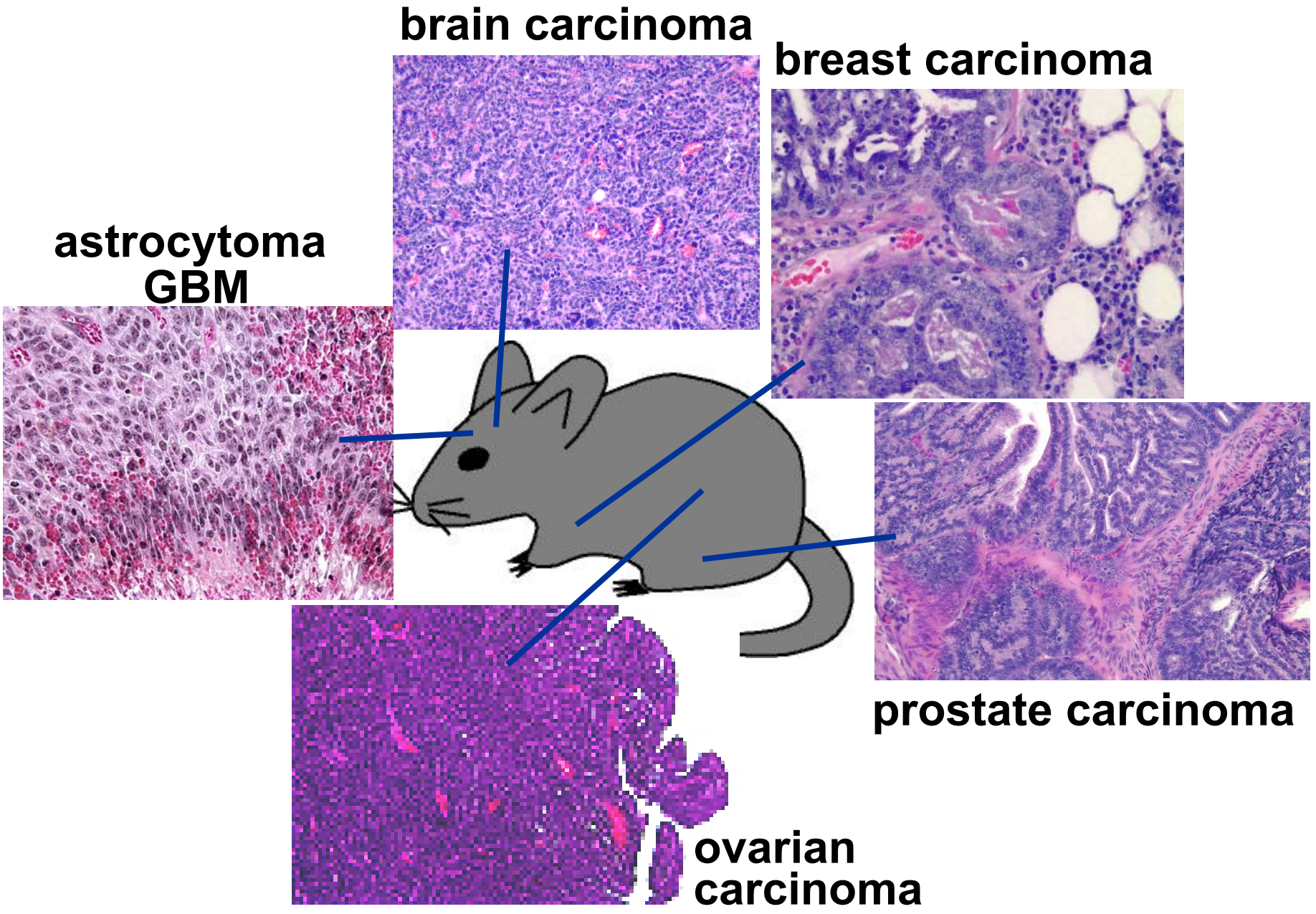
genomics, proteomics



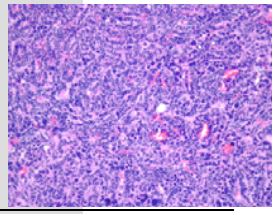
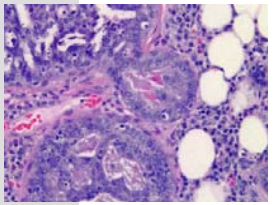
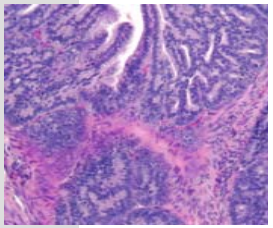
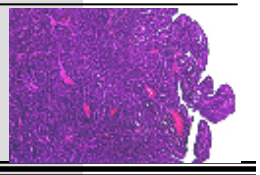
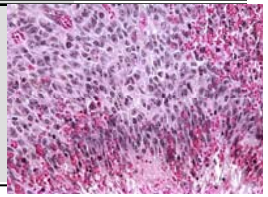


biomarkers, preclinical tests

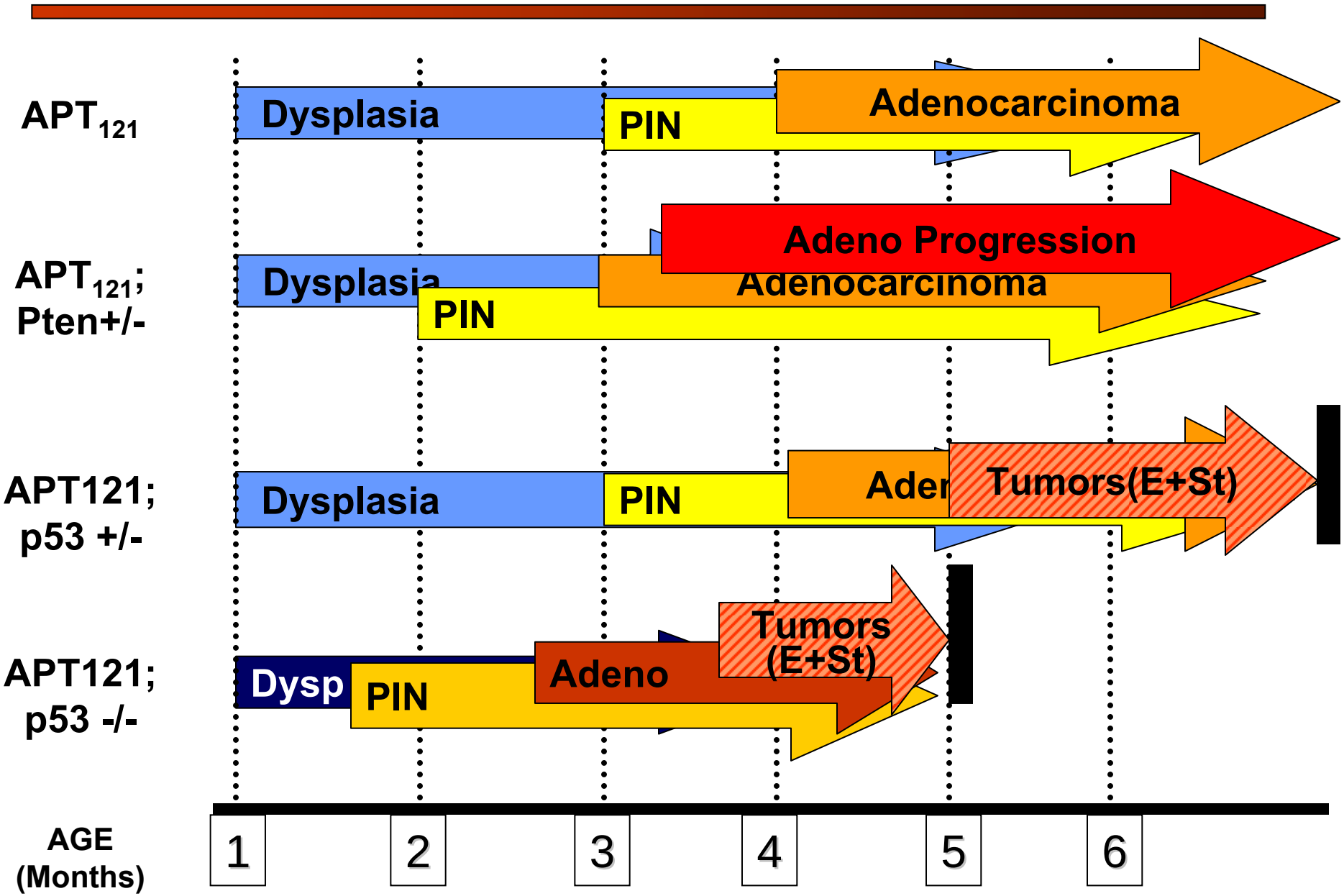
Preclinical GEM Cancer Models (Van Dyke Lab)



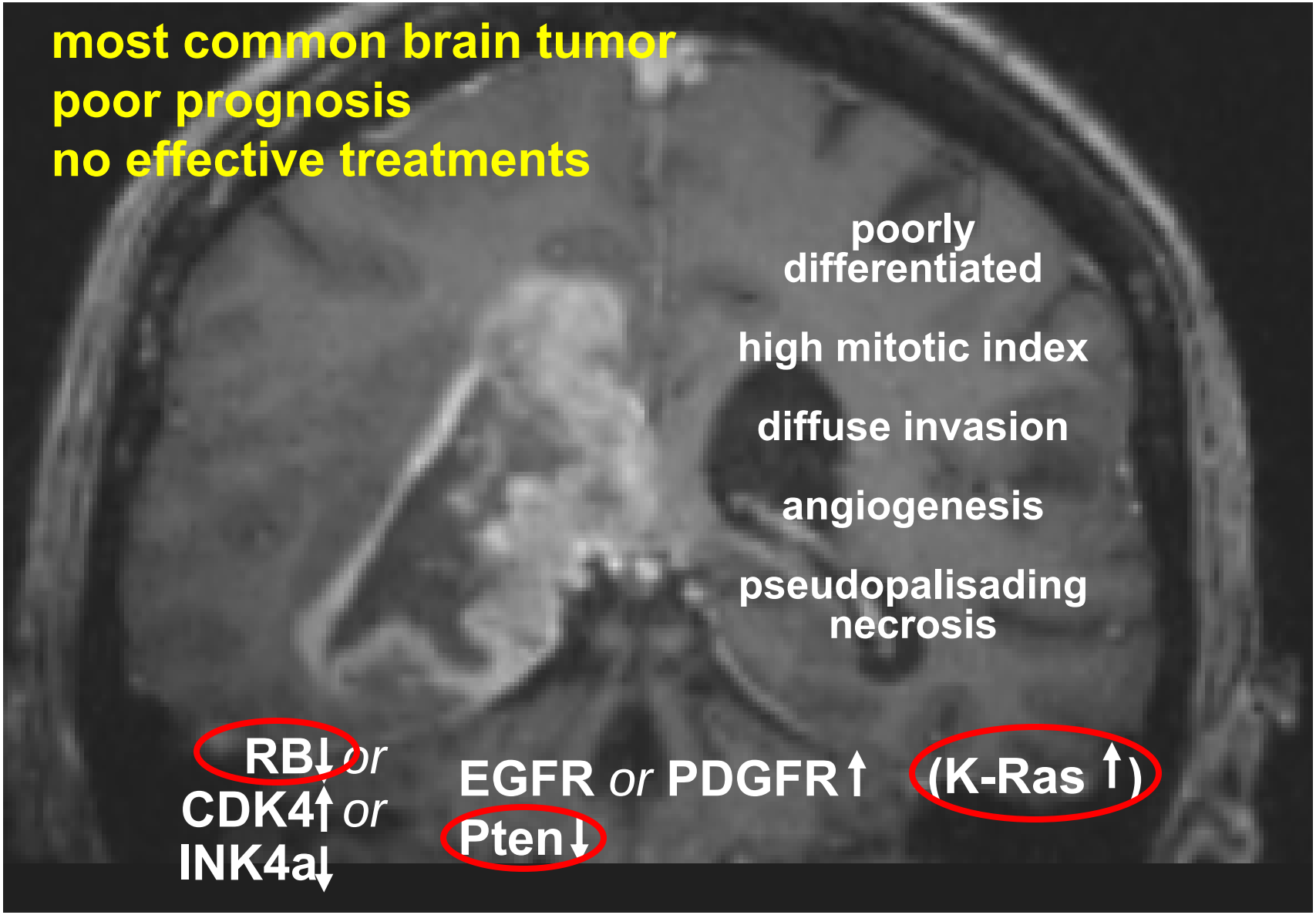
Cancer Initiation and Progression Mechanisms

~~pRb$_f$~~ (T_{121}) →	aberrant proliferation	+	apoptosis	→	additional events; progression	
brain epith. (CPE)	√		√ p53		√ ~~p53~~	
mammary	√		√ p53		√ ~~p53~~	
prostate	√		√ Pten		√ *Pten*↓ ~~*Pten*~~ ~~p53~~	
ovarian	√		√ *nd*		√ *nd*	
astrocytes	√		√ Pten		√ ~~Pten~~ RTK↑	

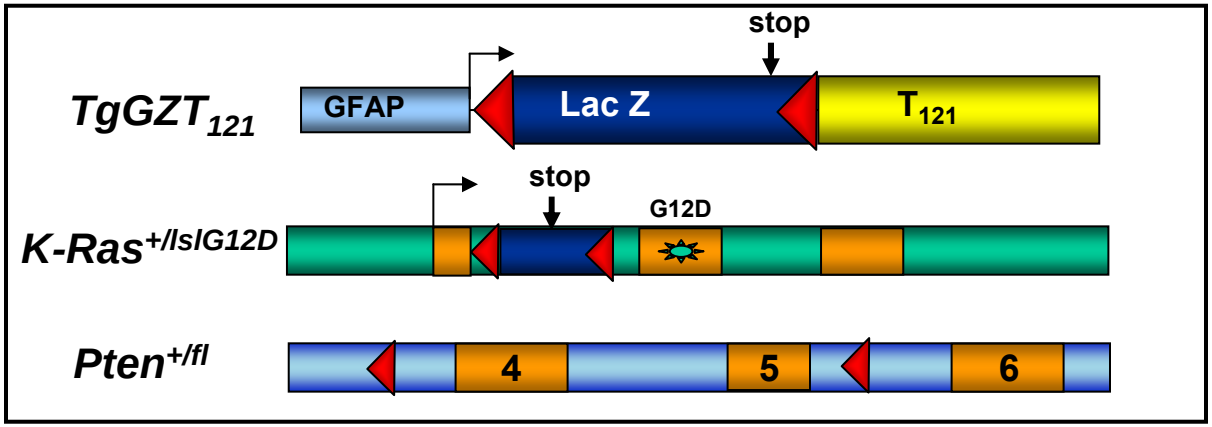
Staged Models of Prostate Cancer



High-grade Astrocytoma



Engineering a Preclinical GBM Model

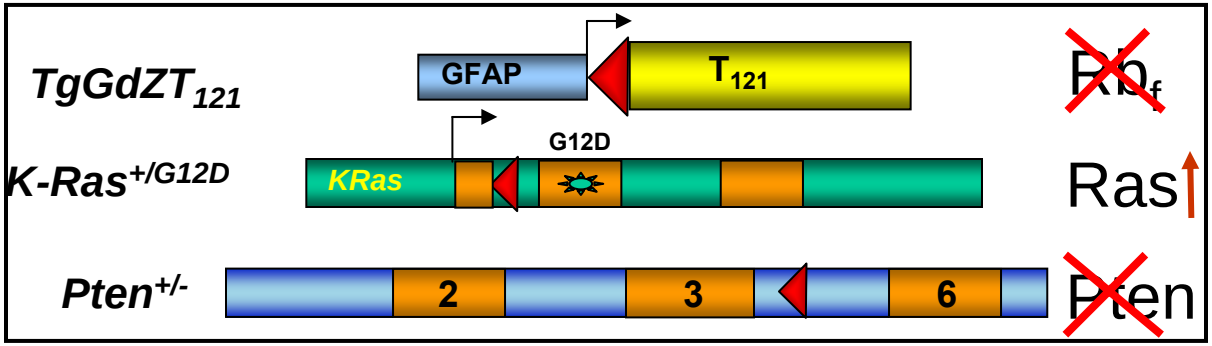


mouse genotype

NORMAL

X *GFAP-CreER^{TAM}* ↓ *+ 4-OHTam*

(K. McCarthy UNC)

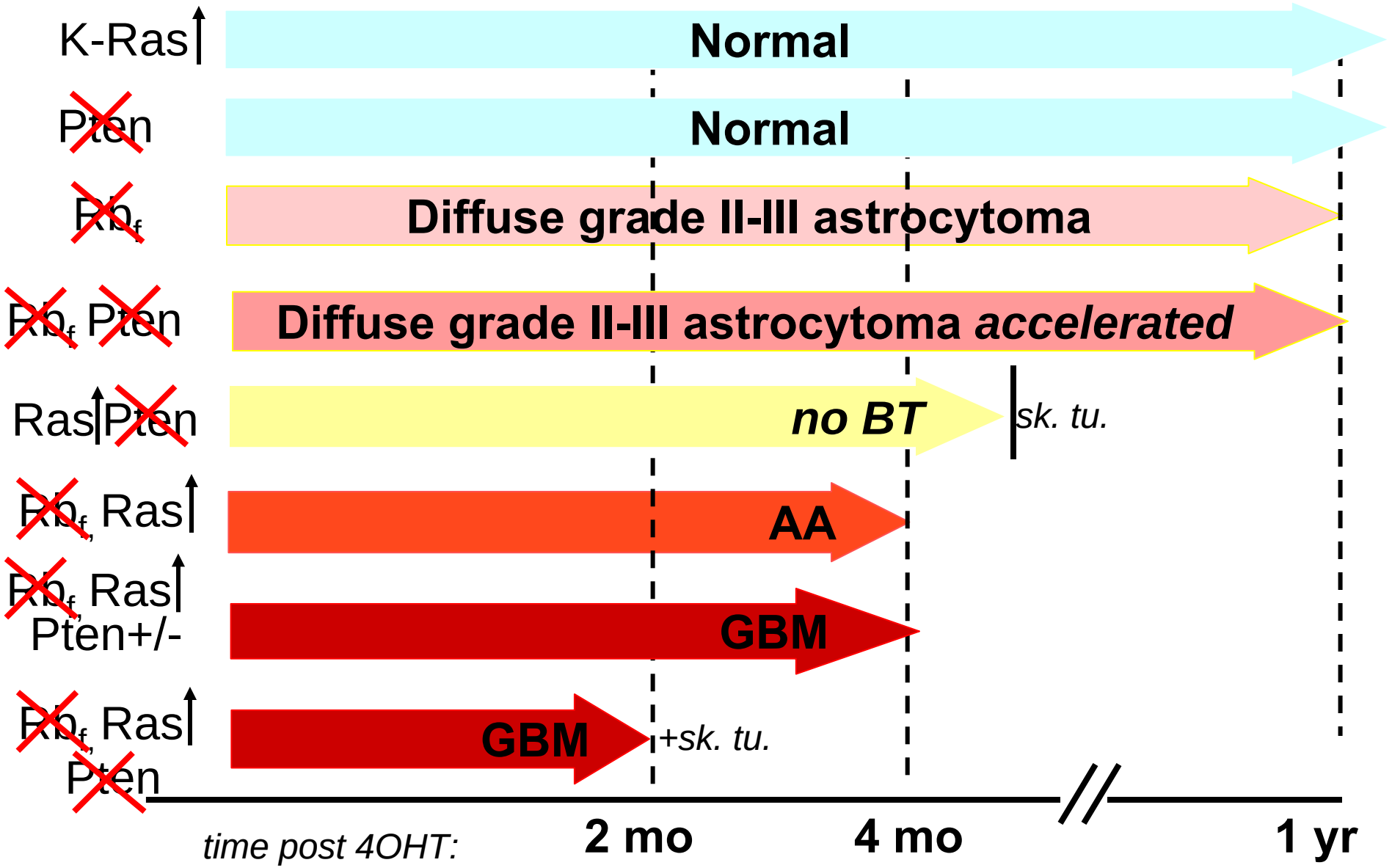


adult astrocyte genotype

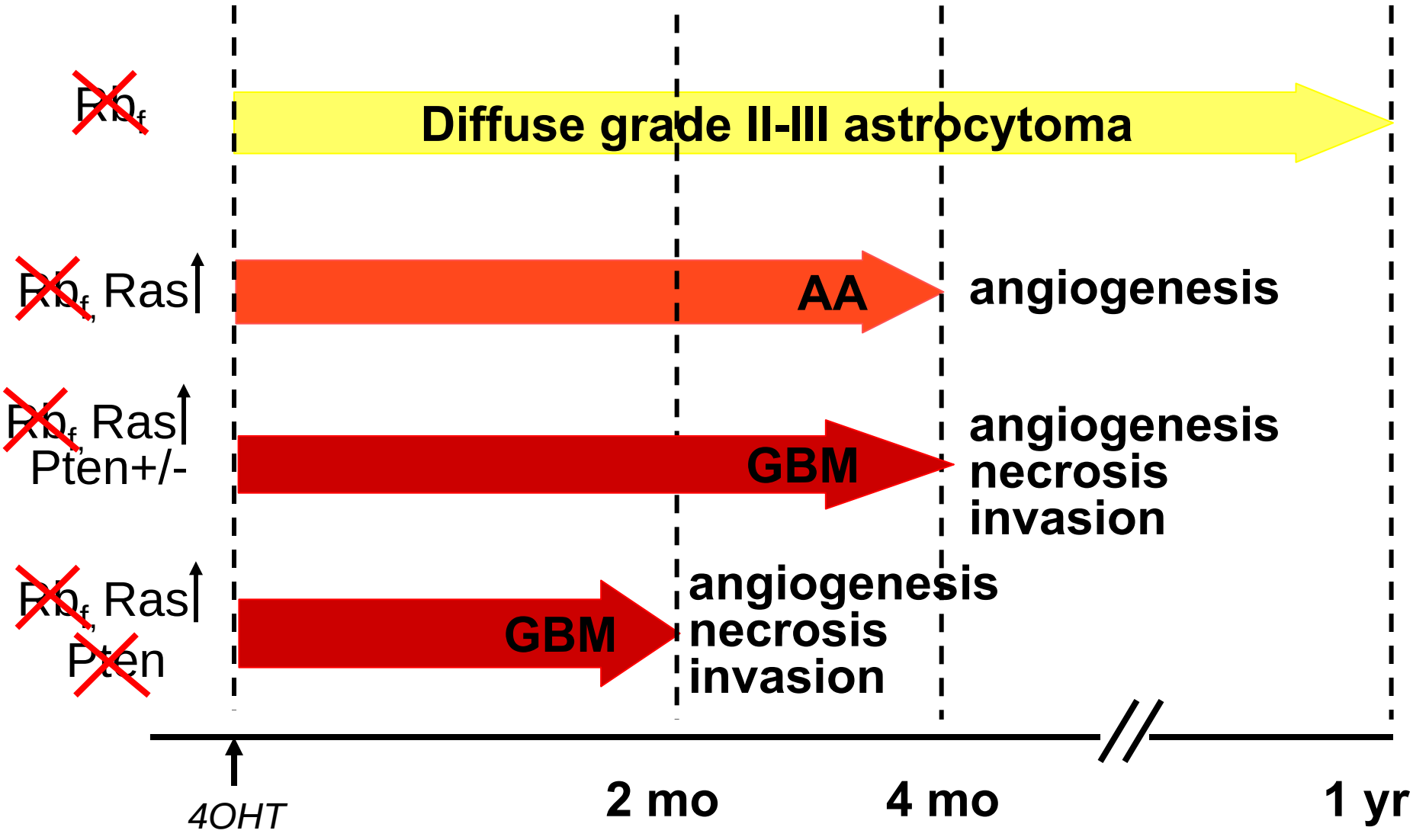
CANCER-CAUSING

Qian Zhang

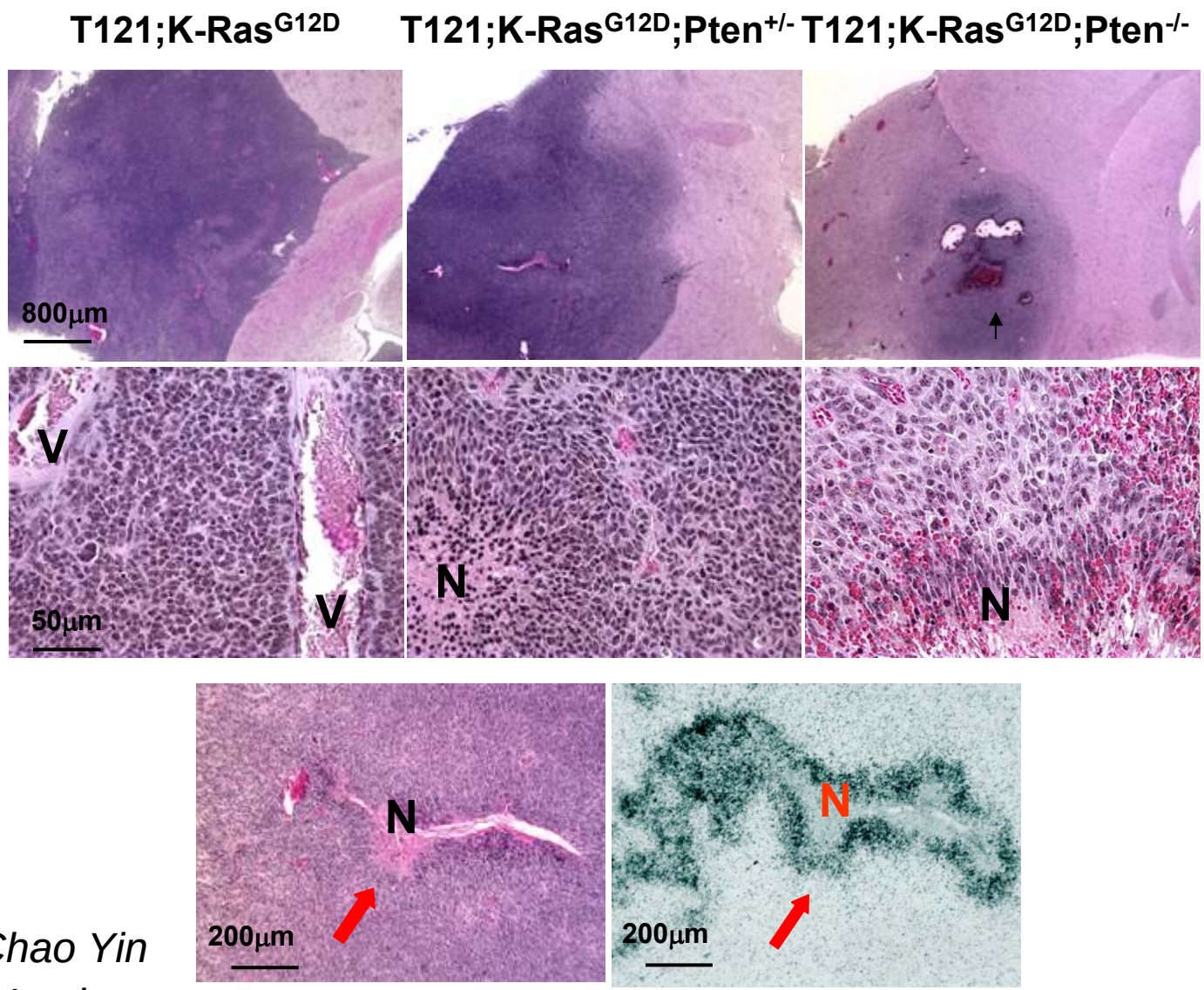
Inducible Astrocytoma Models



Inducible Astrocytoma Models

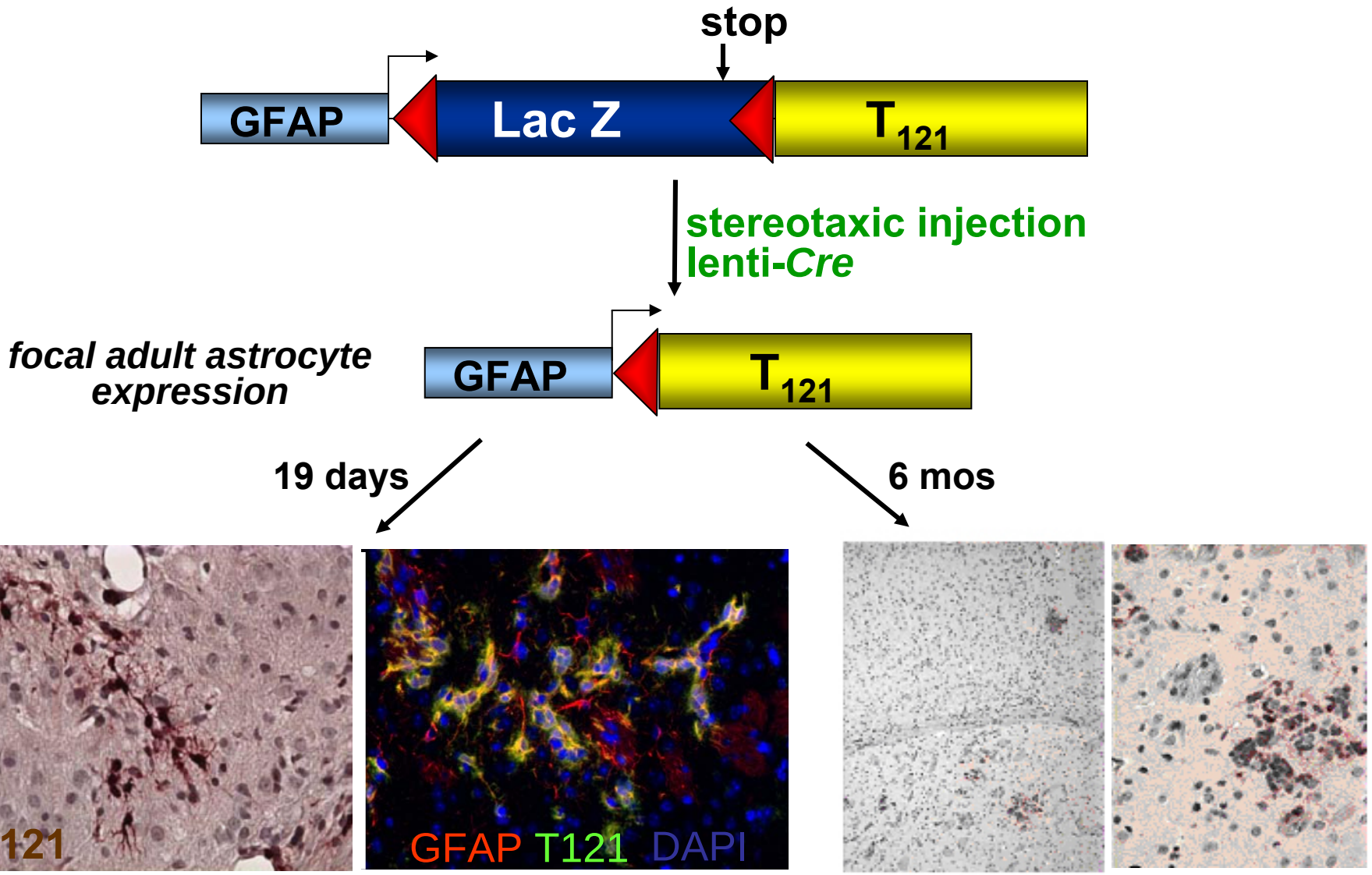


Inducible GBM



Qian Zhang, Chao Yin
R. Miller; D. Louis

Focal Inactivation of Rb Function



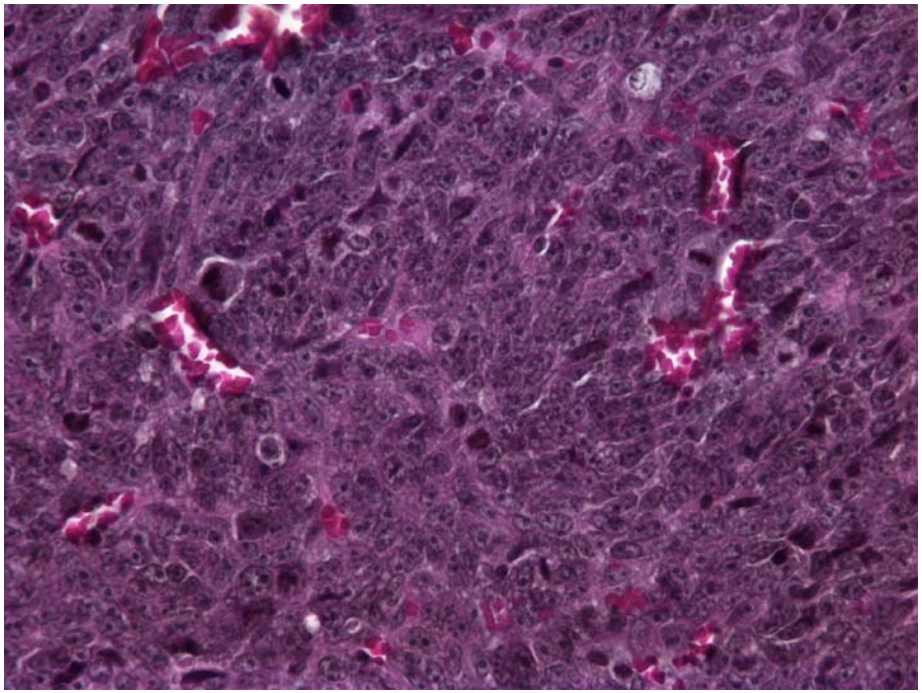
Ryan Bash, Tal Kafri (UNC)

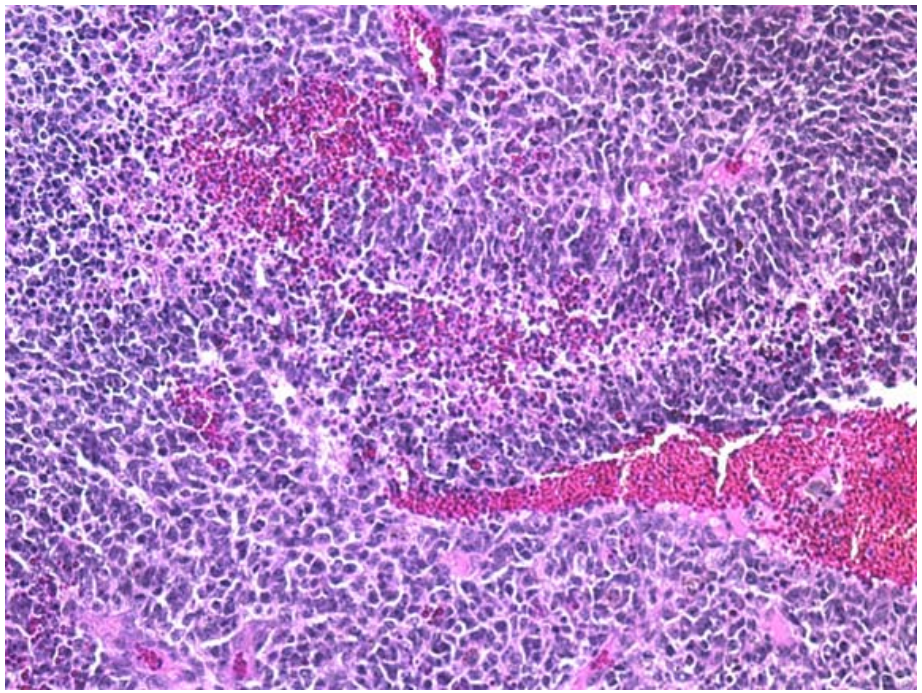
Focal Somatic Induction of GEM-AA and GEM-GBM

frontal cortex *astrocyte* events

~~Rb_f~~, Ras↑

~~Rb_f~~, Ras↑, ~~Pten~~



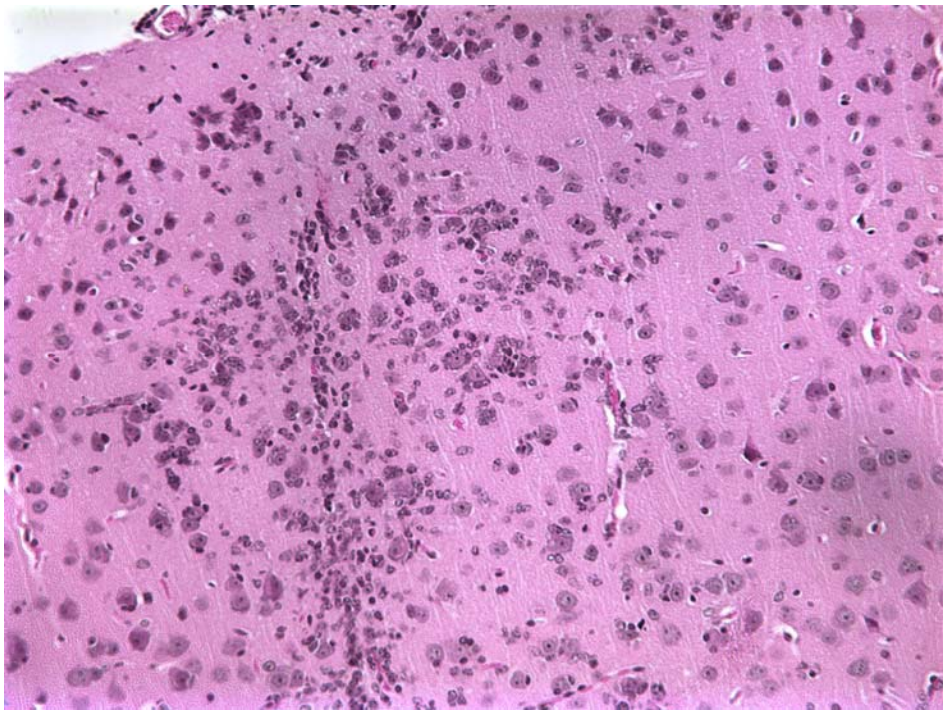


GEM-AA (*9 mo pi*)

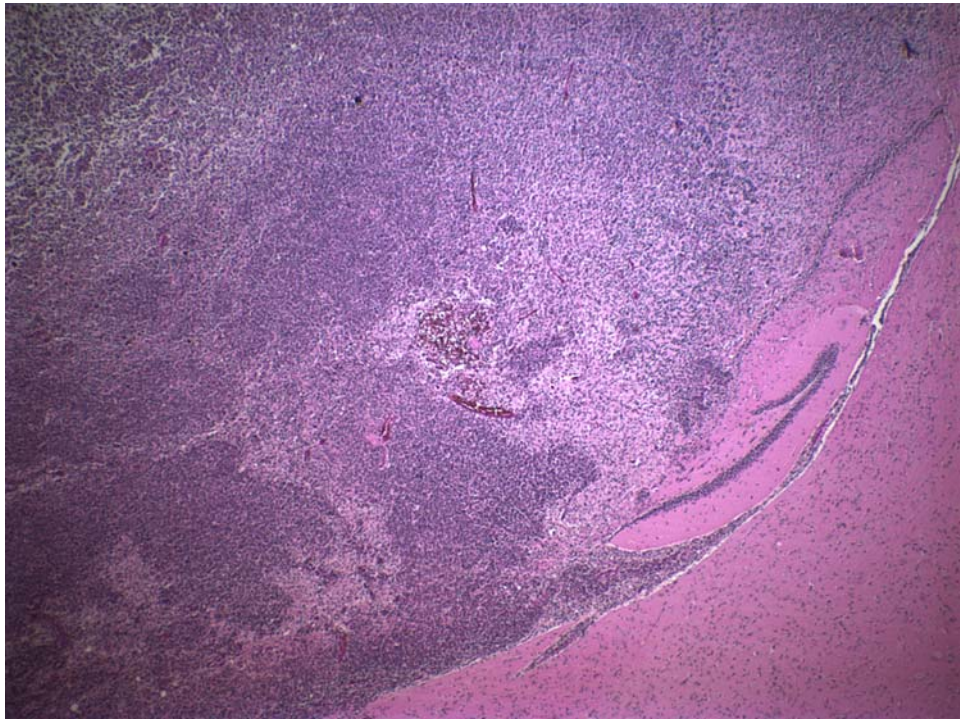
GEM-GBM (*4 mo pi*)

Progression to GEM-GBM

early lesions

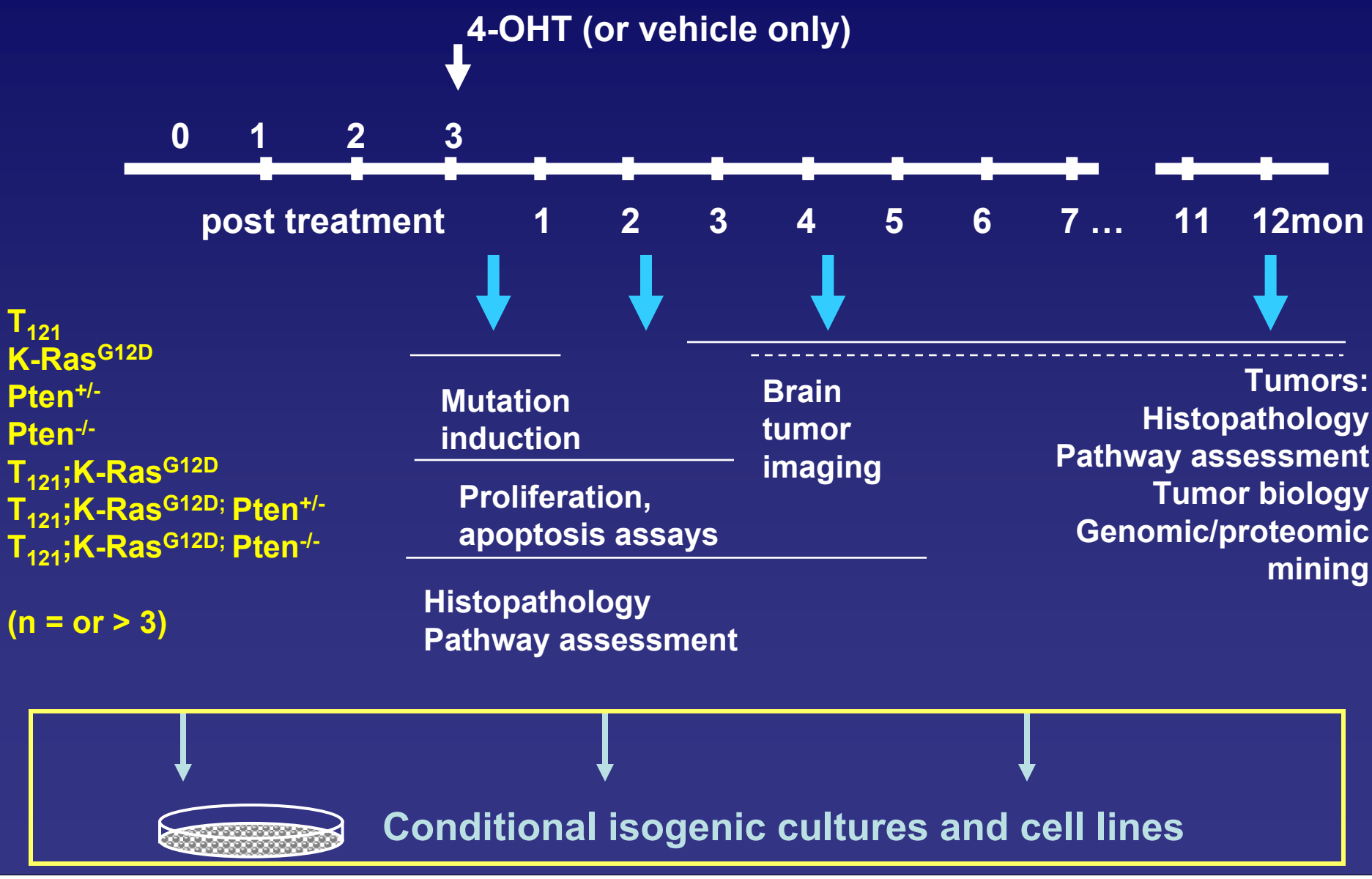


GBM

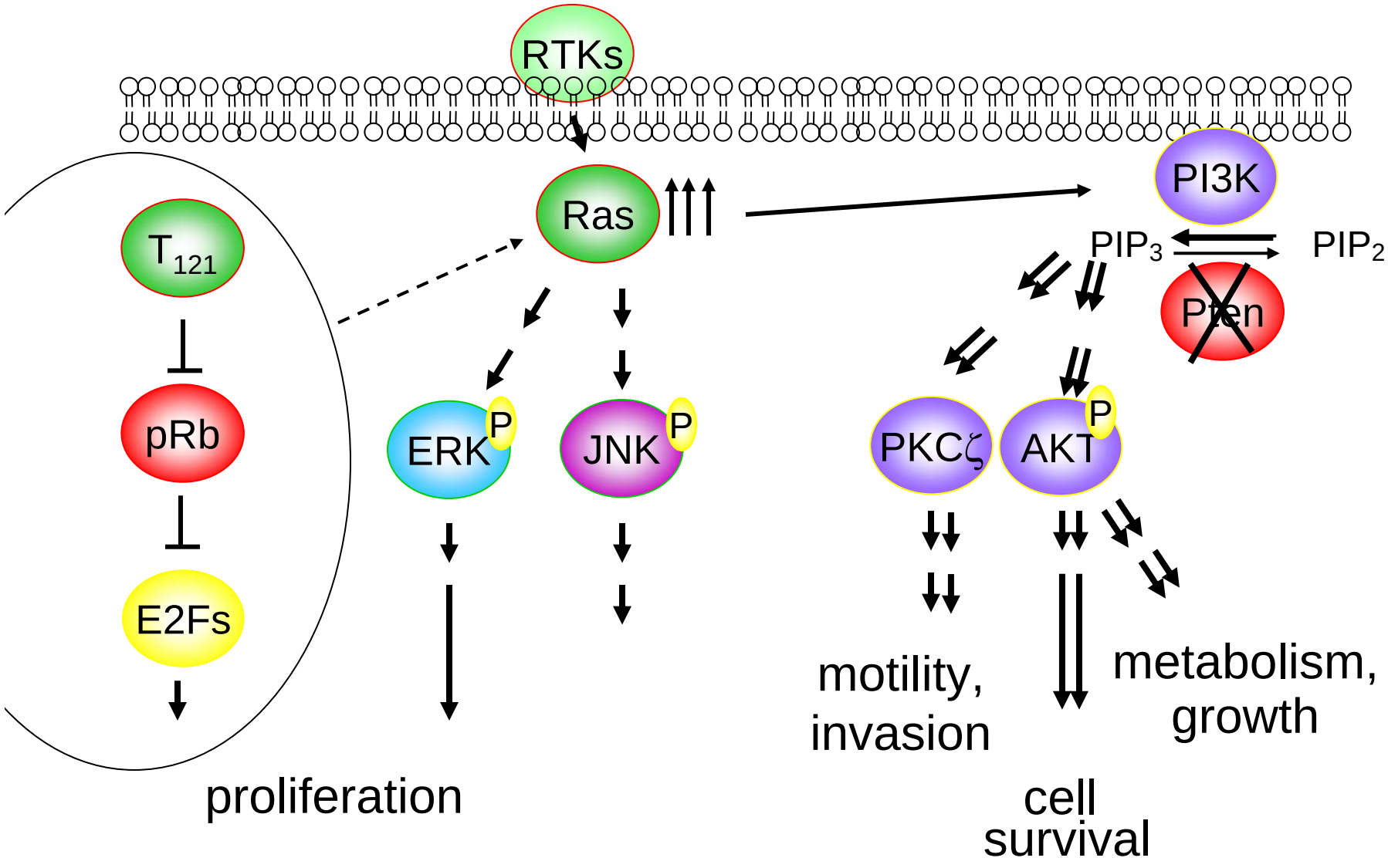


Rb_f, Ras↑, Pten

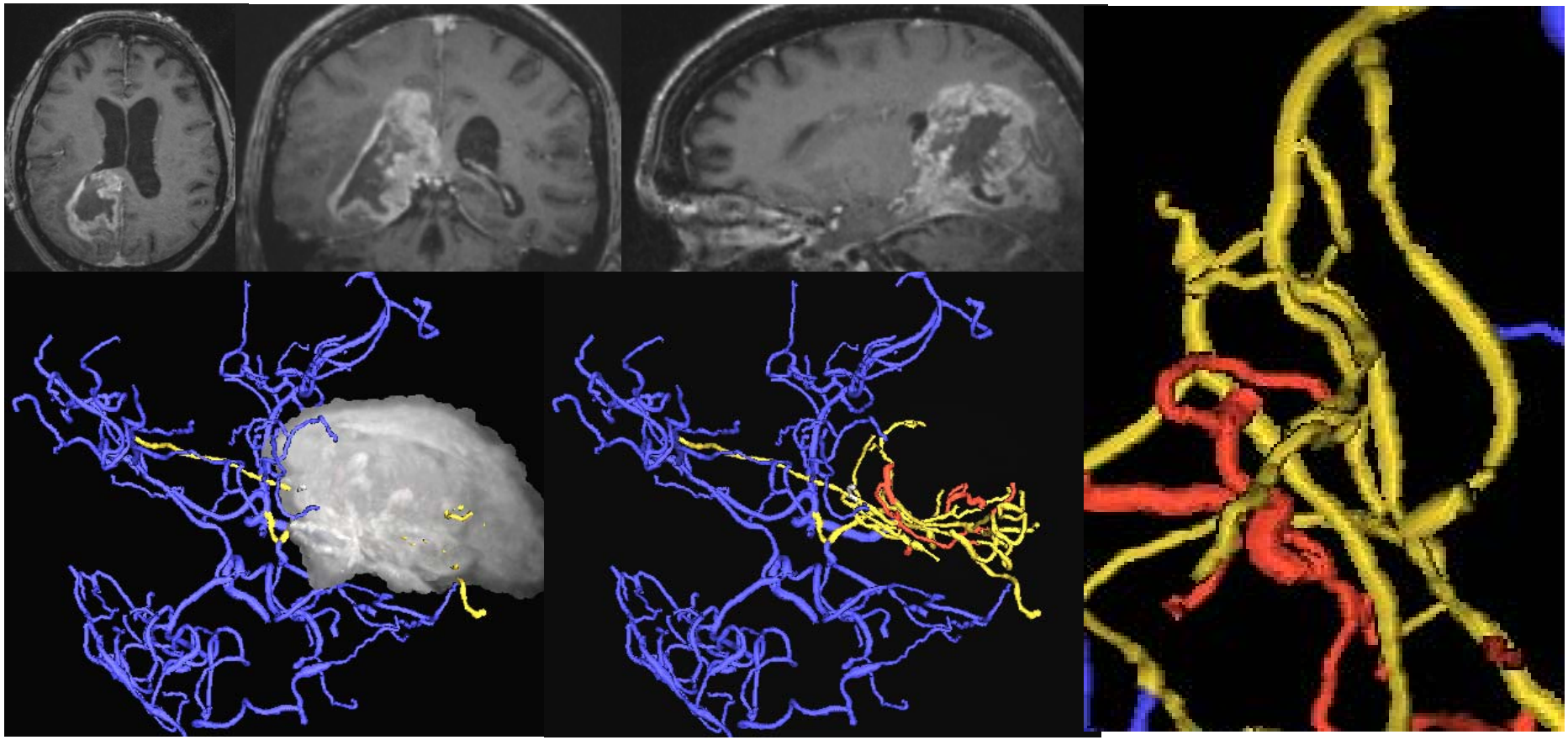
Comprehensive Study of Disease Progression



Pathways to Astrocytoma



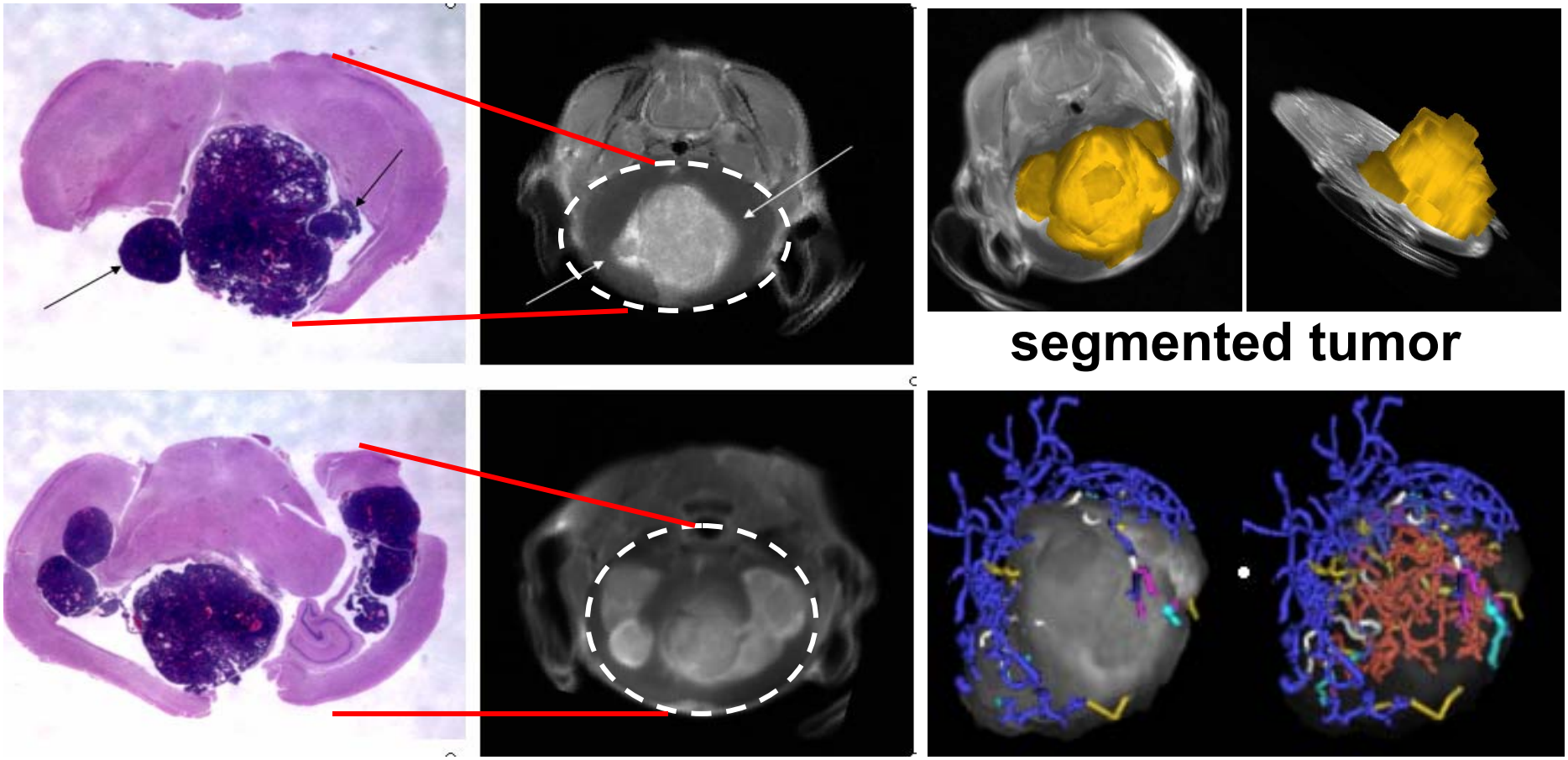
Vessel Analyses of Human Brain Tumors: How Similar is Mouse to Human?



Human Glioblastoma

Elizabeth Bullitt, UNC-CH

MR Analyses of Mouse Brain Tumors



segmented tumor

H&E

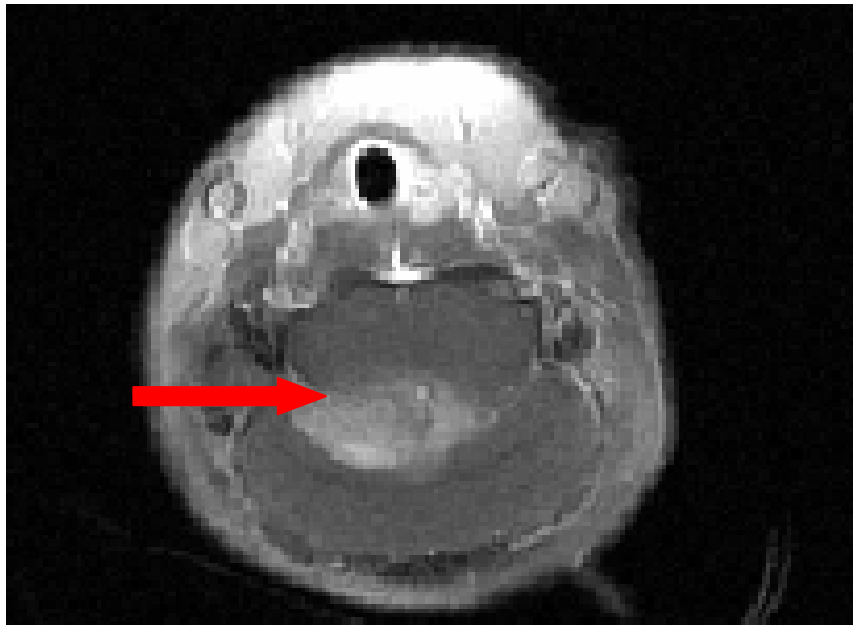
T1-GAD

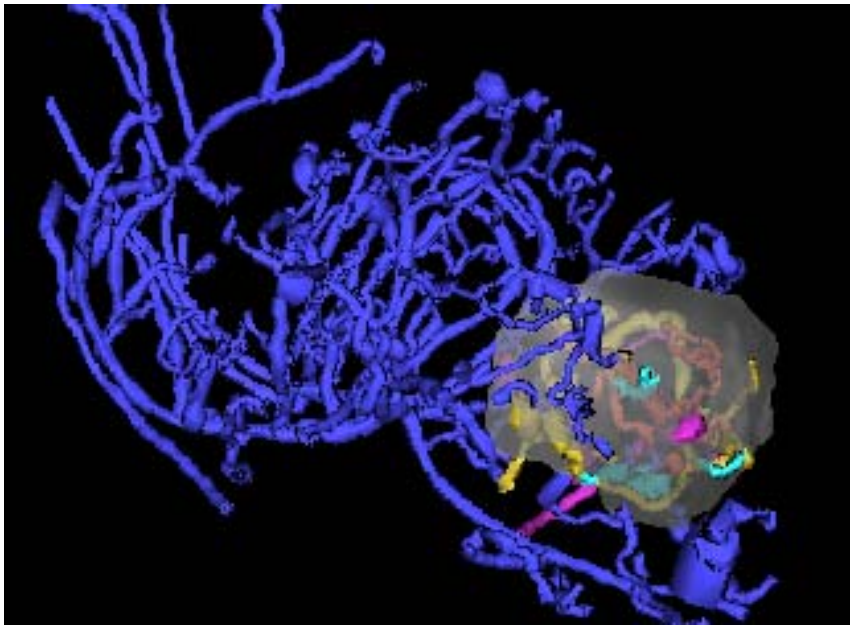
segmented vessels

with Elizabeth Bullitt and Weili Lin, UNC-CH

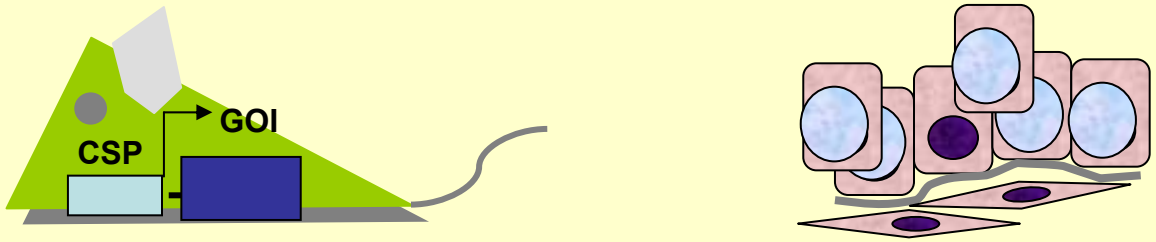
Brubaker et al Cancer Res. 2005
Bullitt et al. AJNR, 2005

Malignant Vessels in GEM-GBM

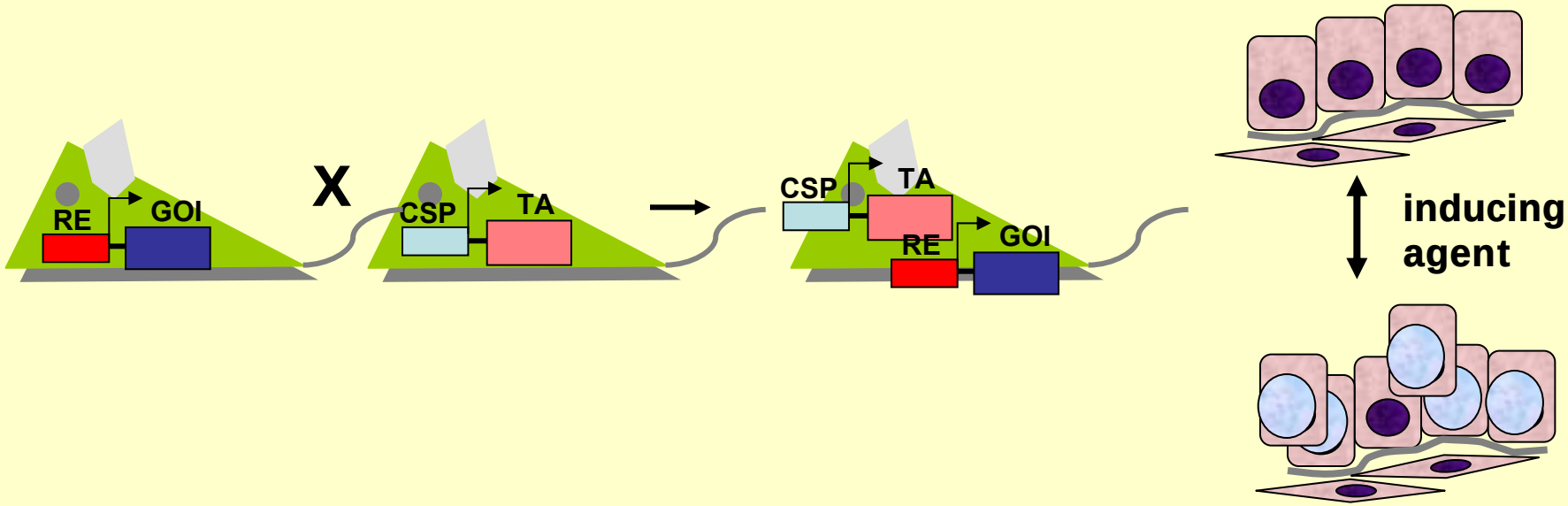




Cell-specific transgene expression

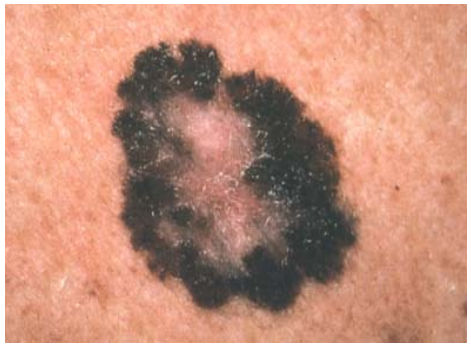


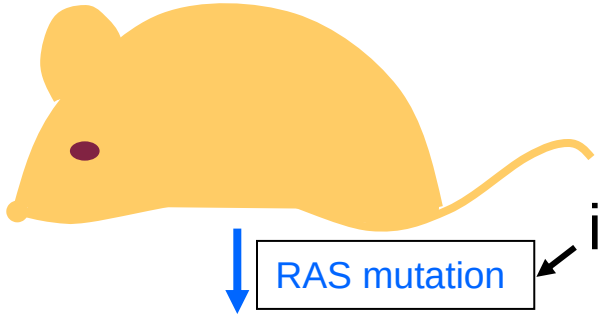
Regulatable transgene expression



Cancer initiation vs tumor maintenance

Lynda Chin, Ron DePinho, Dana Farber



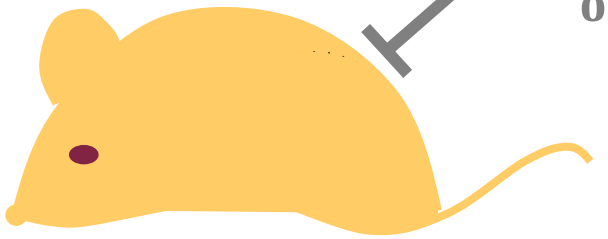


inducible

RAS mutation

Ink4a/Arf loss

Acquired Mutations



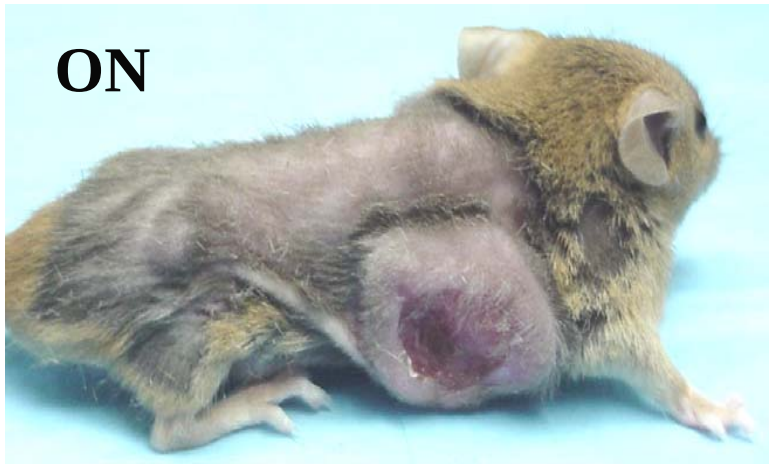
Genetic Inactivation of RAS

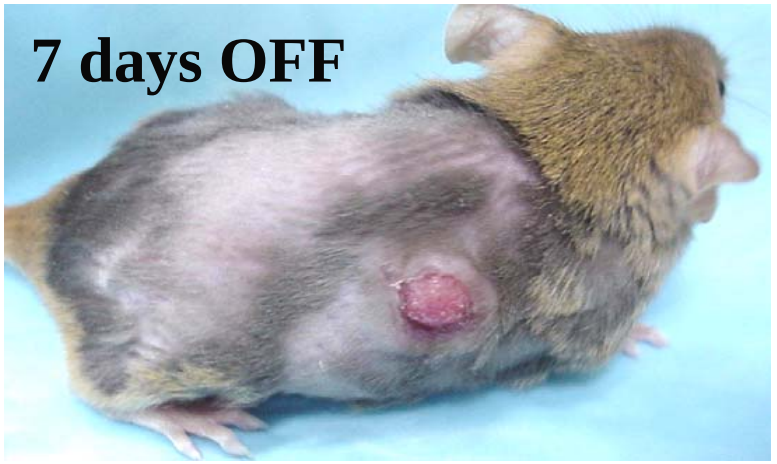
Question: Are initiating mutations still required for tumor maintenance?

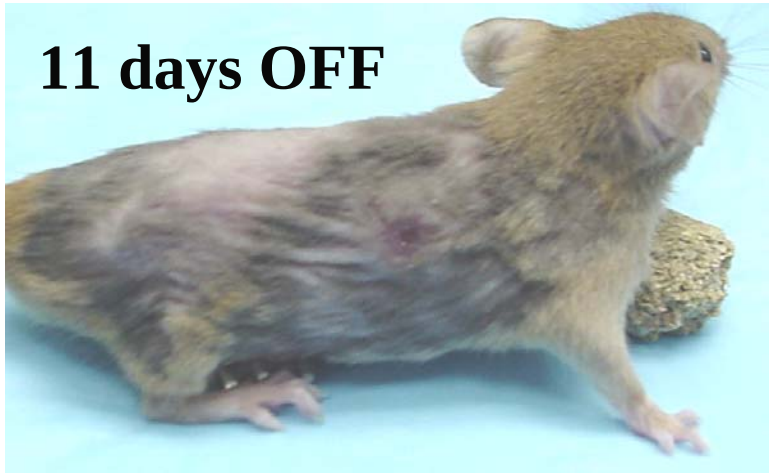
If so, then what is the function of this gene in tumor maintenance?

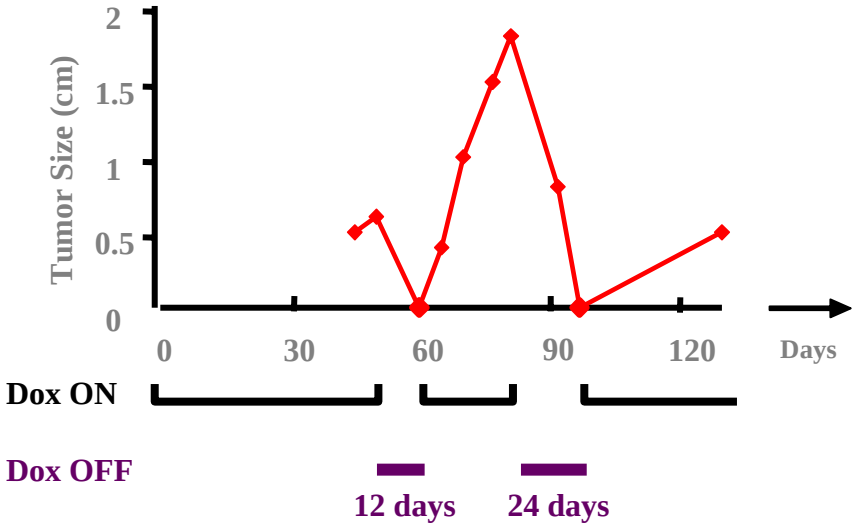
Regression of Established Melanoma after Shutdown of Ras

Lynda Chin, Ron DePinho, Dana Farber

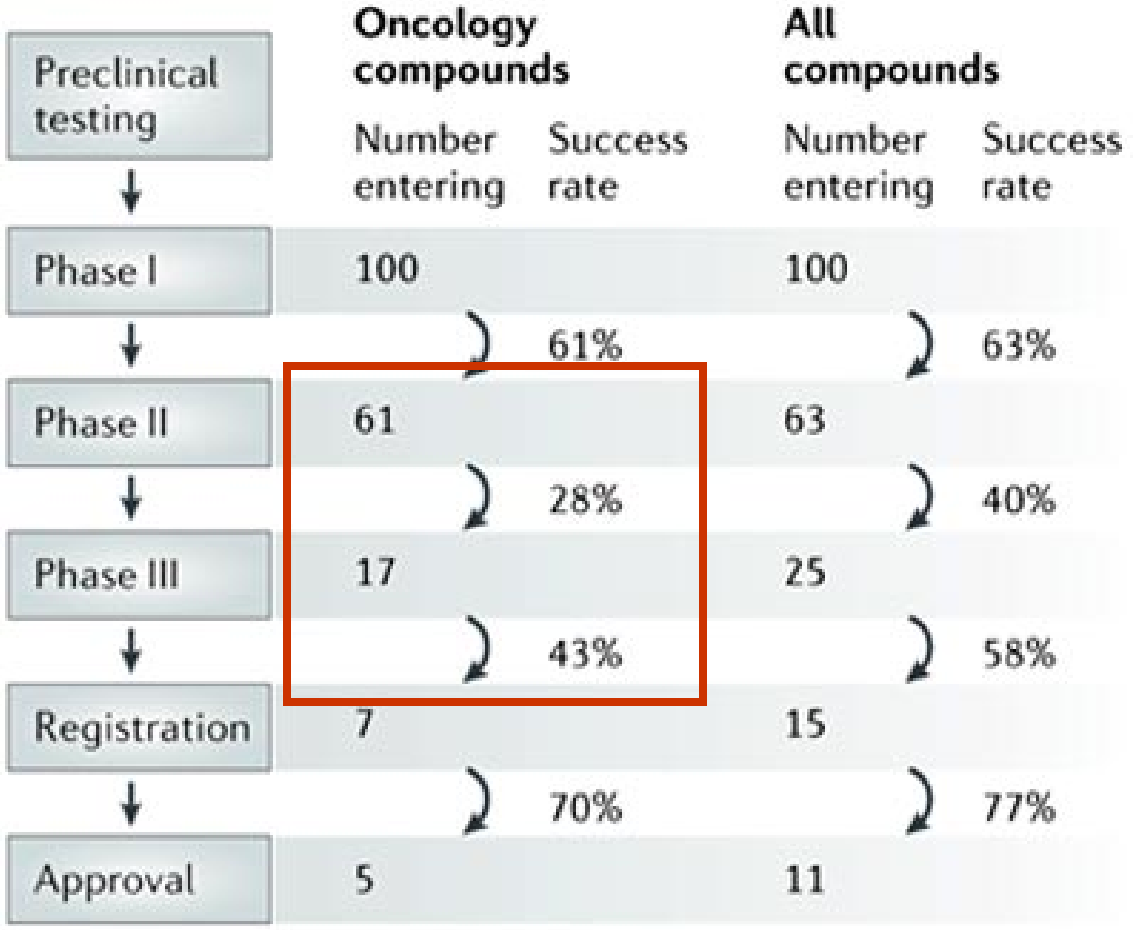








Current Cancer Drug Development



……at an average cost of $1B per drug

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

Targeting EGFR in Cancer

adapted from Ciardiello & Tortora, 2002; courtesy of David Threadgill (UNC)

Targeted Drugs in Clinical Trials: Patient Stratification Required to Assess Efficacy

Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib

Lynch, Thomas J; Bell, Daphne W; Sordella, Raffaella; Gurubhagavatula, Sarada; Okimoto, Ross A; Brannigan, Brian W; Harris, Patricia L; Haserlat, Sara M; Supko, Jeffrey G; Haluska, Frank G; Louis, David N; Christiani, David C; Settleman, Jeff; Haber, Daniel A.
NEJM; 350, 21, 2004, 2129-2139

Also:

Paez et al.(Myerson), 2004, *Science* 304 (2004), pp. 1497–1500.
Pao et al.(Varmus), 2004 , *Proc. Natl. Acad. Sci. USA* 101 (2004), pp. 13306–13311.

Can GEMM Predict Response?

Cancer Cell May '06

The impact of human EGFR kinase domain mutations on lung tumorigenesis and in vivo sensitivity to EGFR-targeted therapies

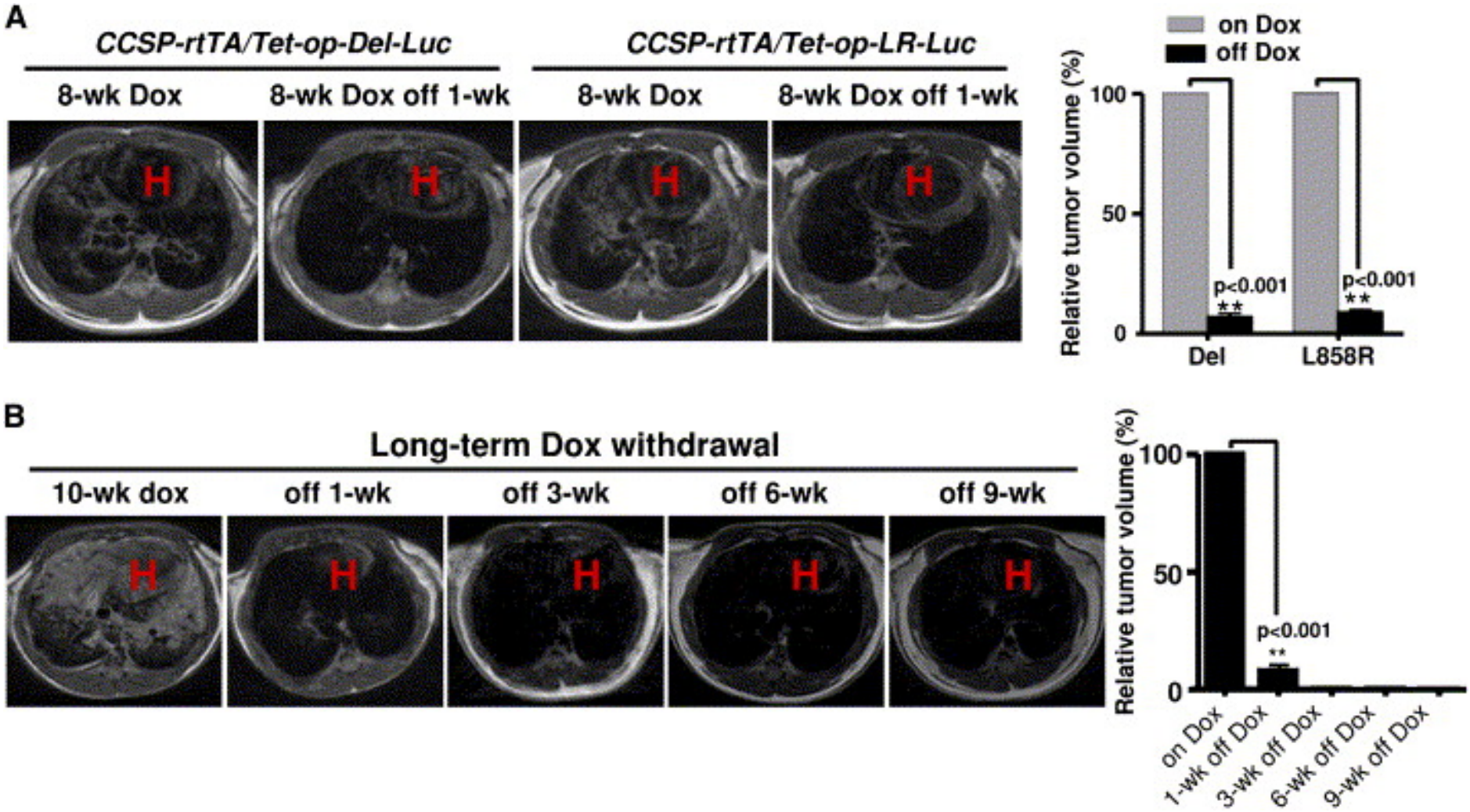
Hongbin Ji,1,2 Danan Li,1,2 Liang Chen,1 Takeshi Shimamura,1 Susumu Kobayashi,3 Kate McNamara,1Umar Mahmood,4 Albert Mitchell,5 Yangping Sun,5 Ruqayyah Al Hashem,5 Lucian R. Chirieac,6 Robert Padera,6 Roderick T. Bronson,7 William Kim,8 Pasi A. Ja¨ nne,1,9 Geoffrey I. Shapiro,1,9 Daniel Tenen,3 Bruce E. Johnson,1,9 Ralph Weissleder,4 Norman E. Sharpless,8 and Kwok-Kin Wong1,9,*

Genes & Development May '06

Lung adenocarcinomas induced in mice by mutant EGF receptors foundin human lung cancers respondto a tyrosine kinase inhibitor orto down-regulation of the receptors

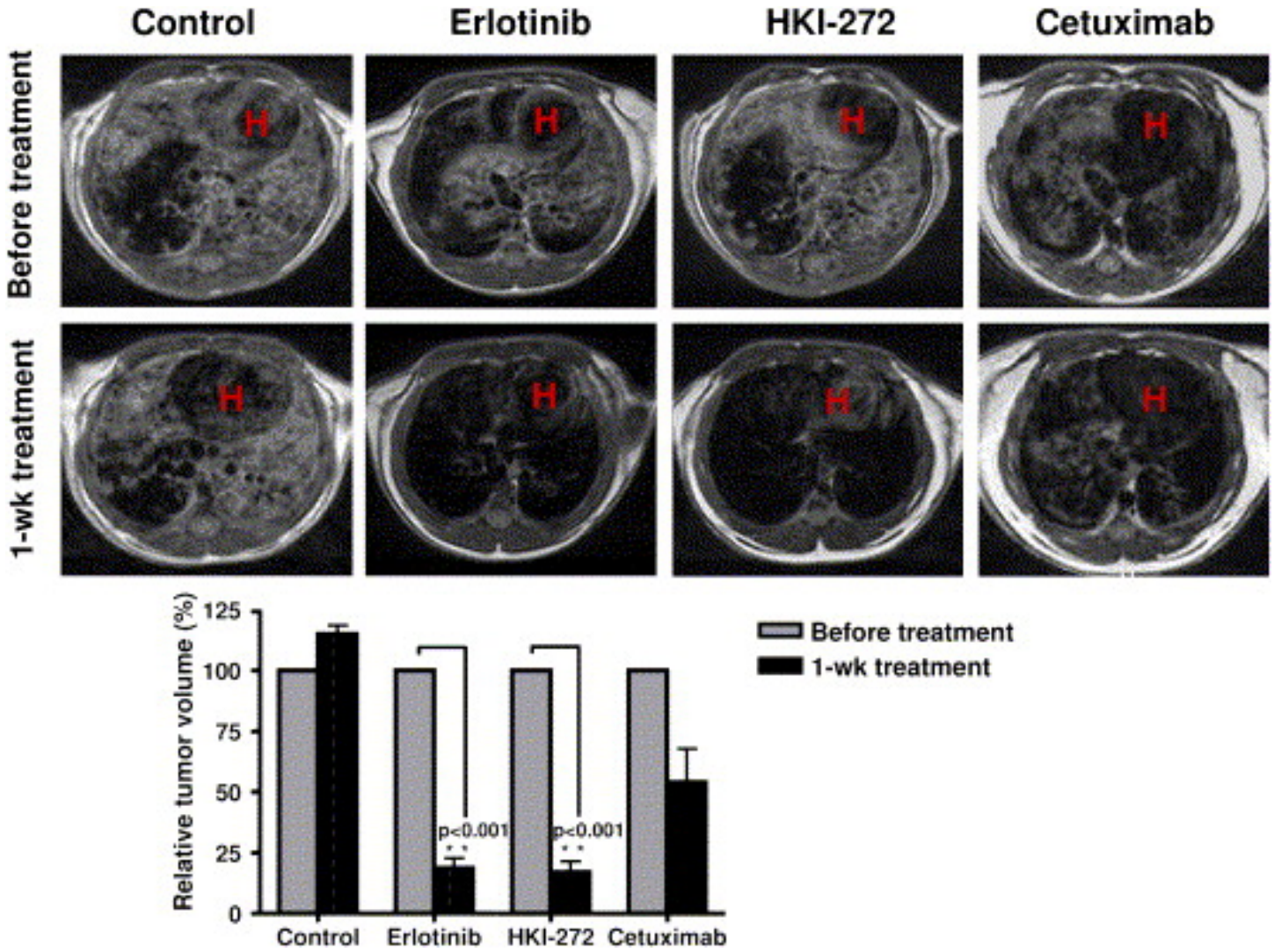
Katerina Politi1,4, Maureen F. Zakowski2, Pang-Dian Fan1, Emily A. Schonfeld1, William Pao3 and Harold E. Varmus1

Human EGFR Mutants induce Lung Cancer Dependent on EGFRm Expression



Hongbin et al, Cancer Cell '06

Anti EGFR Therapies Effective in GEMM

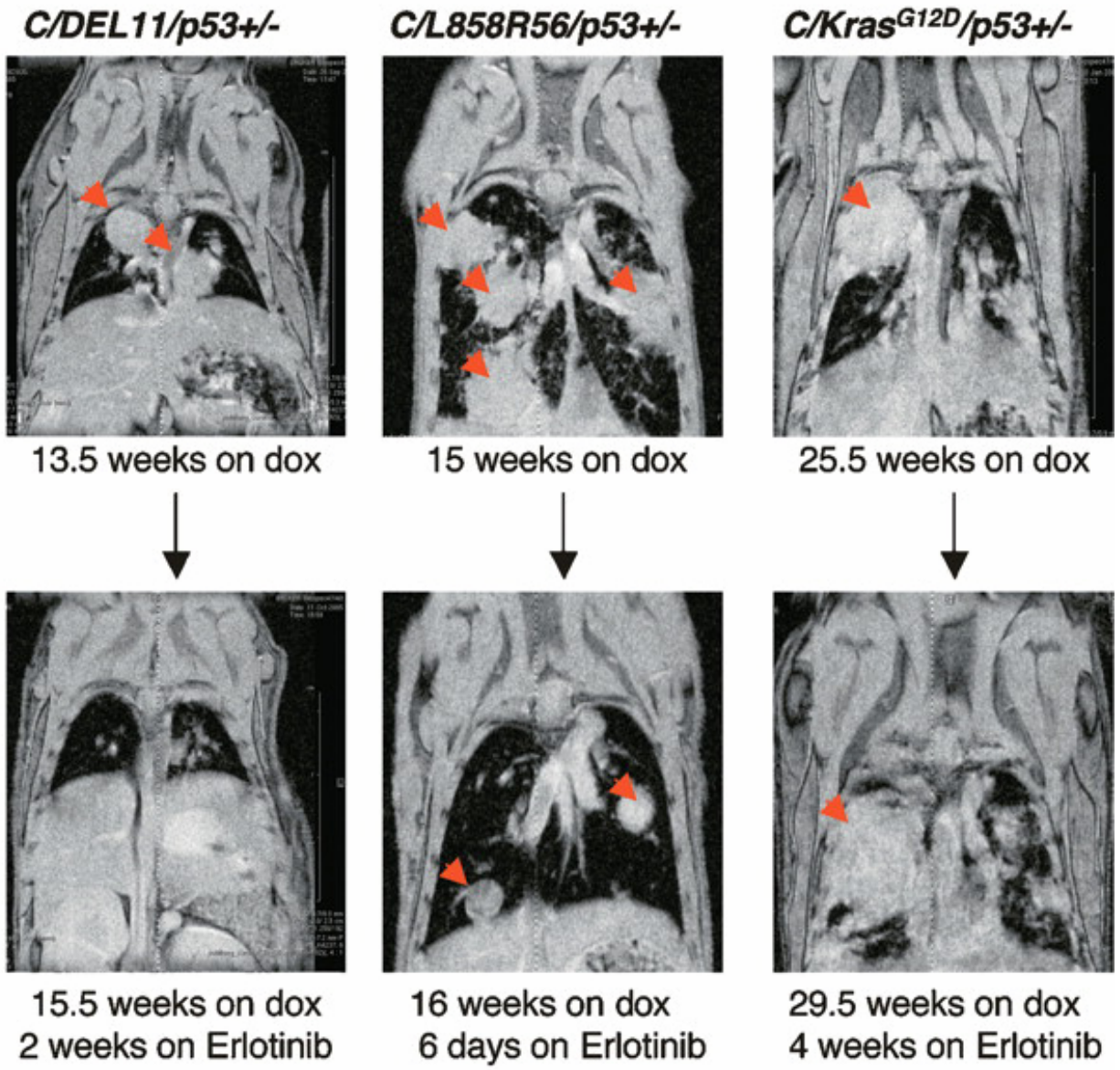


Hongbin et al, Cancer Cell '06

Targeting EGFR in Cancer

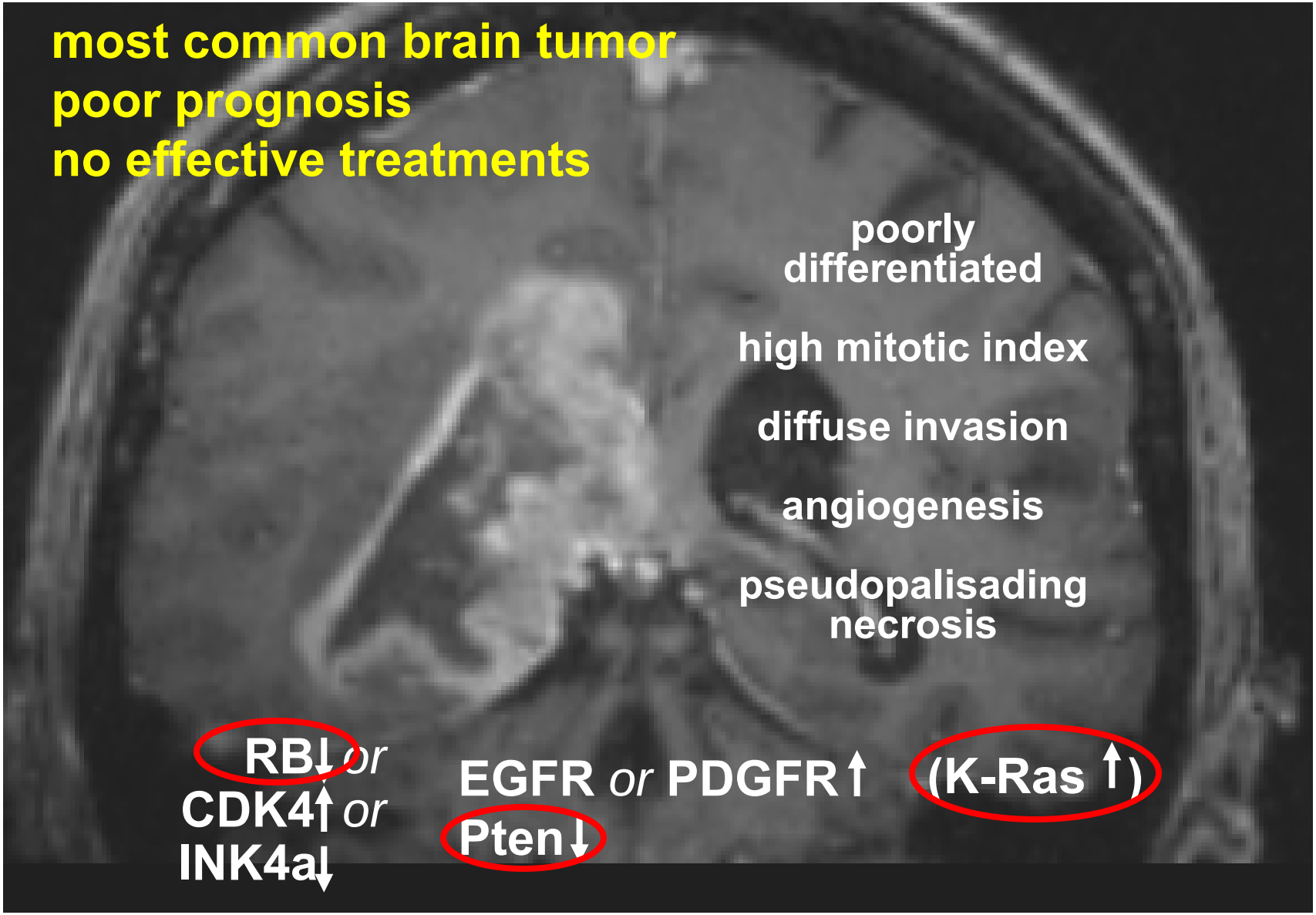
adapted from Ciardiello & Tortora, 2002; courtesy of David Threadgill (UNC)

EGFR Inhibitor Responses Depend on Pathways Disrupted as in Human Trials

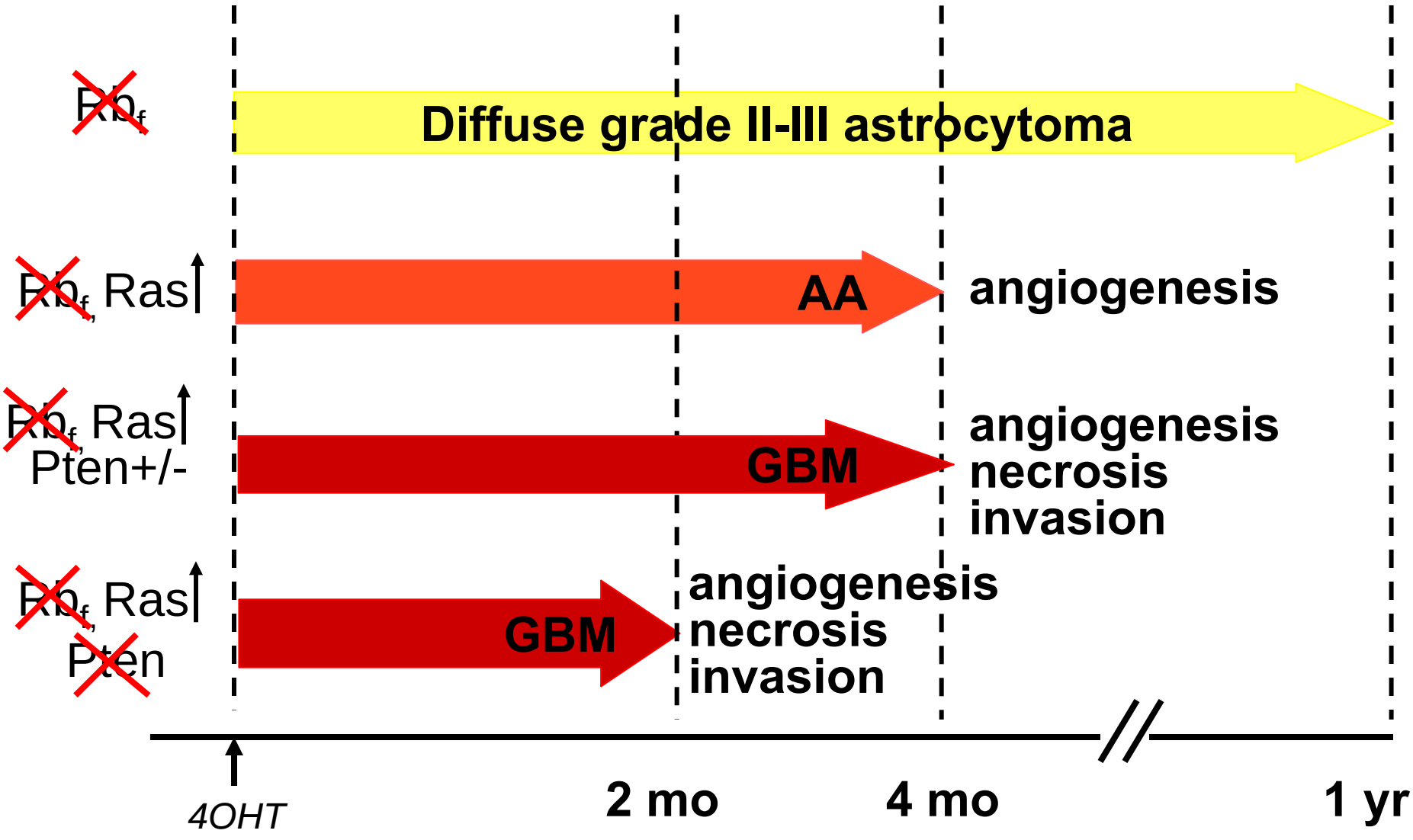


Politi et al, Genes & Dev '06

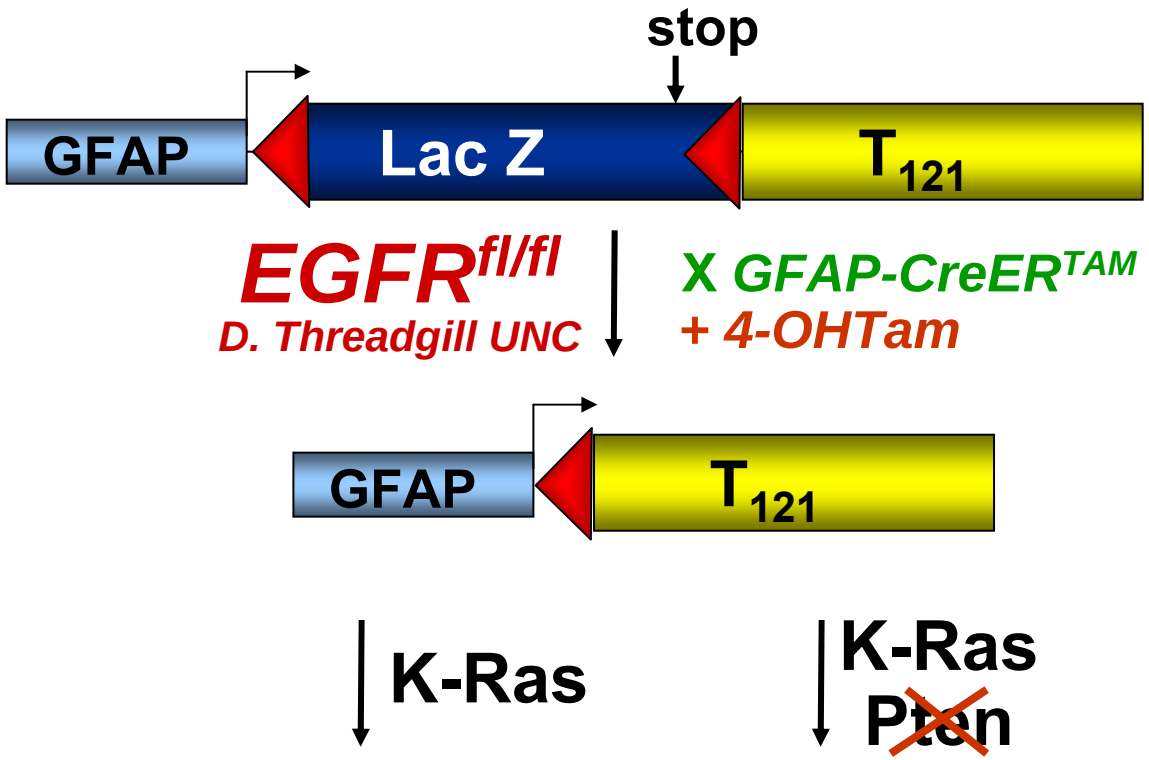
High-grade Astrocytoma



Inducible Astrocytoma Models



Is EGFR Required?

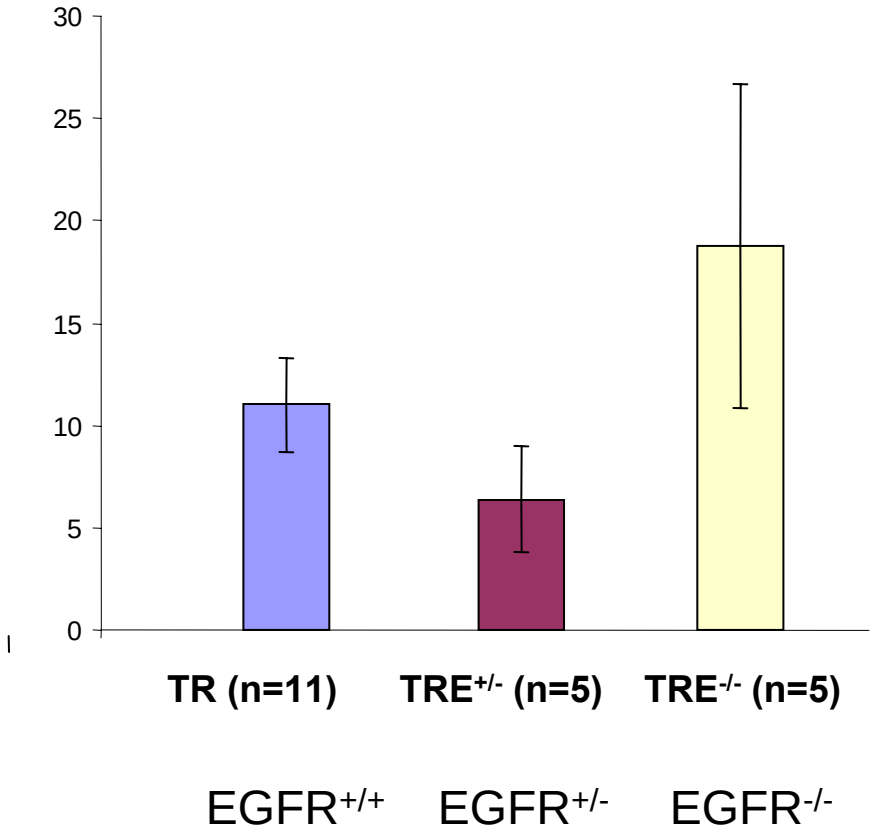


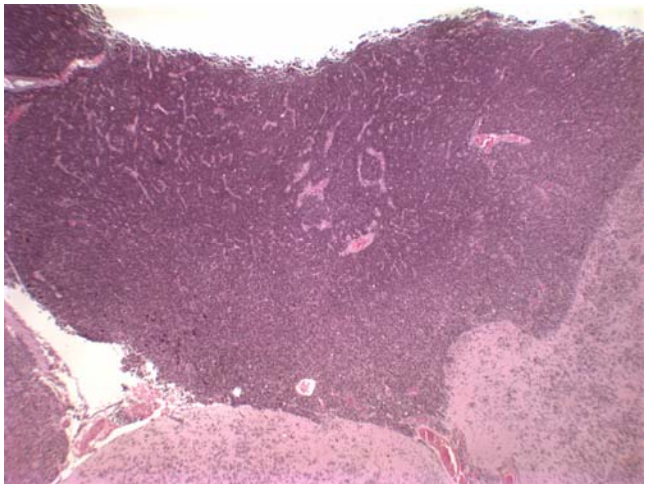
GBM?

Qian Zhang

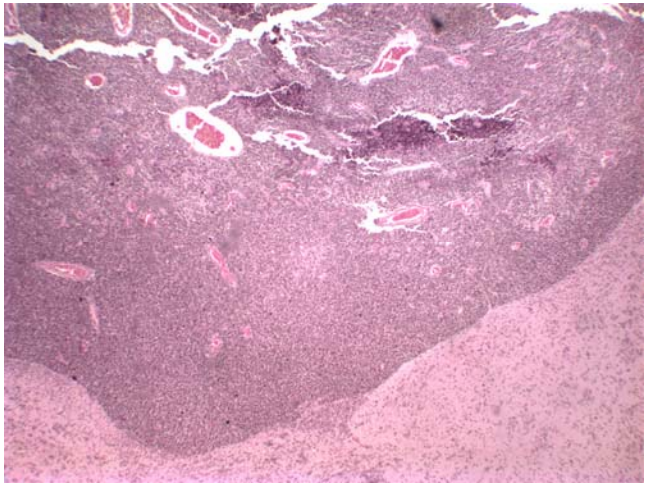
In collaboration with D. Threadgill; UNC

Reduced EGFR, but not Inactivation Inhibits Tumor Growth





T_{121};K-Ras^{G12D};EGFR$^{+/-}$

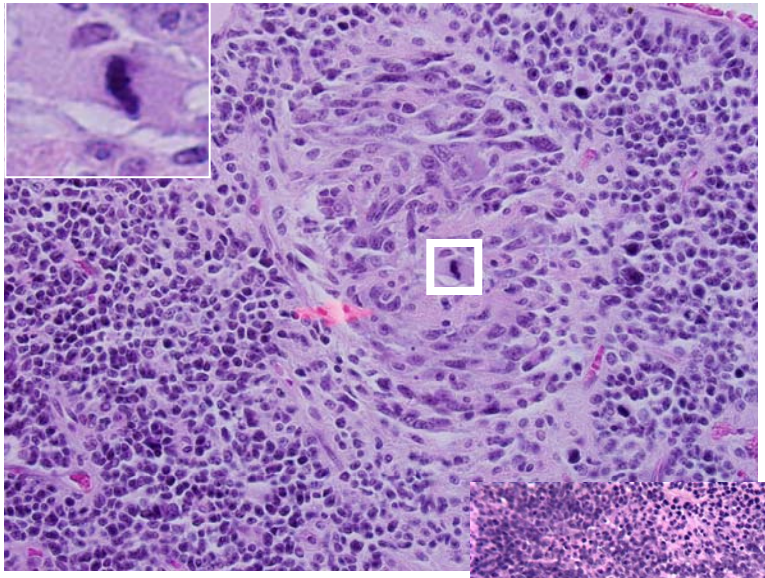


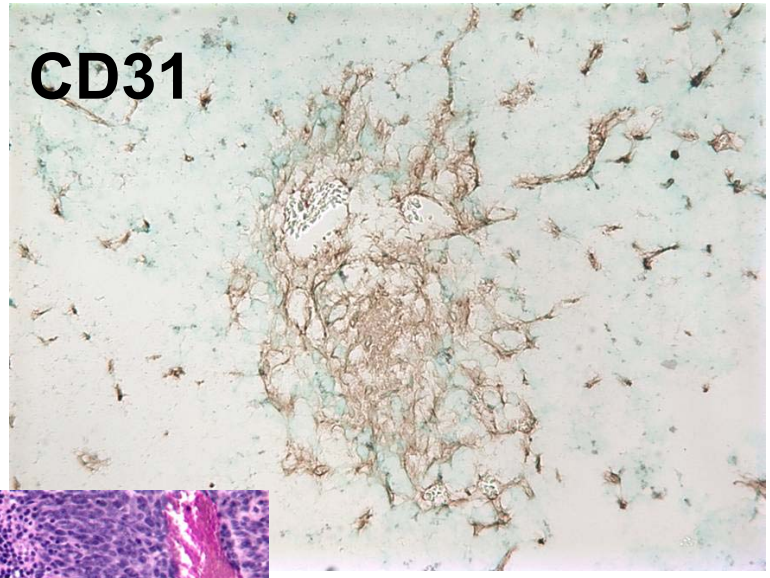
T_{121};K-Ras^{G12D};EGFR$^{-/-}$

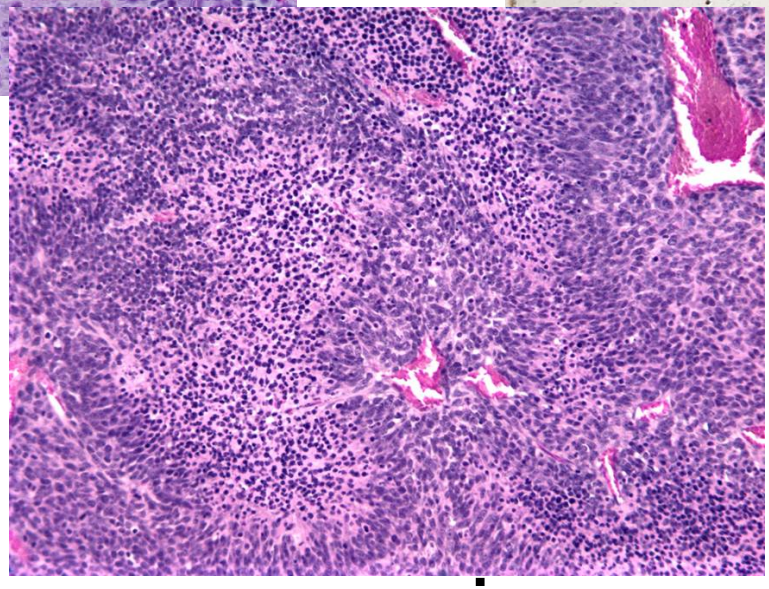
Q. Zhang

EGFR Inactivation Increases Astrocytoma Severity

microvascular proliferation







100μm

necrosis

Q. Zhang

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Mutations in the Epidermal Growth Factor Receptor and in KRAS Are Predictive and Prognostic Indicators in Patients With Non–Small-Cell Lung Cancer Treated With Chemotherapy Alone and in Combination With Erlotinib

David A. Eberhard, Bruce E. Johnson, Lukas C. Amler, Audrey D. Goddard, Sherry L. Heldens, Roy S. Herbst, William L. Ince, Pasi A. Jänne, Thomas Januario, David H. Johnson, Pam Klein, Vincent A. Miller, Michael A. Ostland, David A. Ramies, Dragan Sebisanovic, Jeremy A. Stinson, Yu R. Zhang, Somasekar Seshagiri, and Kenneth J. Hillan

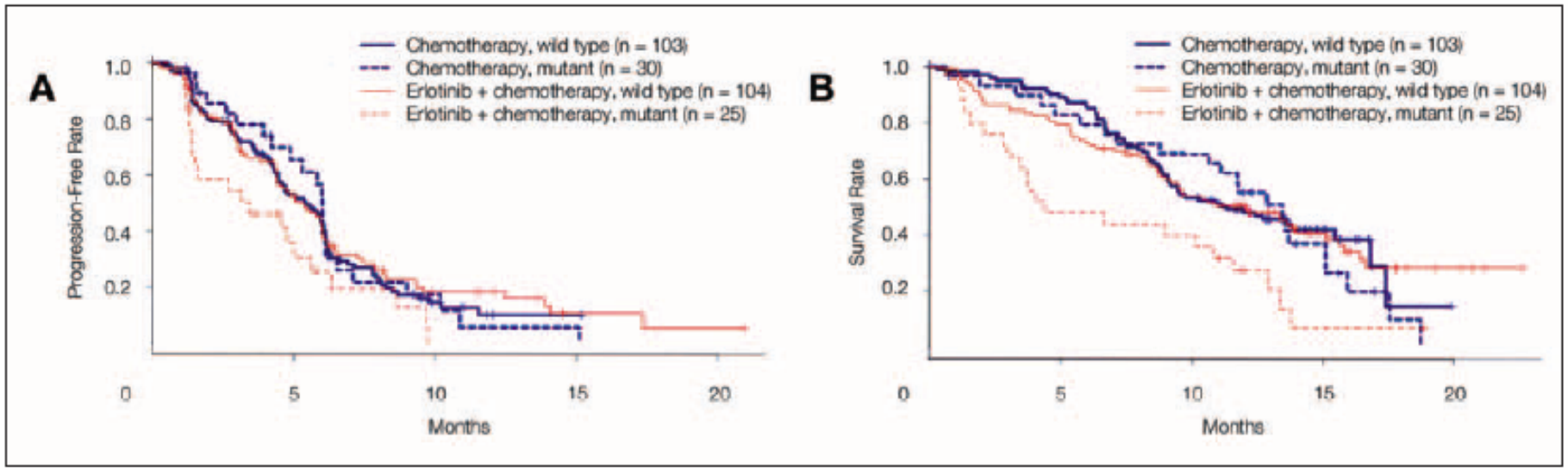
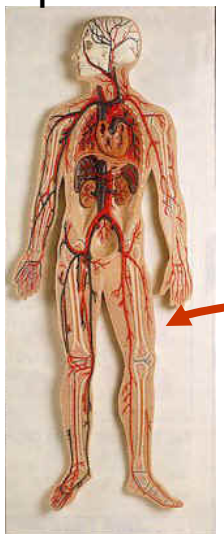


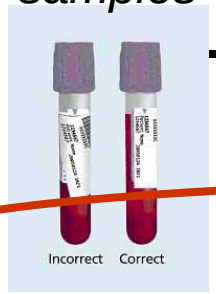
Fig 2. Kaplan-Meier curves by treatment received and KRAS-mutation status. Two KRAS-wild-type patients had missing values for treatment received and were excluded from Figures 2A and 2B. The tick marks indicate patients who were still alive at the time of the analyses or who were censored. All *P* values refer to log-rank tests. (A) Time to progression, by treatment received and KRAS-mutation status: $P = .03$ for erlotinib plus chemotherapy versus chemotherapy alone among patients with KRAS-mutant tumors (dashed lines) and $P = .668$ for erlotinib plus chemotherapy versus chemotherapy alone among patients with wild-type tumors (solid lines). (B) Survival, by treatment received and KRAS-mutation status: $P = .019$ for erlotinib plus chemotherapy versus chemotherapy alone among patients with KRAS-mutant tumors (dashed lines) and $P = .792$ for erlotinib plus chemotherapy versus chemotherapy alone among patients with wild-type tumors (solid lines).

Predictive Preclinical Models Revolutionize Clinical Development

patient



diseased samples

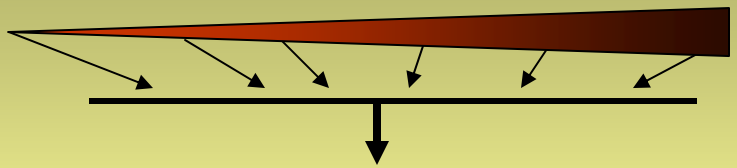


assess abnormalities

programmed disease in preclinical model

No disease

disease initiation and stages



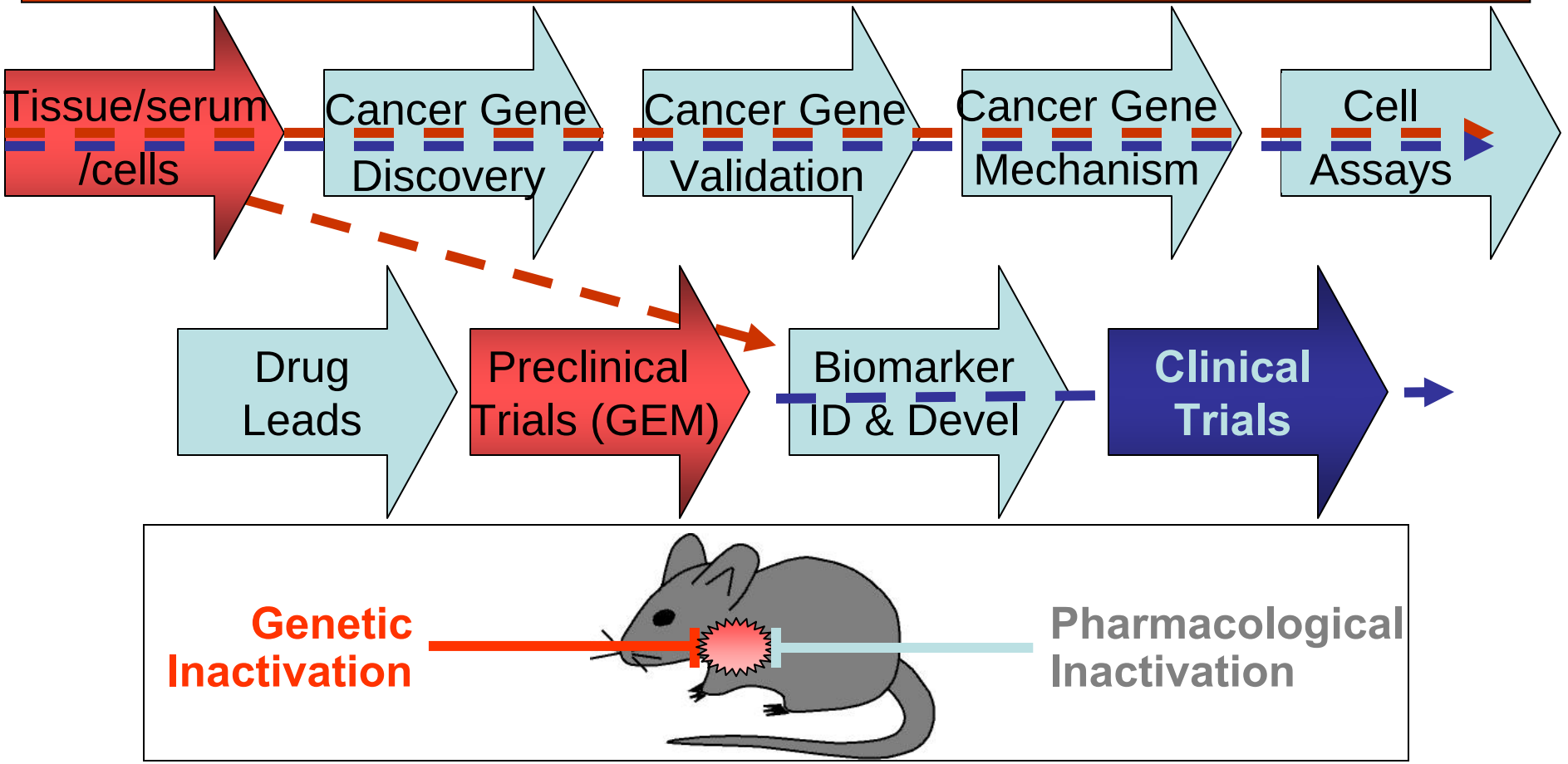
Full disease

•Discover disease biomarkers (early detection, monitor treatment)

•Identify new drug targets

•Predict and evaluate drug efficacy

GEM Models in Cancer Drug Discovery/Development



➔ *Identify and validate leads to move into Phase I*
➔ *Identify surrogates of drug efficacy and specificity*
➔ *Identify biomarkers (early detection; monitor therapy)*

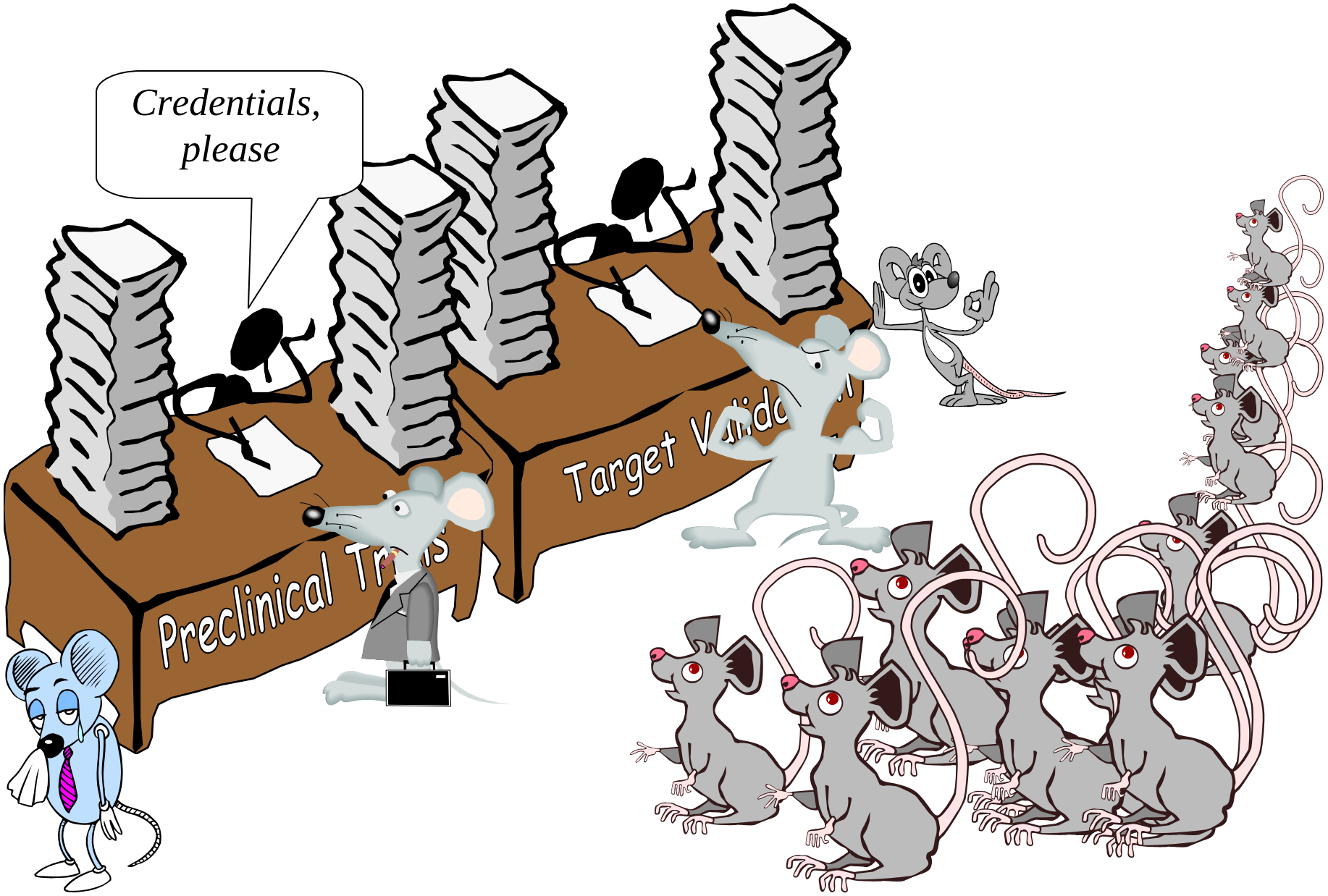
GEM utilization Human studies

OK, so tell me *which* models are "valid" models of human cancer?

Because cancers have many different traits, and mice are not humans, models should often be assessed trait by trait ("credentialed")

NCI's Mouse Models of Human Cancer Consortium

“Credentialing” Mouse Models: Many Traits Define a Cancer



Why Have Spontaneous Cancer Models *not* been Incorporated into Drug Discovery Preclinical Assessment?

DuPont

FDA

expensive compared to xenografts

old dogs and new tricks

academic-private technology transfer

requires major expertise in cancer mechanisms, GEMM, genetics *and* drug development

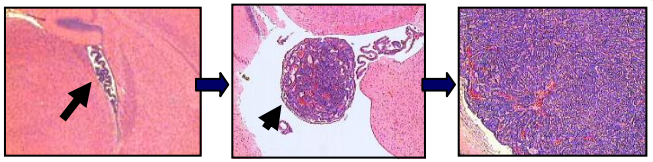
NCI-CAPR

Center for Advanced Preclinical Studies

Disease Models at the Frontiers of Basic and Clinical Discovery

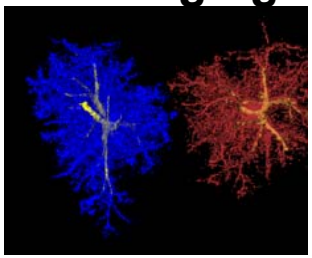
Therapeutic development

Diagnosis

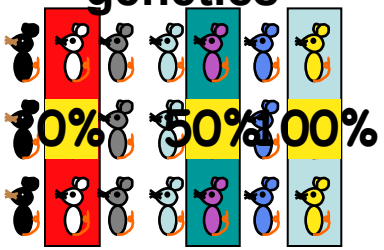


histopathology, physiology

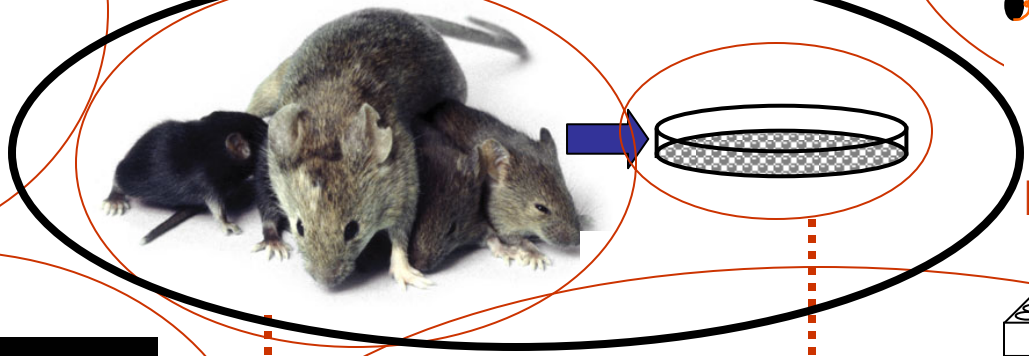
cell biology & imaging

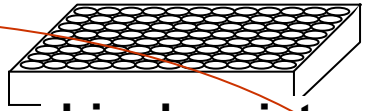


complex genetics

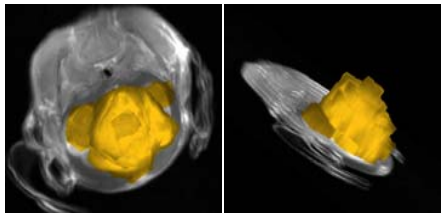


Risk assessment
Therapy response
Pharmacogenomics



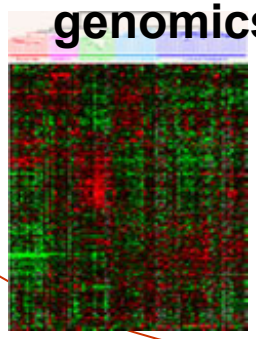


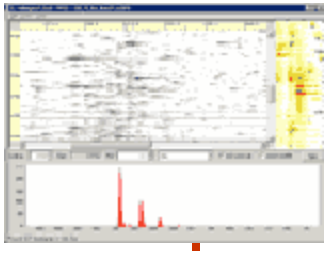
biochemistry genomics



animal imaging

genomics,proteomics





Diagnosis
Monitor treatment

Target validation
Therapeutic testing

HT cell-based screens

Target discovery
Diagnosis
Early detection
Monitor treatment