

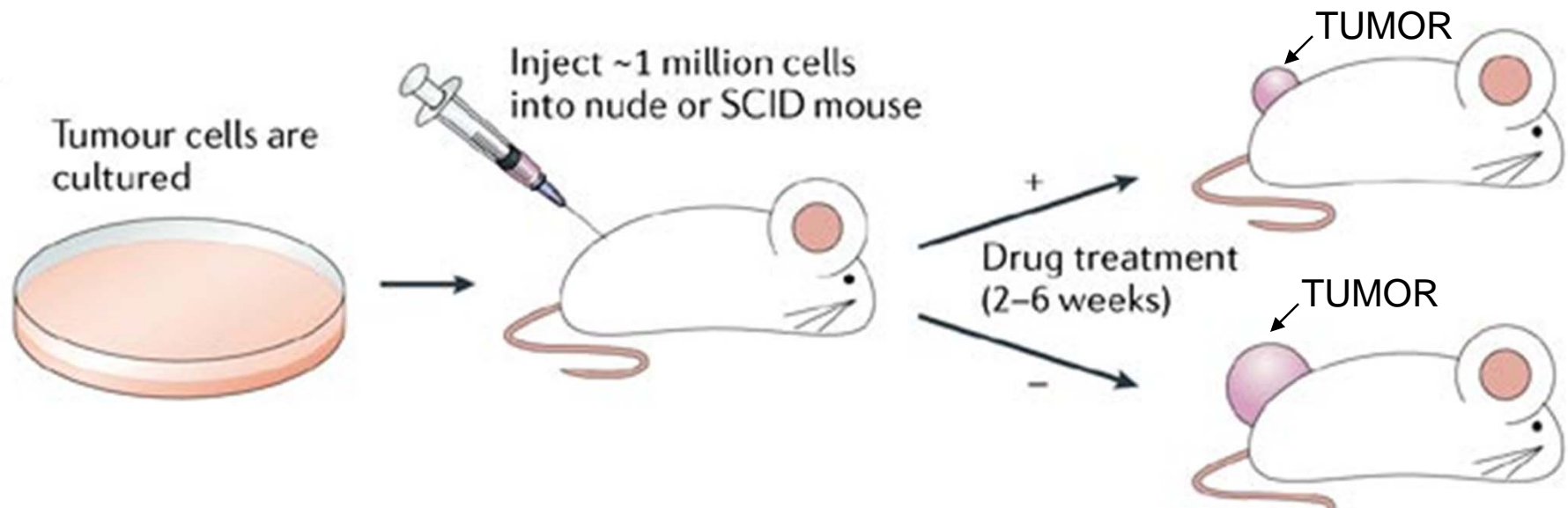
Current Cancer Drug Development

| | Oncology compounds | | All compounds | |
|---------------------|--------------------|--------------|-----------------|--------------|
| | Number entering | Success rate | Number entering | Success rate |
| Preclinical testing | | | | |
| ↓ | | | | |
| Phase I | 100 | | 100 | |
| ↓ | | 61% | | 63% |
| Phase II | 61 | | 63 | |
| ↓ | | 28% | | 40% |
| Phase III | 17 | | 25 | |
| ↓ | | 43% | | 58% |
| Registration | 7 | | 15 | |
| ↓ | | 70% | | 77% |
| Approval | 5 | | 11 | |

.....at an average cost of \$1B per drug

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

Work ~~Hor~~ Mouse in Cancer Drug Development



(xenograft: cells from one species transplanted into another)

in cancer drug testing: subcutaneous injection of established human cancer cell lines into immunocompromized mice

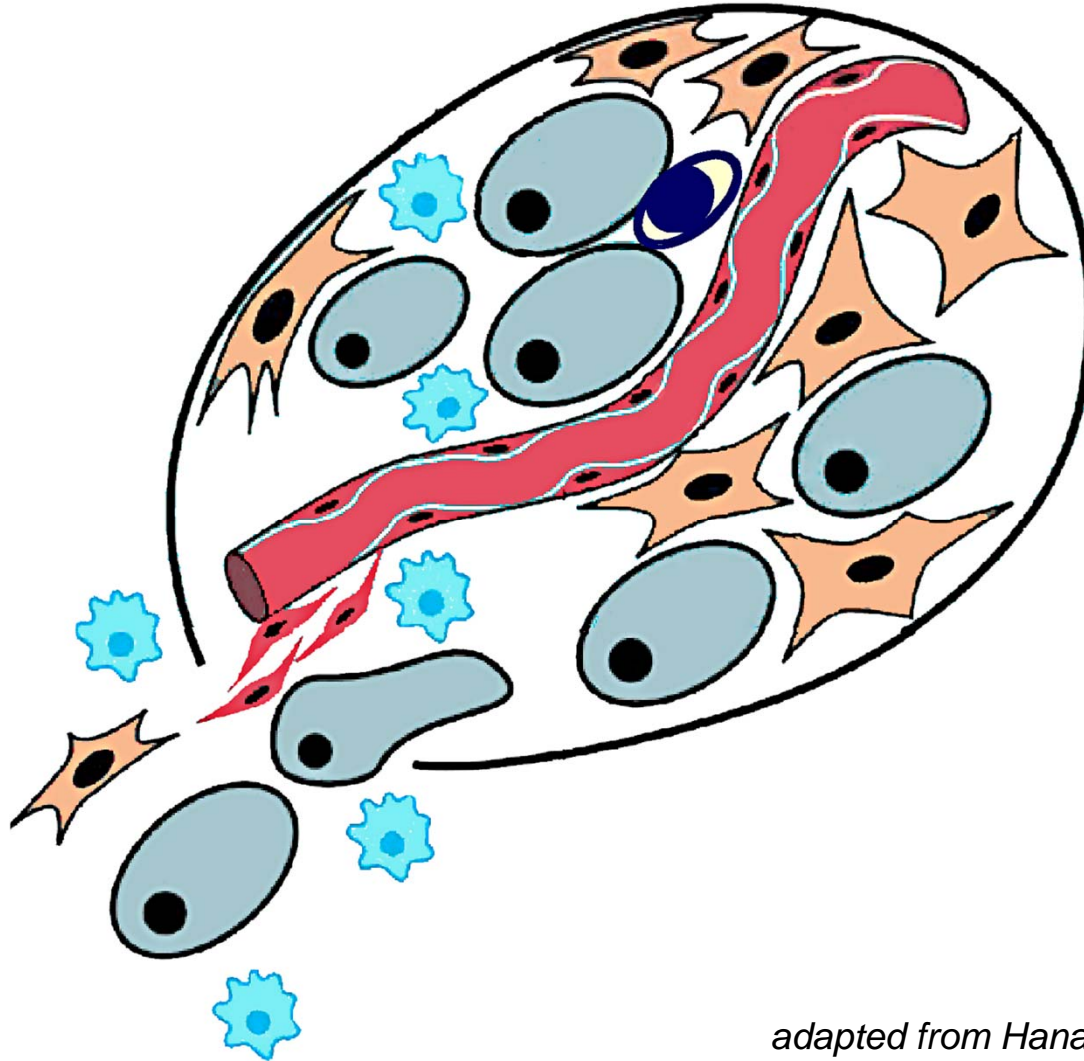
*adapted from: Sharpless and DePinho;
Nature Reviews Drug Discovery '06*

“We’ve cured plenty of cancers in mice, but only very few in humans....

The mouse is not a good model”

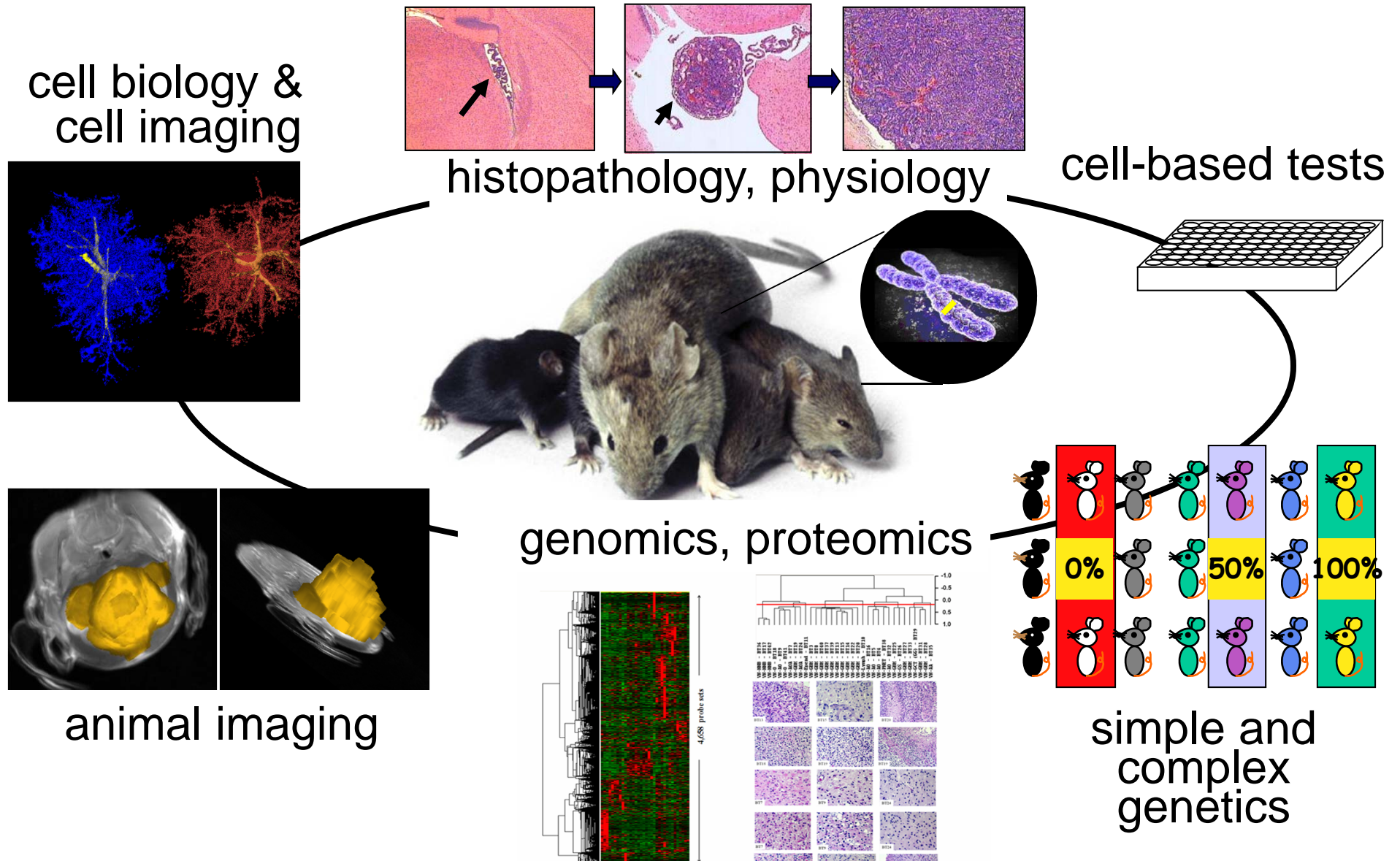
many reasonable people

Cancer is a Dynamic and Evolutionary Process

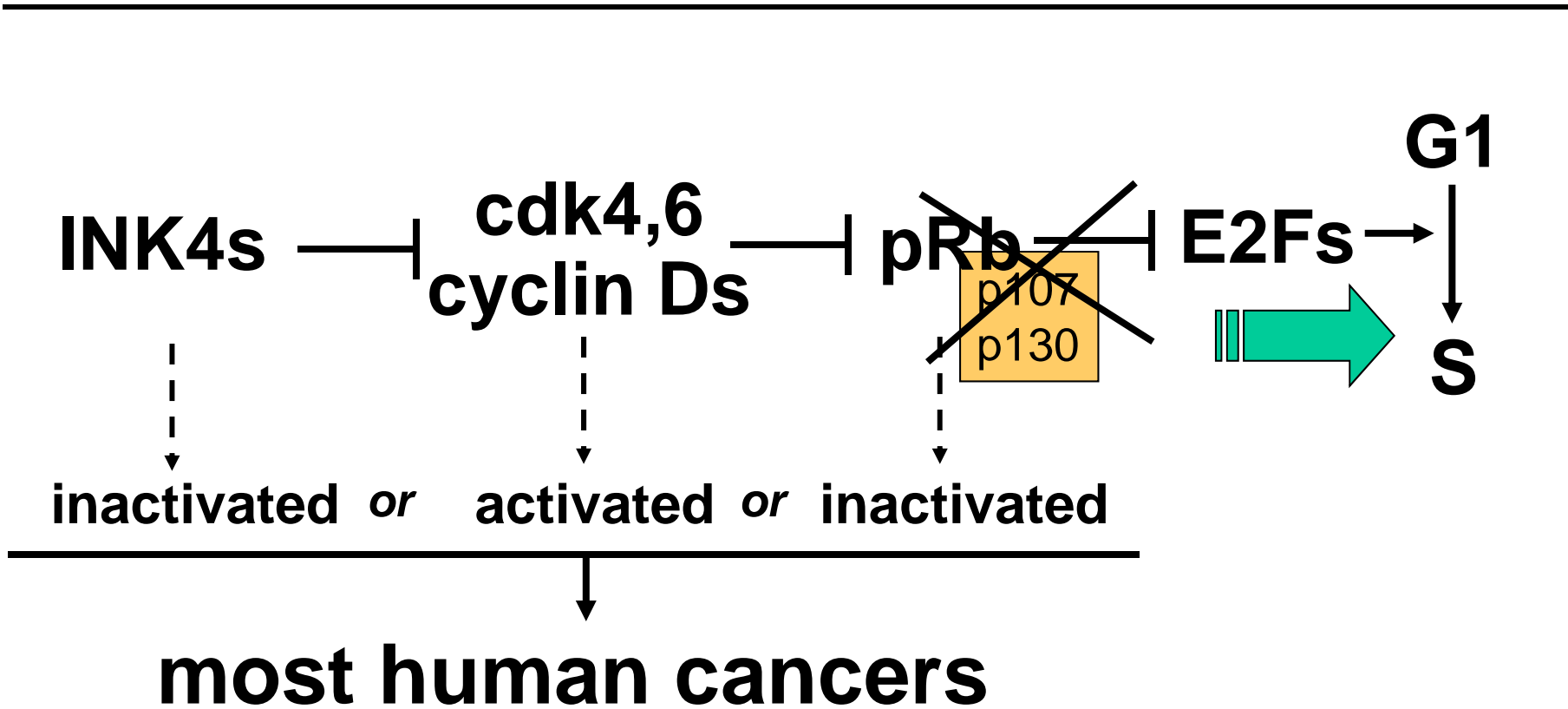


adapted from Hanahan and Weinberg, Cell 2000

Mutant Mice in Integrated Disease Analyses: Two Decades of Development

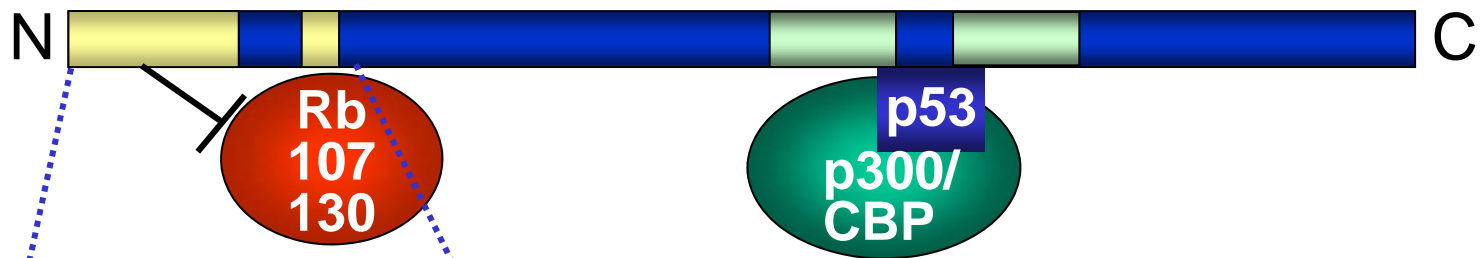


Rb Pathway Commonly Aberrant in Human Cancers



A Tool for Cell-Specific Inactivation of pRb Function

SV40 T Ag

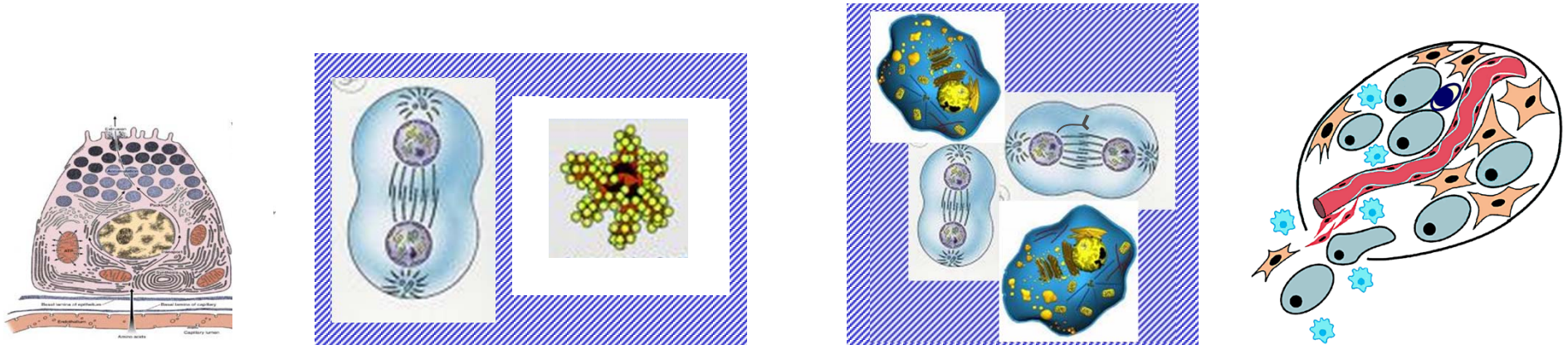


T₁₂₁



pRb, p107, p130
Inactivation

Cancer Evolution as Deciphered in GEM



normal cell



proliferation + cell death



loss of many biological controls



progression

aberrant signals to proliferate

evolutionary selection for impaired cell death

evolution/selection

~~pRb~~

~~p53~~

or

~~Pten~~

common among most cell types

cell type/tissue specific

Cancer models

*Choroid plexus
Mammary/breast
Prostate
Ovarian
Astrocytoma*

High-grade Astrocytoma

Grade III: anaplastic astrocytoma

Grade IV: glioblastoma

most common brain tumors

poor prognosis

no effective treatments

poorly
differentiated

high mitotic index

diffuse invasion

angiogenesis

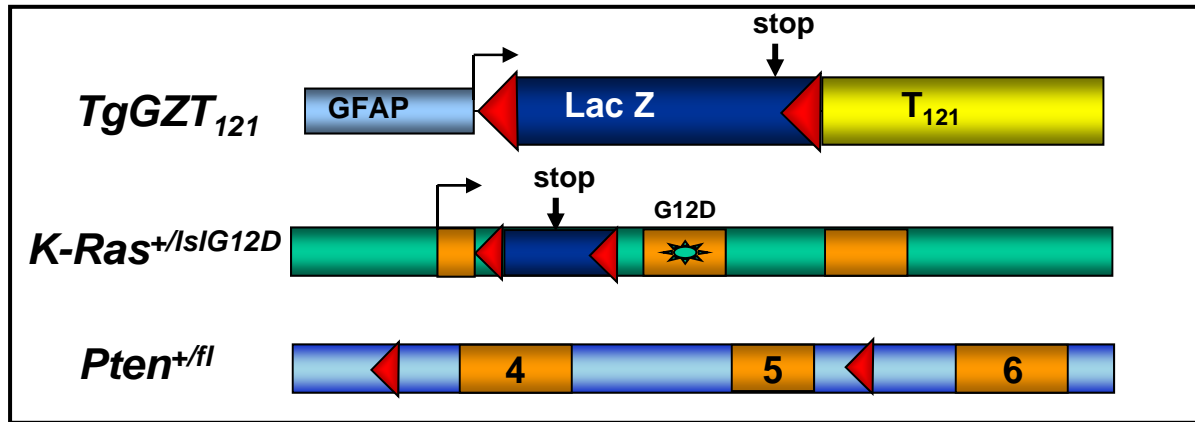
pseudopalisading
necrosis

RBI↓ or
CDK4↑ or
INK4a↓

EGFR or **PDGFR↑**
Pten↓

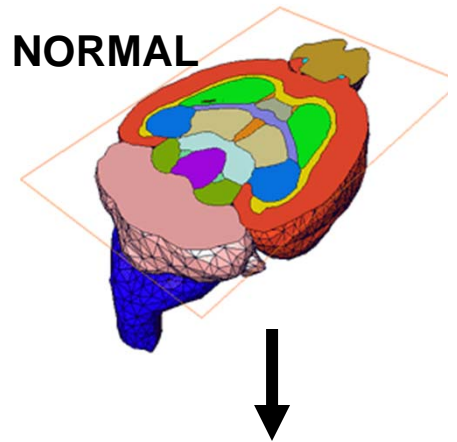
(K-Ras ↑)

Astrocytoma Model Engineering

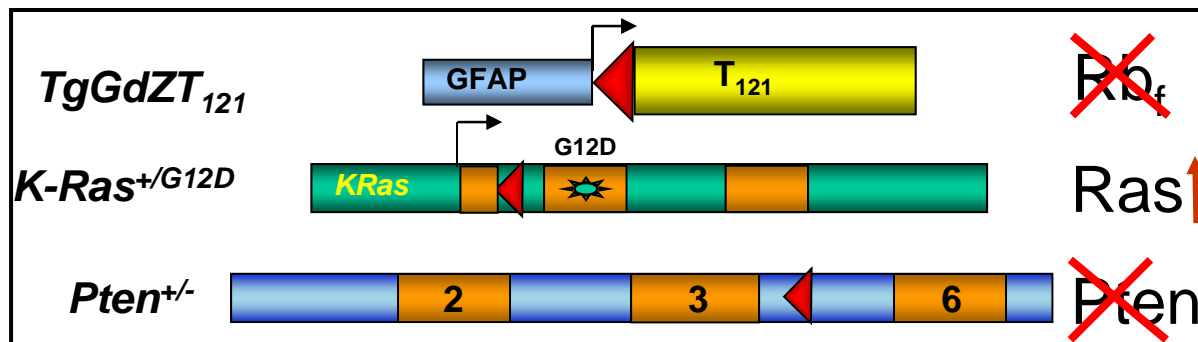


mouse genotype

NORMAL

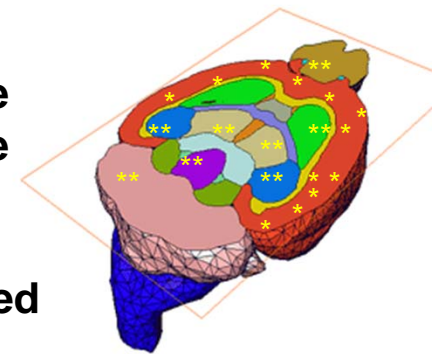


\times *GFAP-CreER*^{TAM} + 4-OHTam
 (K. McCarthy UNC)



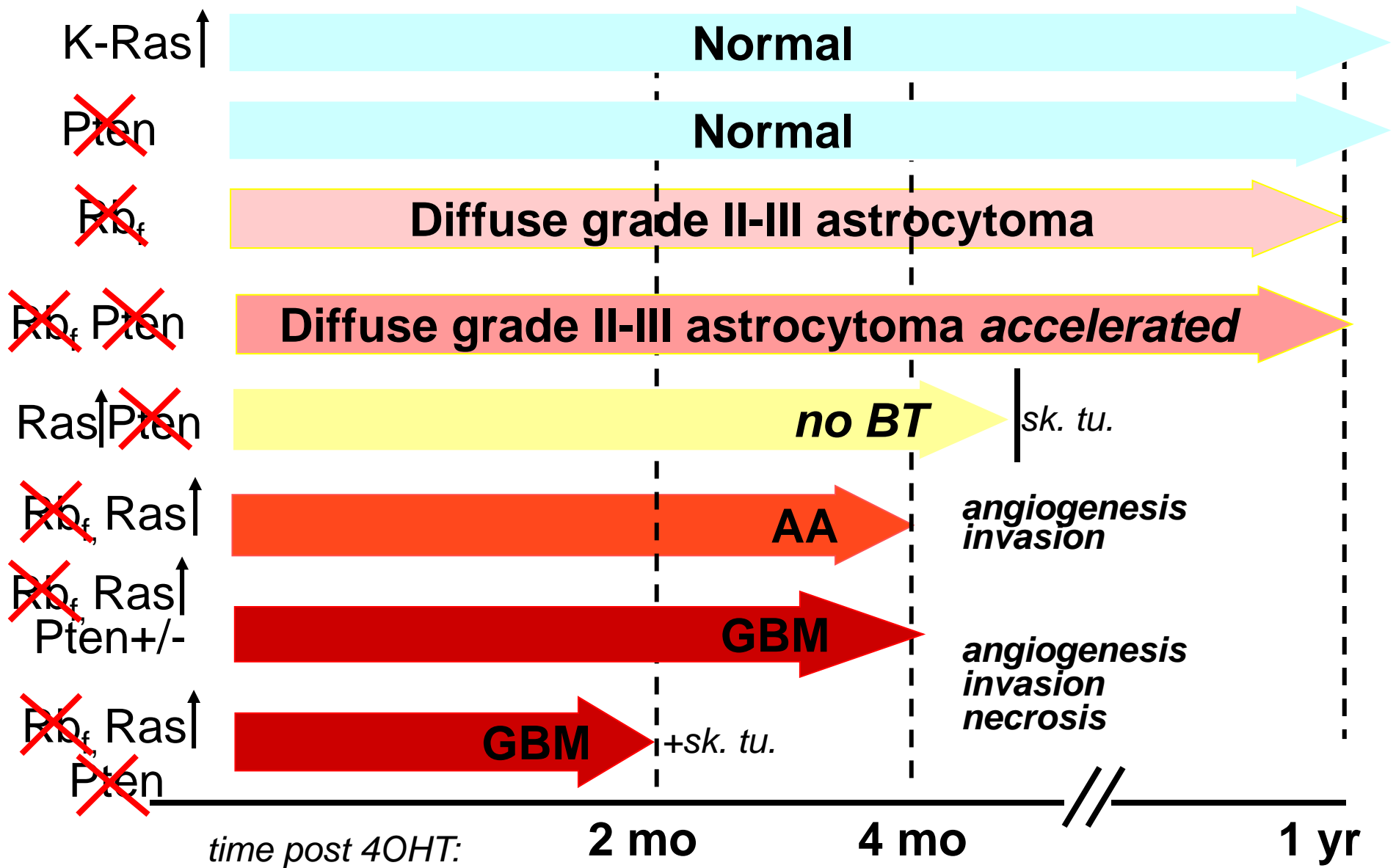
*adult astrocyte genotype

Cancer-associated

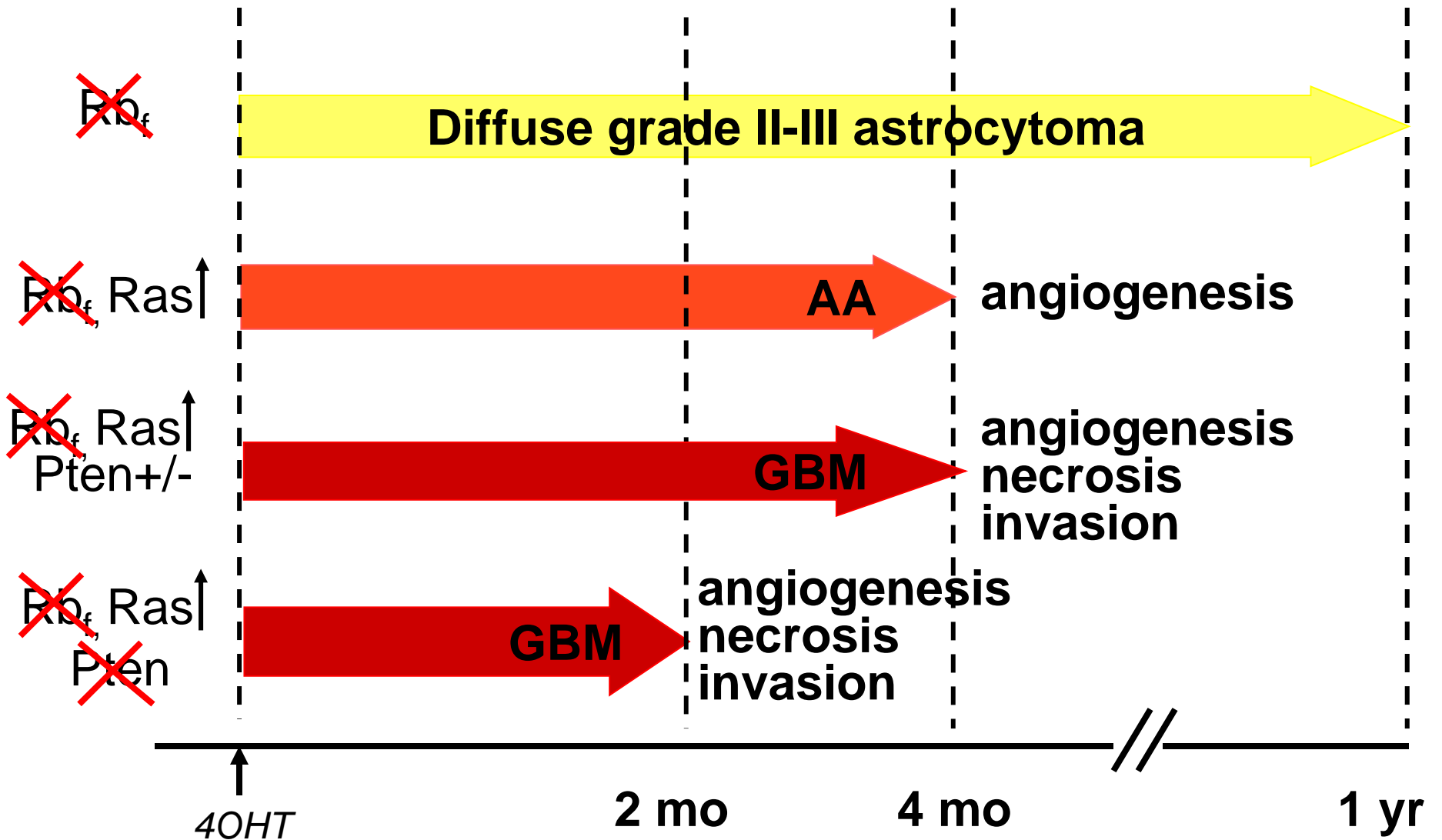


Qian Zhang

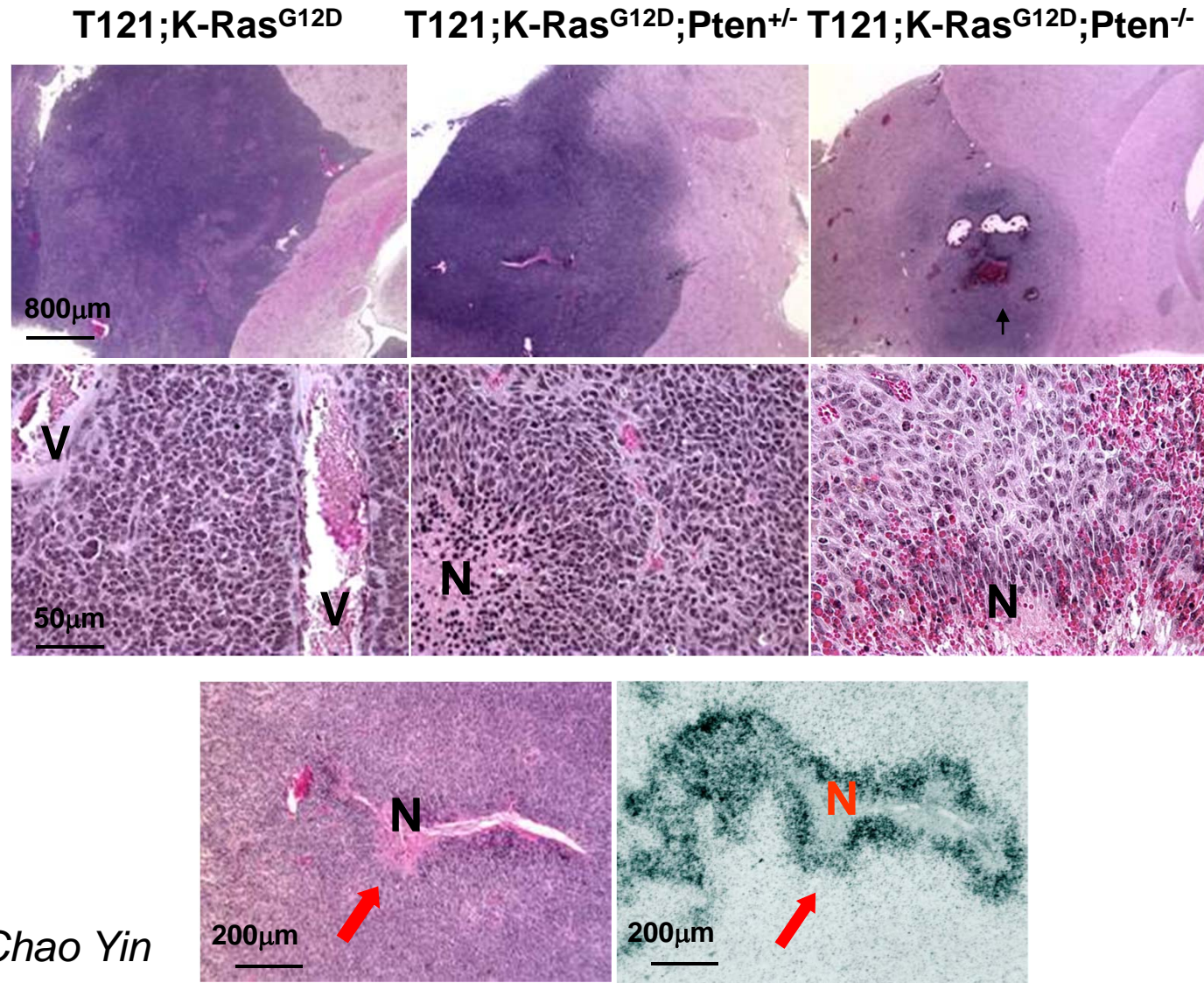
Inducible Astrocytoma Model Assessment



Inducible Astrocytoma Models

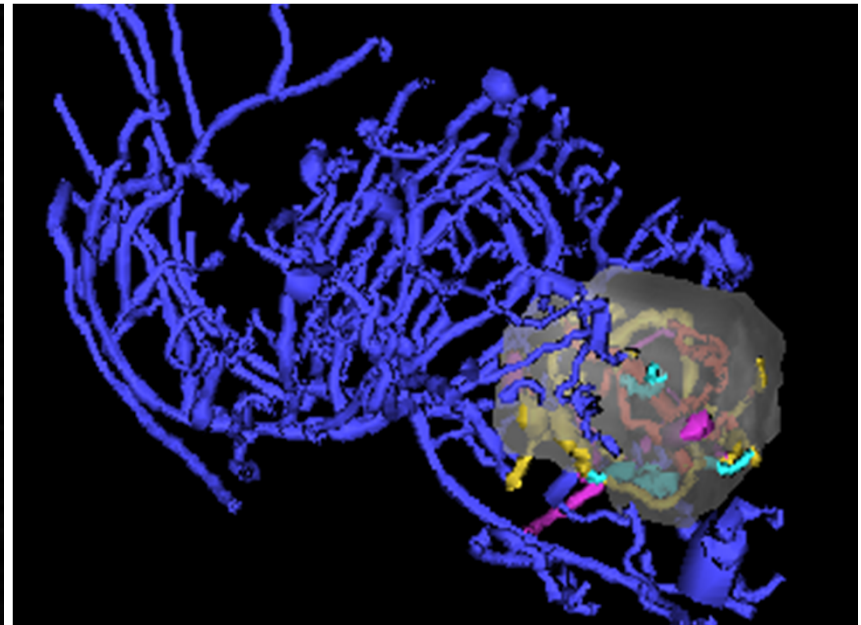
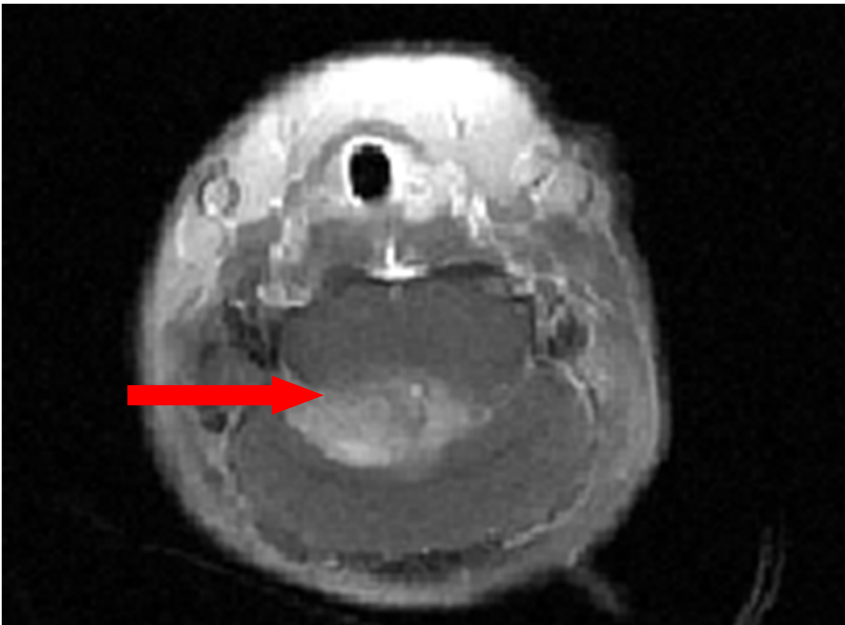


GEM Astrocytoma: Human Disease Properties



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

Malignant Vessels in GEM-GBM

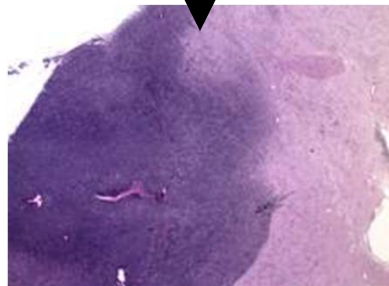
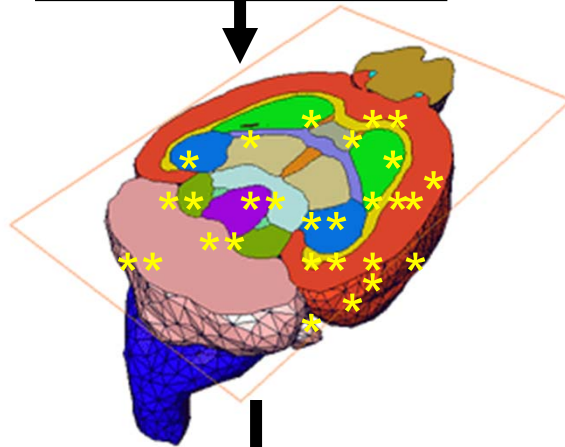


Bullitt, Lin, Van Dyke UNC

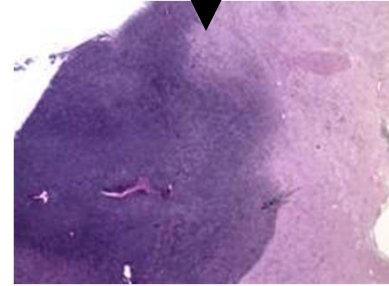
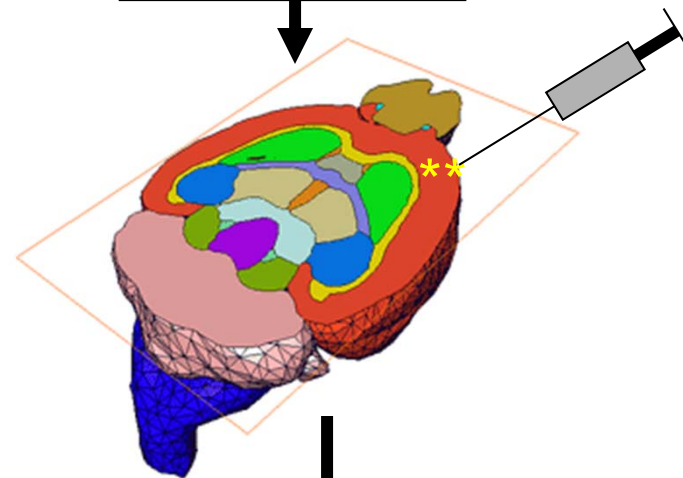
Scheme for Integrated Disease Analysis

inducible cell-type-targeted events 

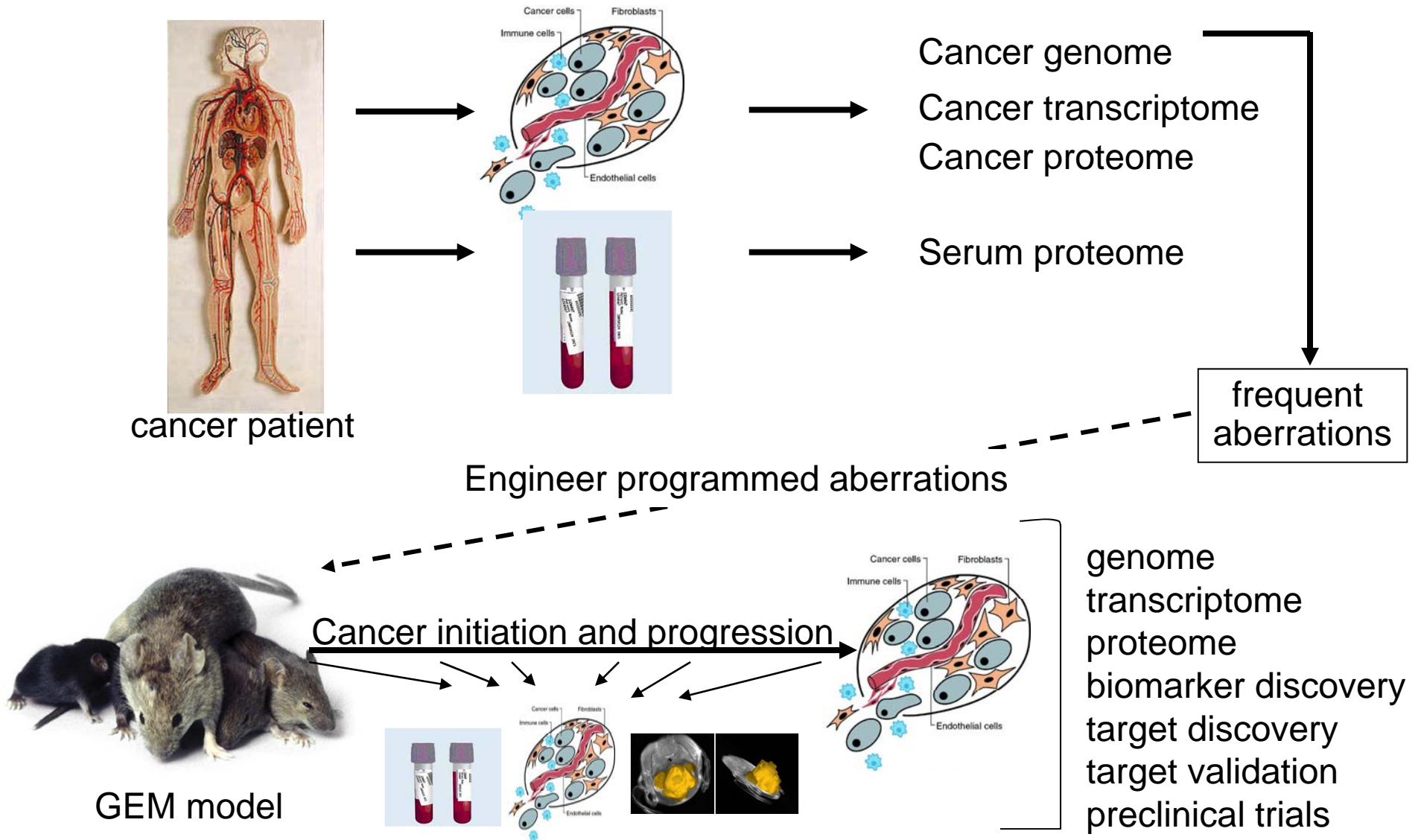
widespread
induction



focal
induction



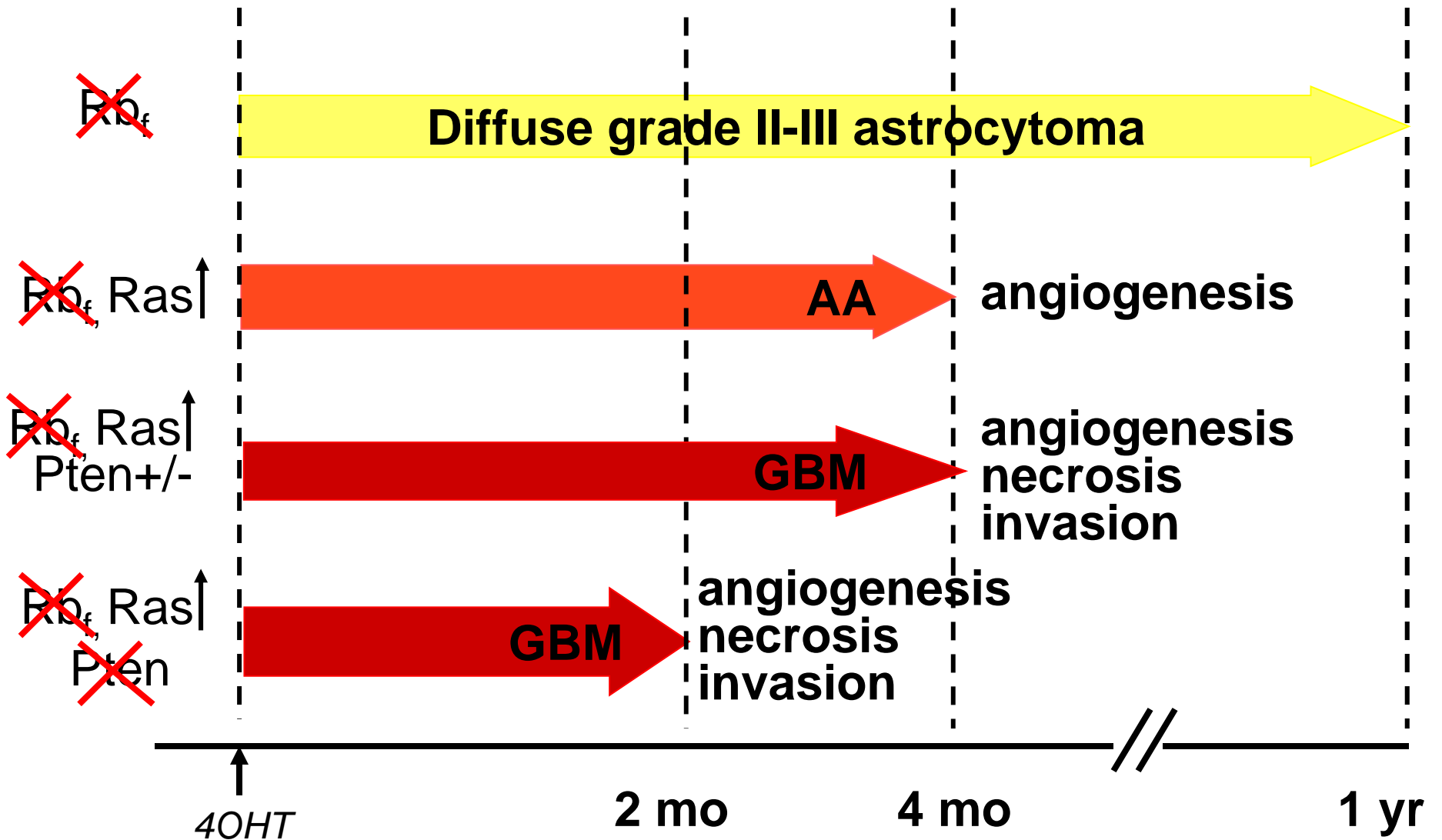
GEM in Clinical Translation



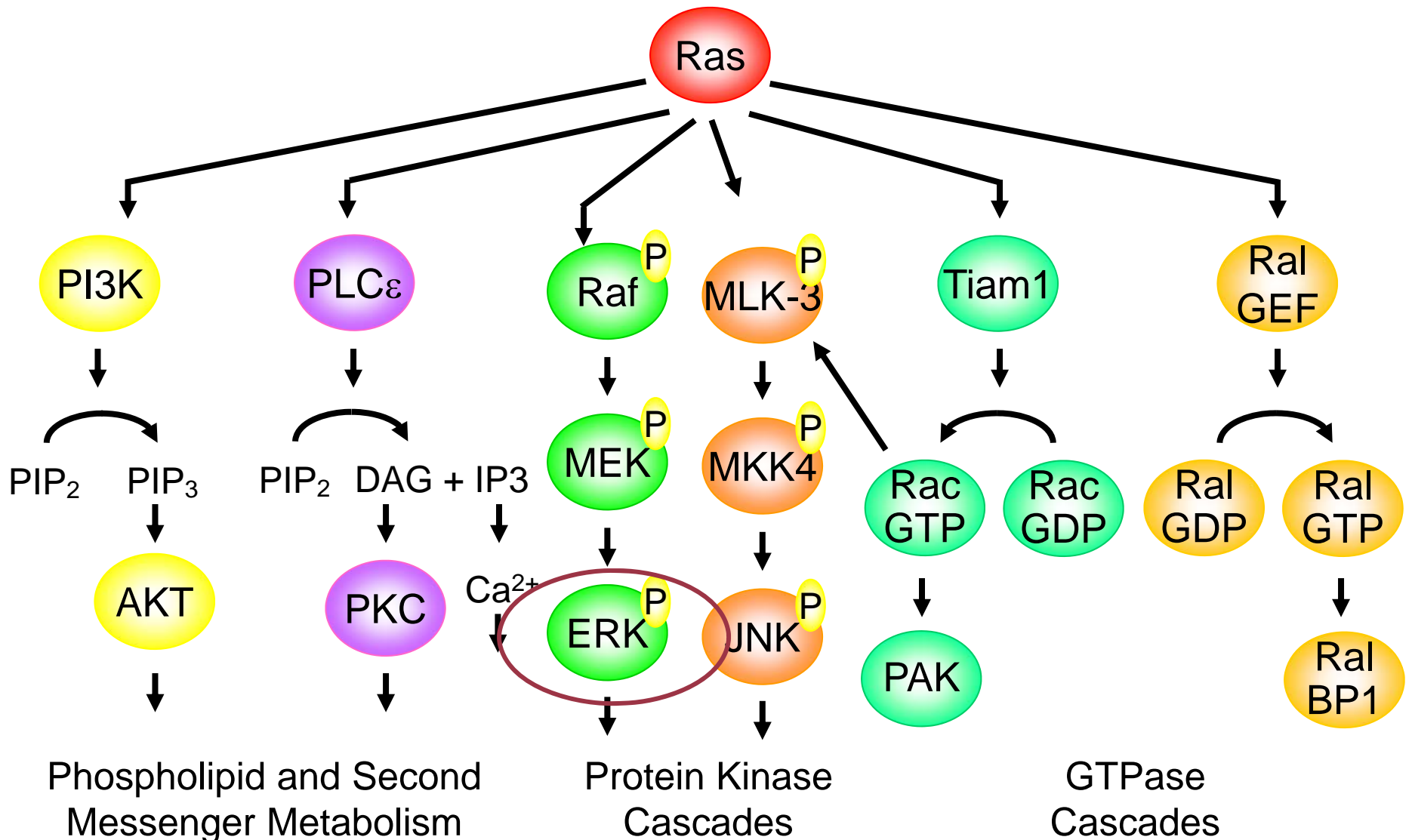
In Vivo Pathway Analyses:

What are the ***Critical*** Cause-
Effect Relationships ***in the***
Context of Natural
Microenvironment?

Inducible Astrocytoma Models

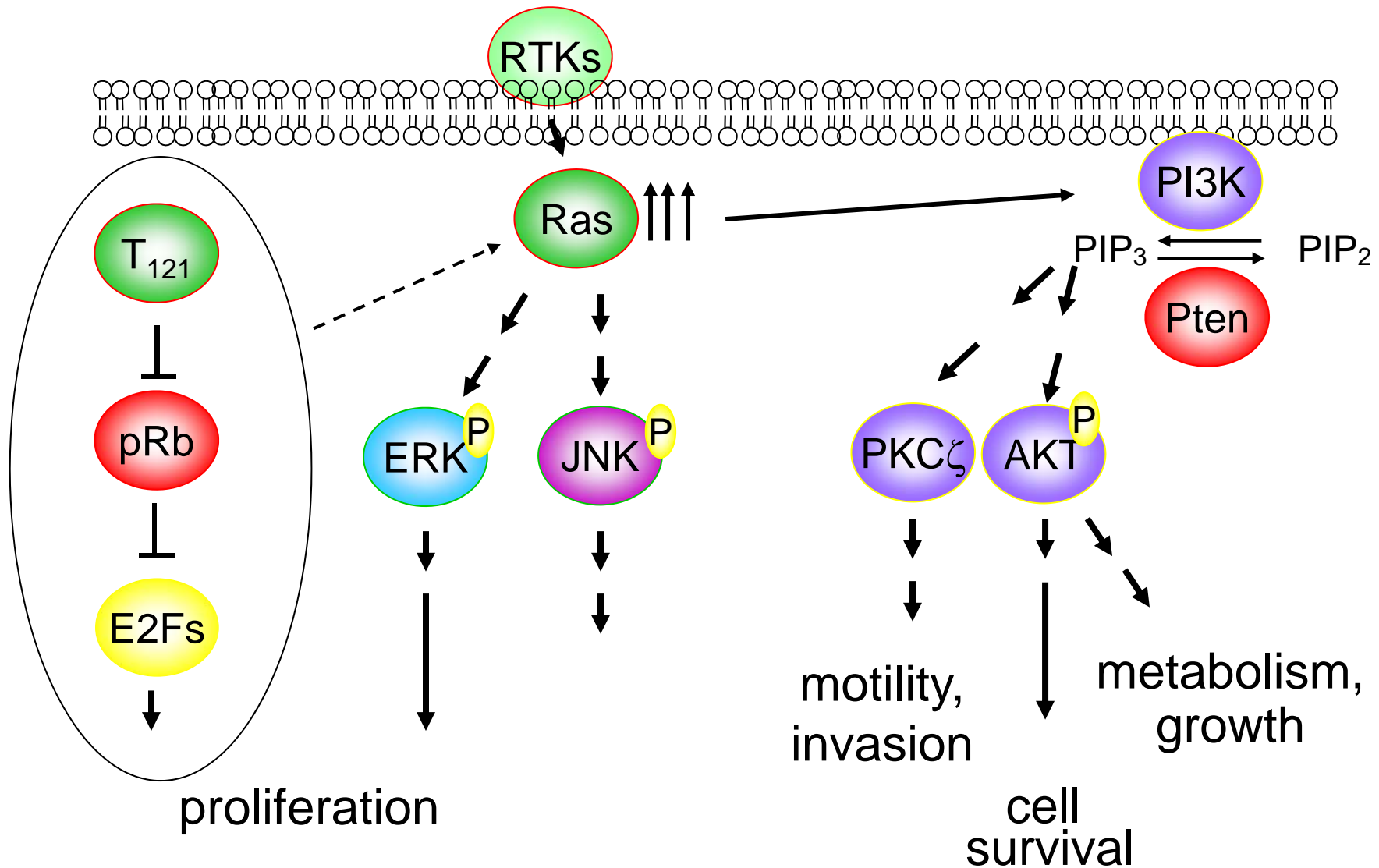


Ras activates multiple effector signaling pathways

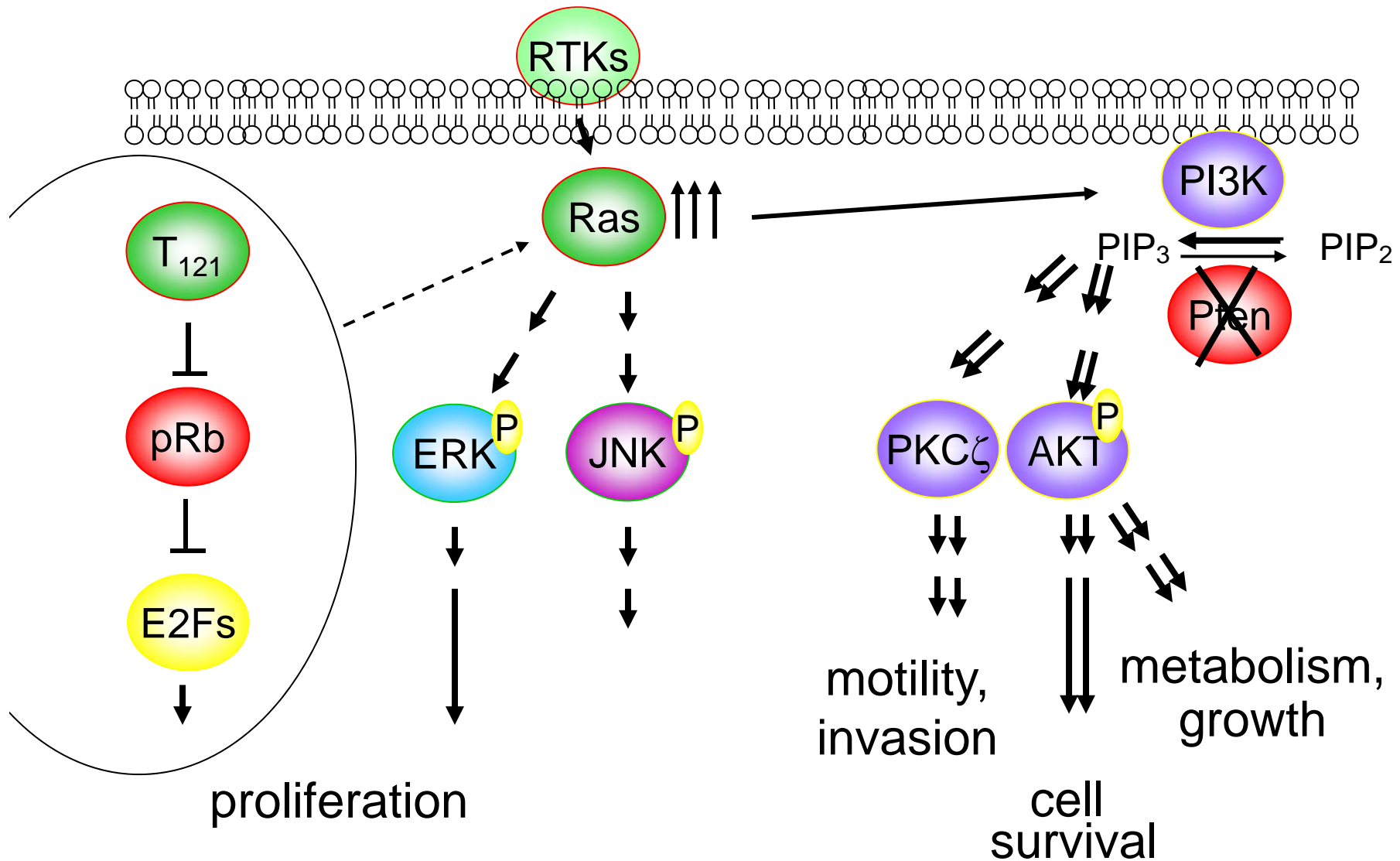


courtesy of Channing Der, UNC

Pathways to Astrocytoma



Pathways to Astrocytoma

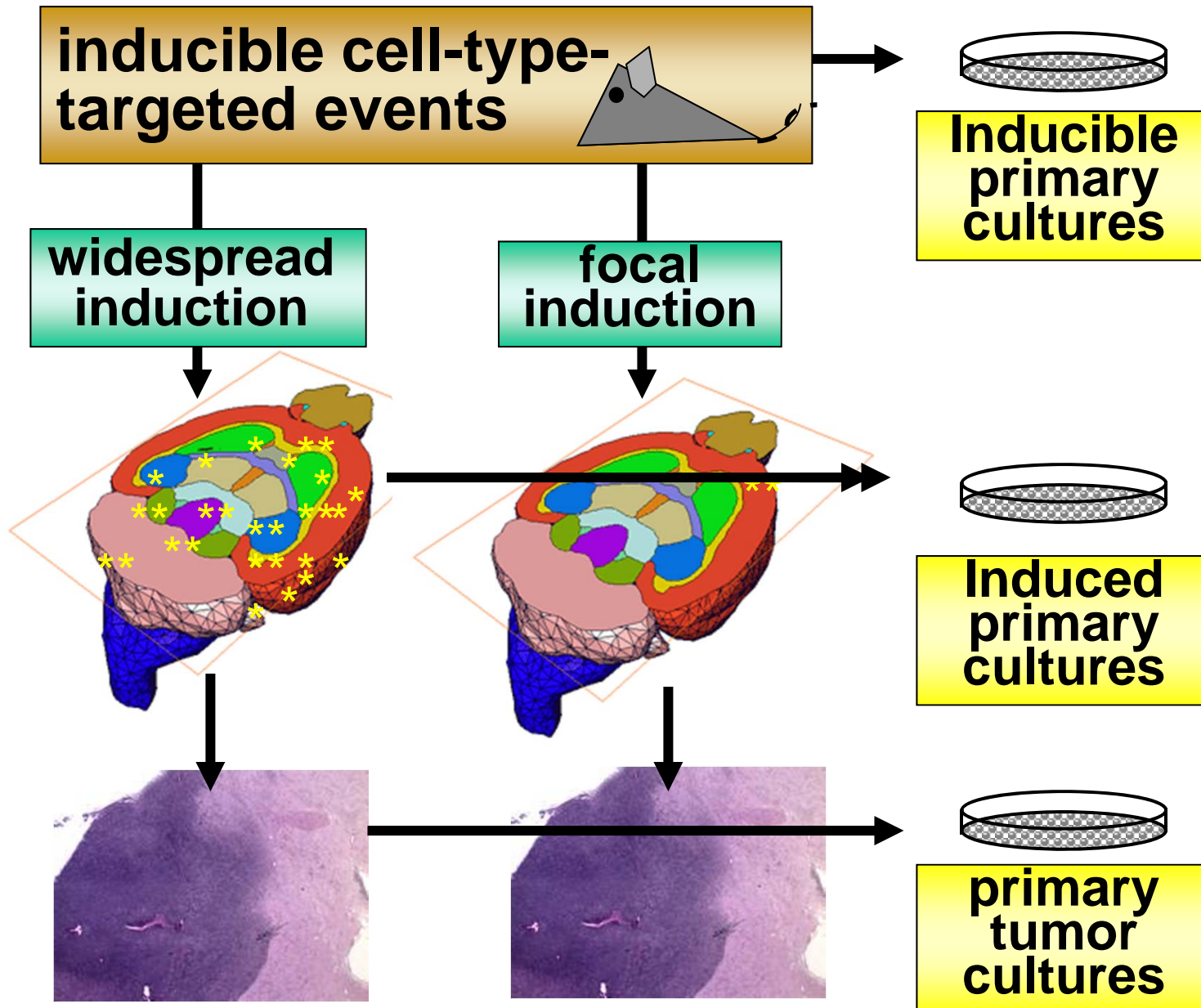


In Vitro Pathway Analyses:

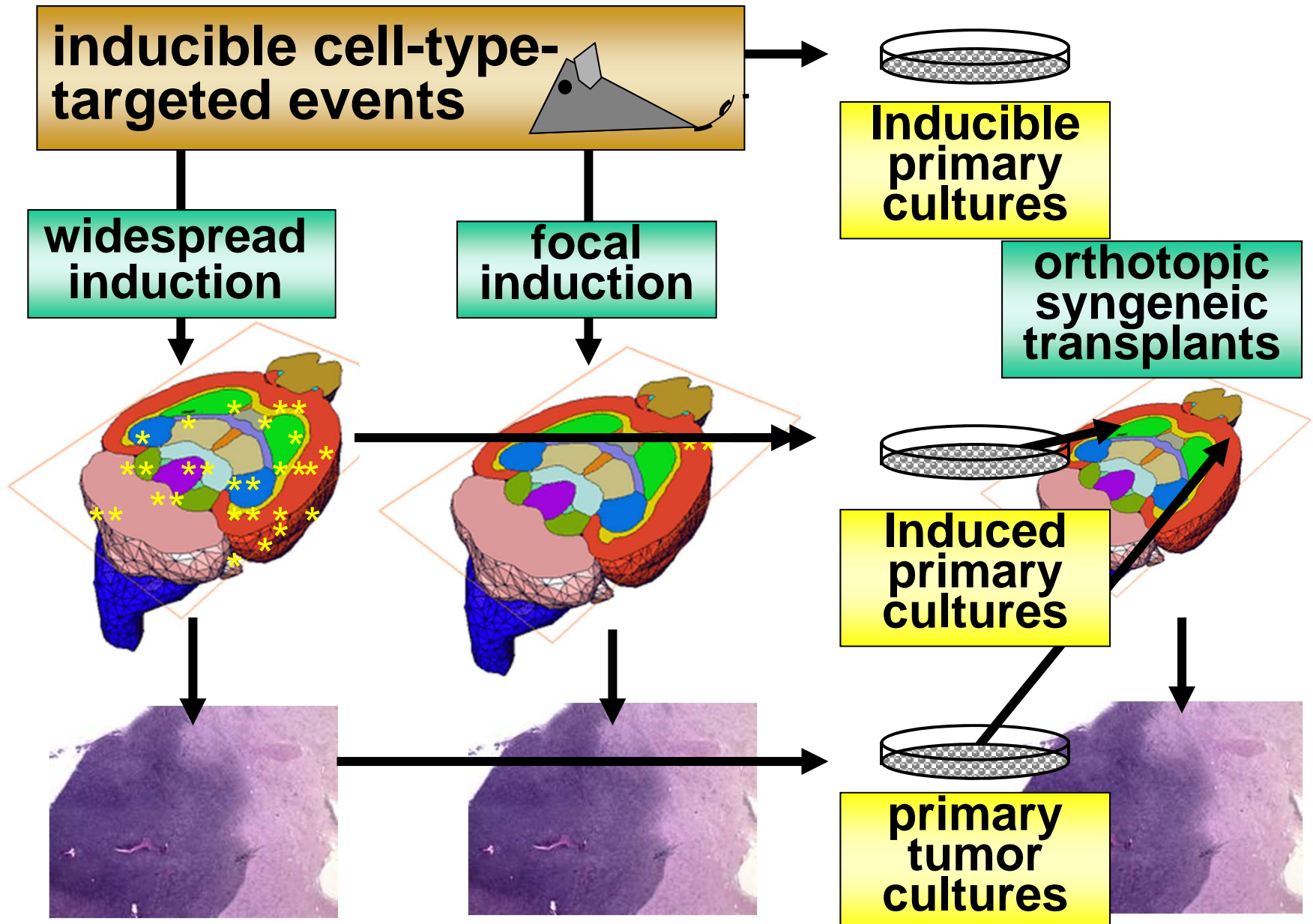
What are the likely ***Mechanistic***
Cause-Effect Relationships ***of***
Pathways Perturbed In Vivo?

What are the ***Critical Therapeutic***
Targets?

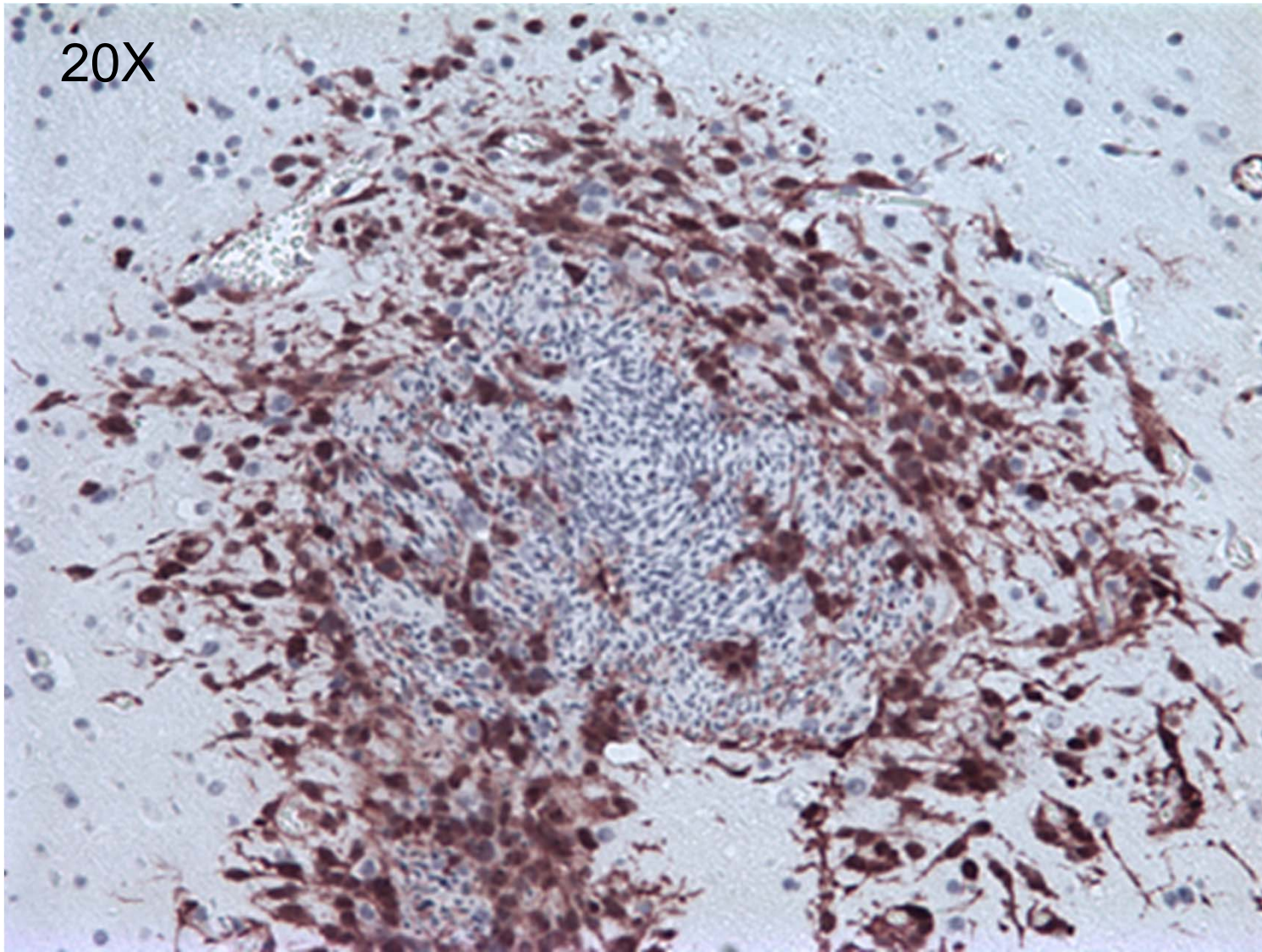
Scheme for Integrated Disease Analysis



Scheme for Integrated Disease Analysis

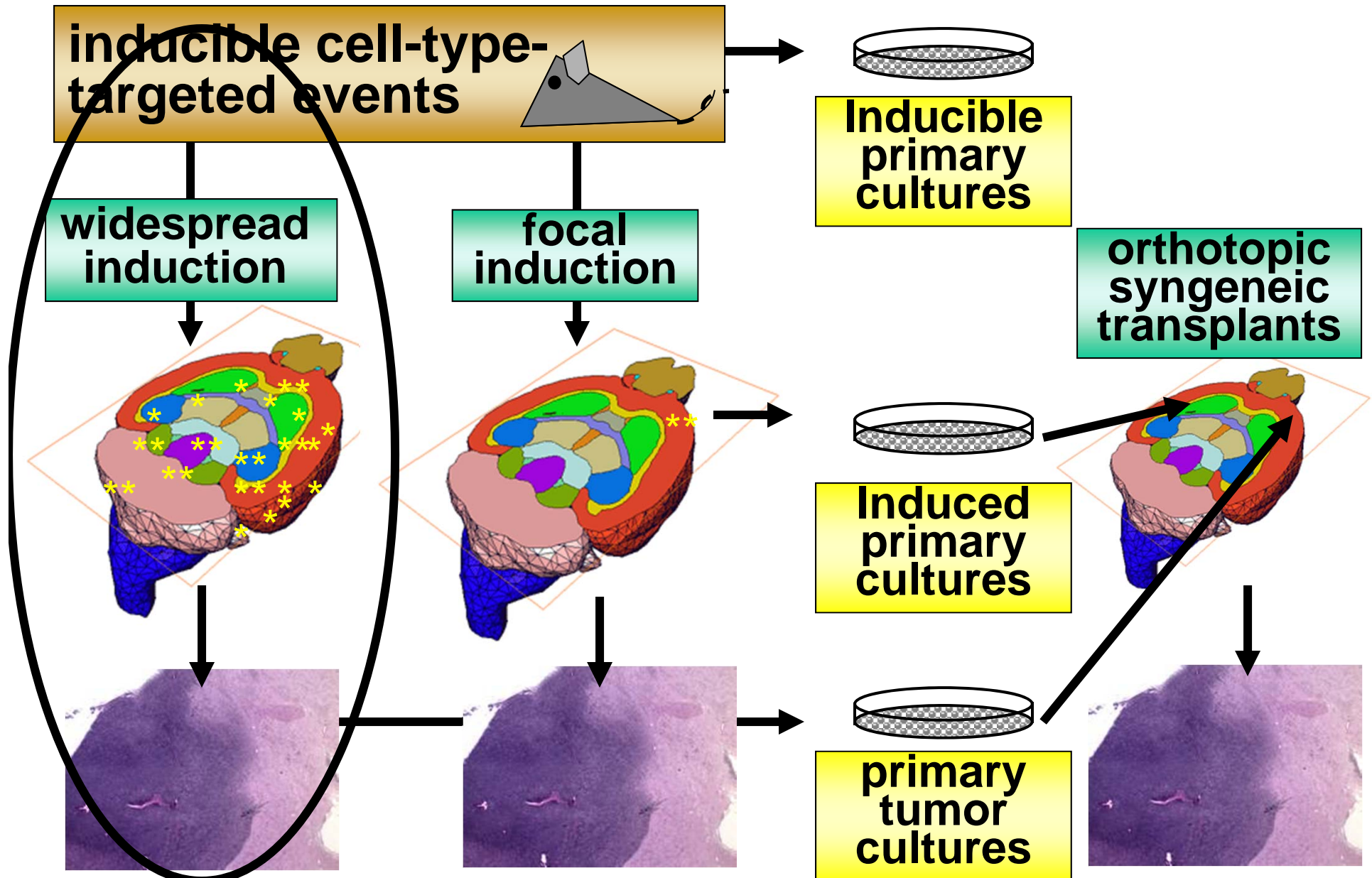


Orthotopic Syngeneic Transplant Model for “Rapid” Pathway/Microenvironment Assessment

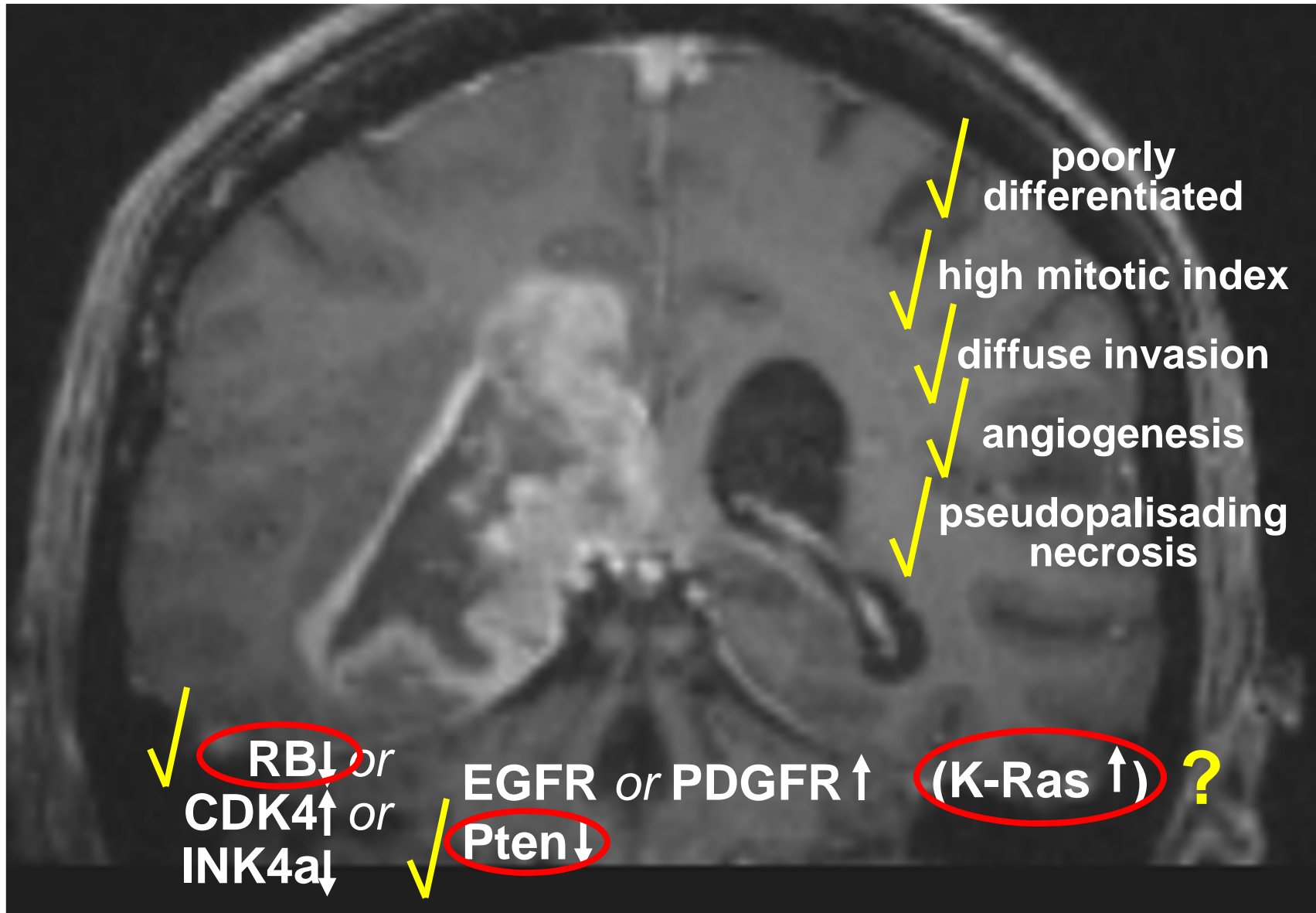


Ryan Bash, Natalie Karpinich, Ryan Miller

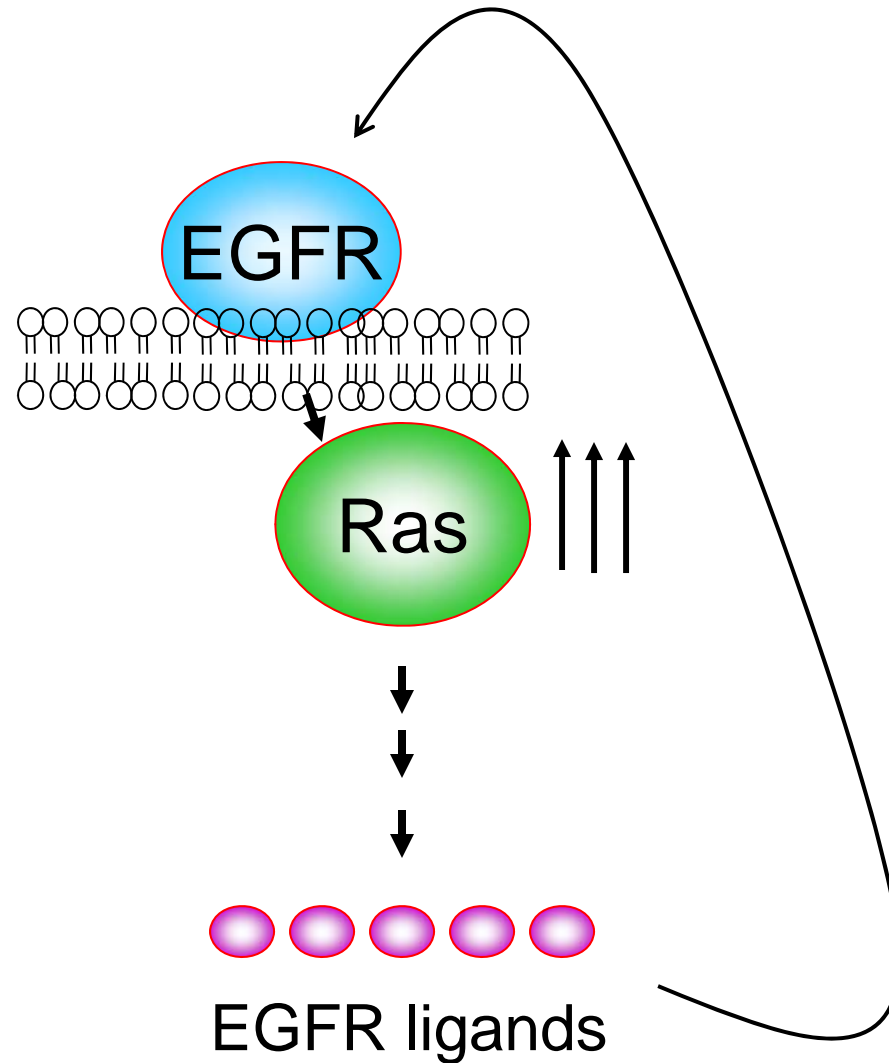
Scheme for Integrated Disease Analysis



High-grade Astrocytoma

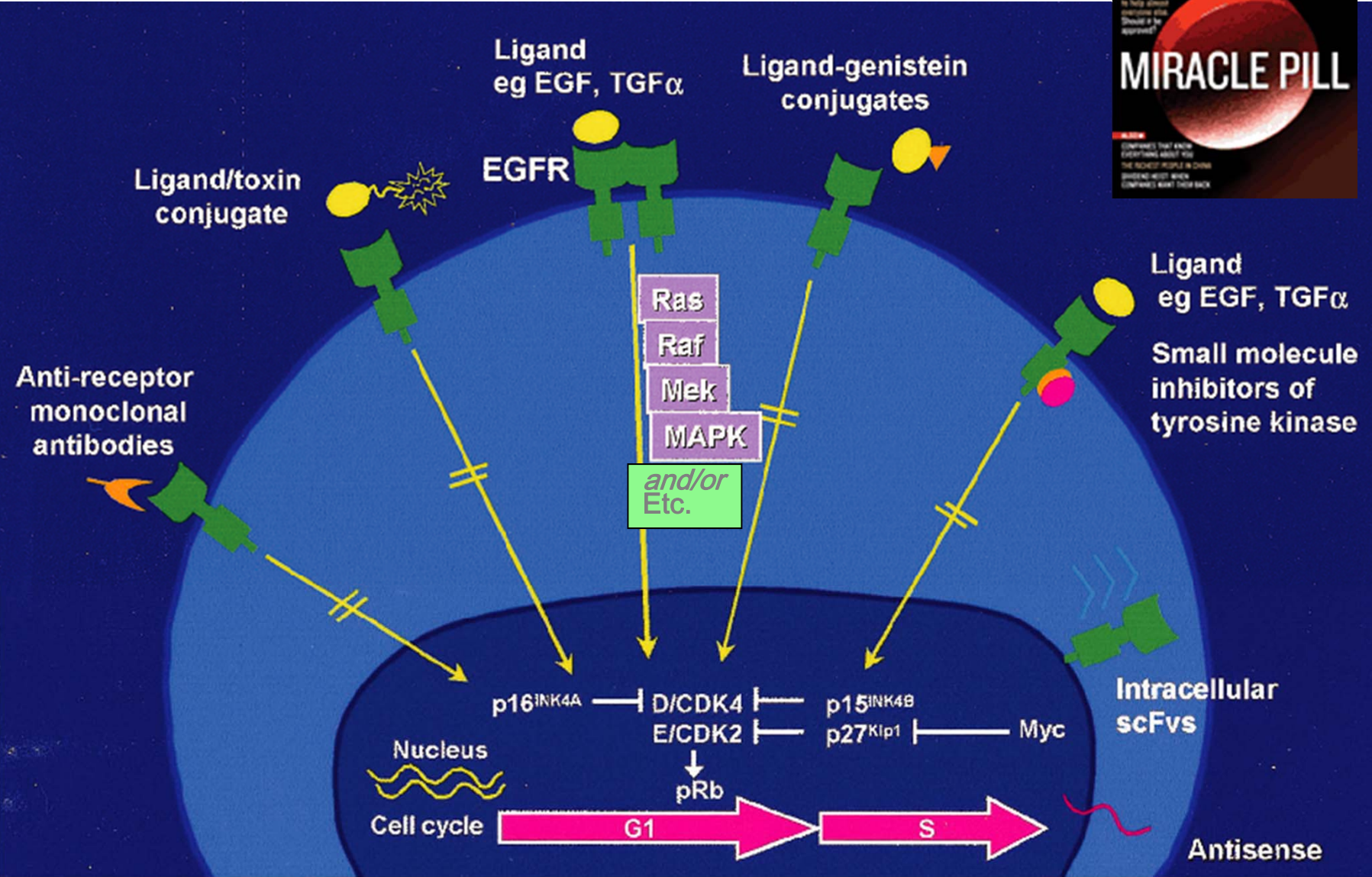


EGFR Signal Activation via Ras Activation



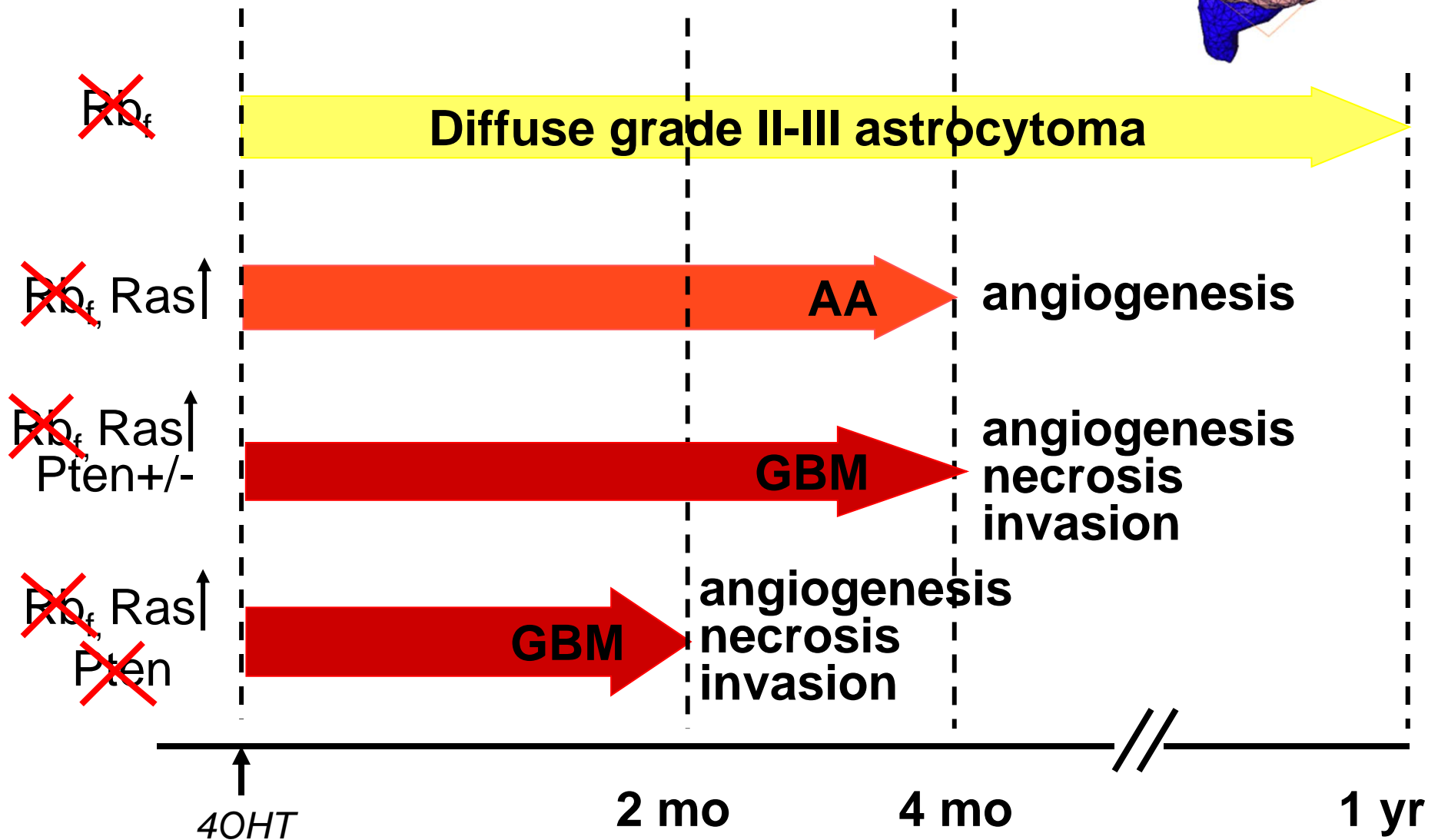
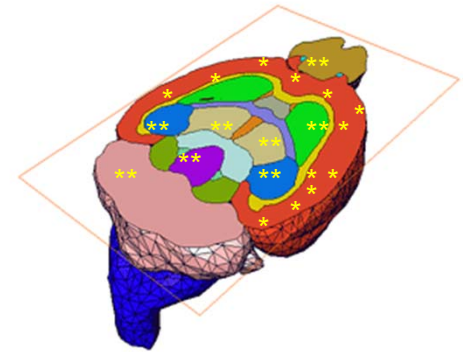


Targeting EGFR in Cancer

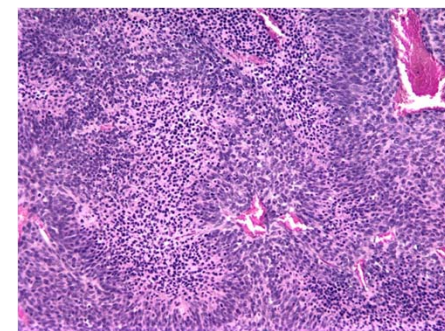
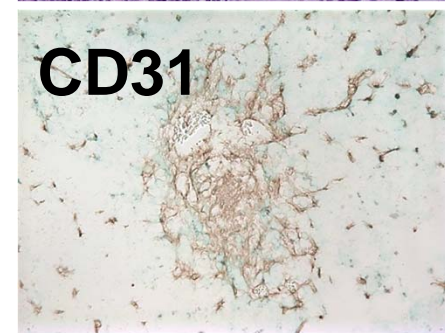
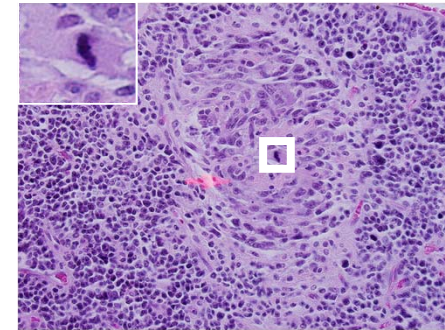
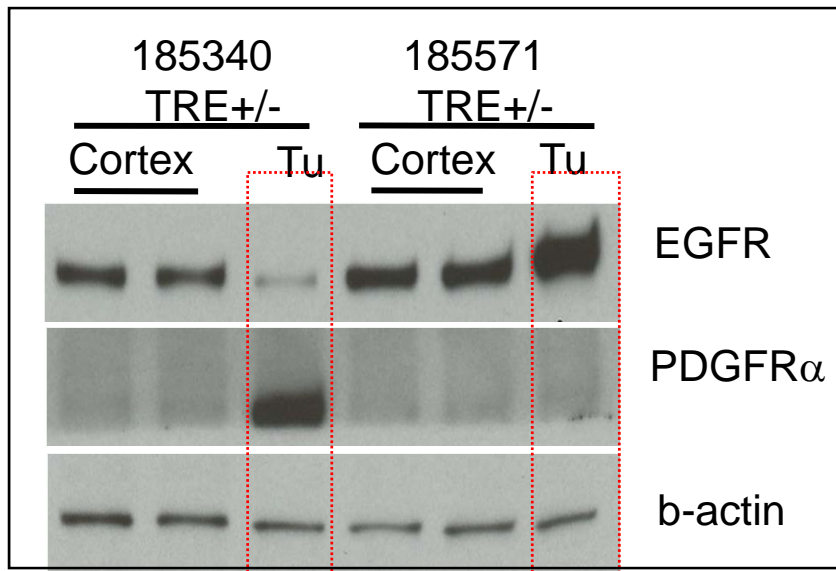
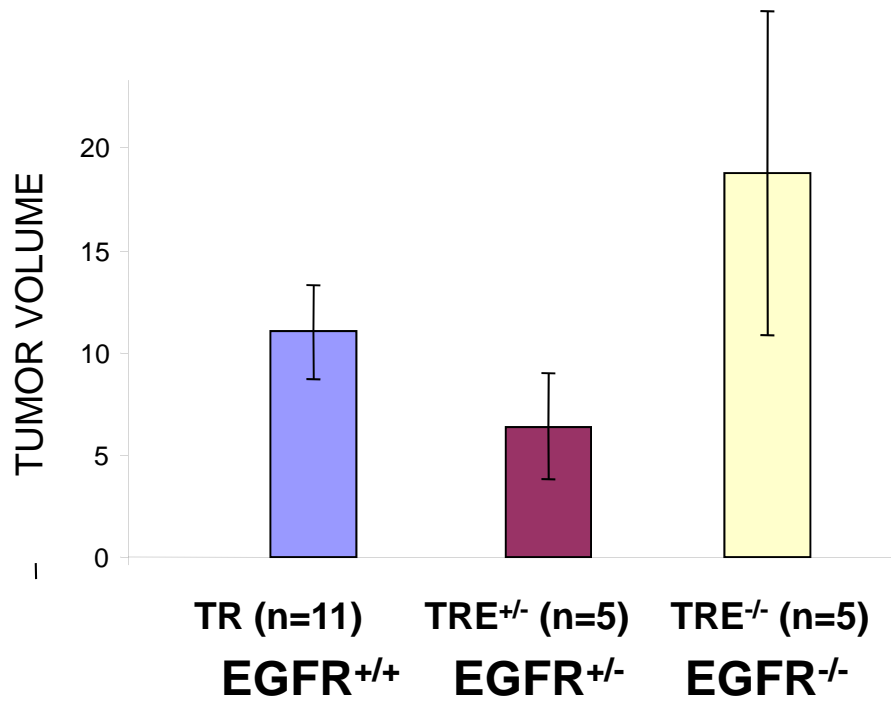


adapted from Ciardiello & Tortora, 2002; courtesy of David Threadgill (UNC)

Inducible Astrocytoma Models



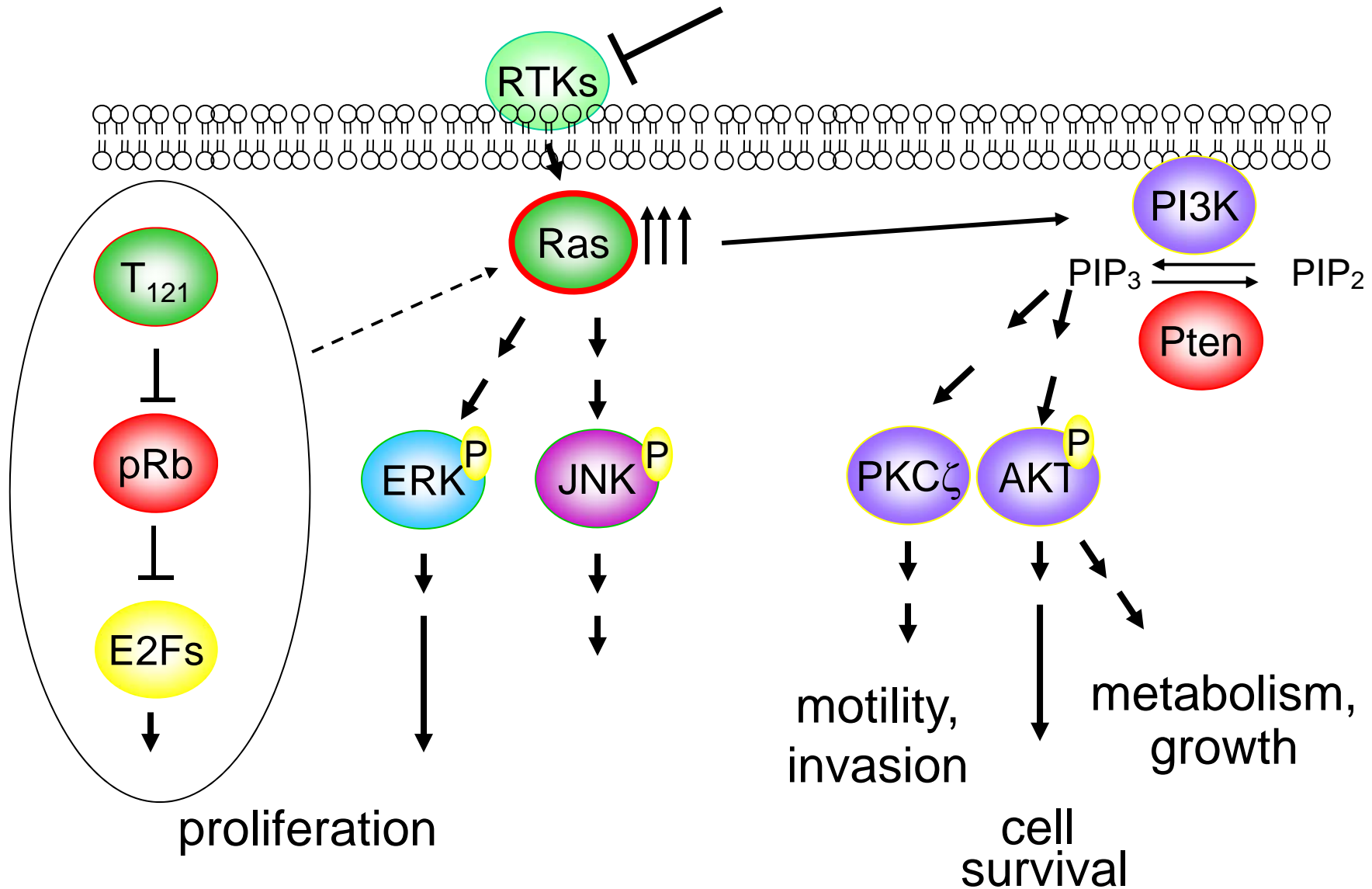
EGFR Inactivation INCREASES Severity



T₁₂₁;K-Ras^{G12D};EGFR^{-/-}

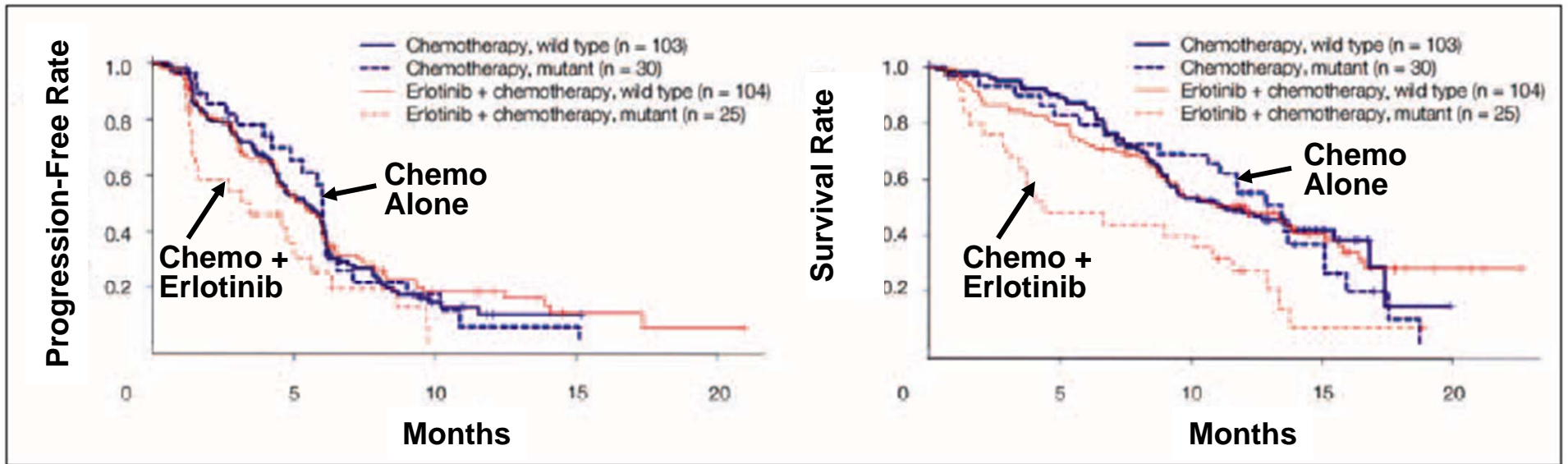
Q. Zhang, D. Threadgill

Pathways to Astrocytoma

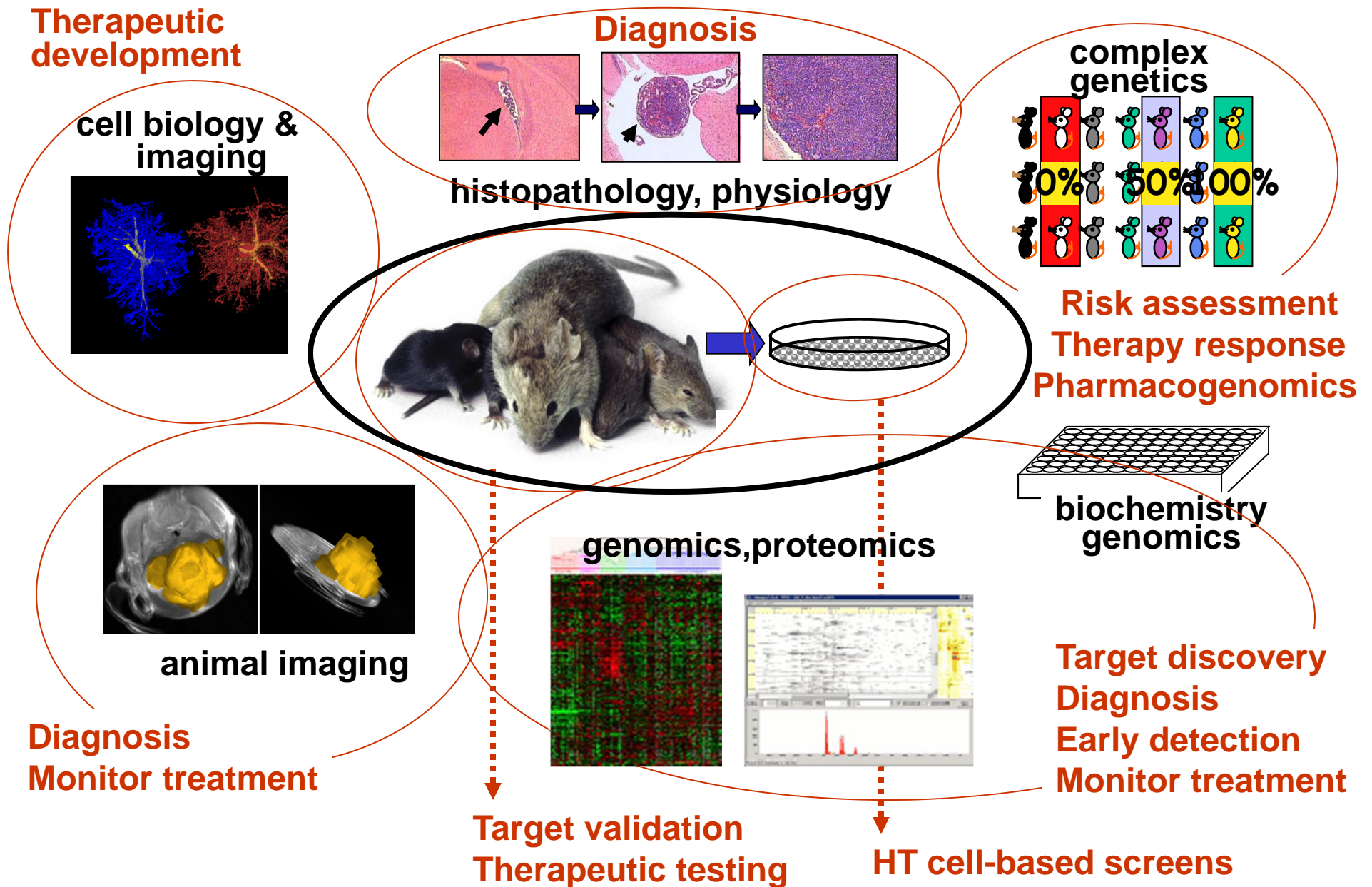


Mutations in the Epidermal Growth Factor Receptor and in KRAS Are Predictive and Prognostic Indicators in Patients With Non-Small-Cell Lung Cancer Treated With Chemotherapy Alone and in Combination With Erlotinib

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



Disease Models at the Frontiers of Basic and Clinical Discovery



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, pathways, GEMM, genetics, drug development *and* clinical care

requires uncommon research culture

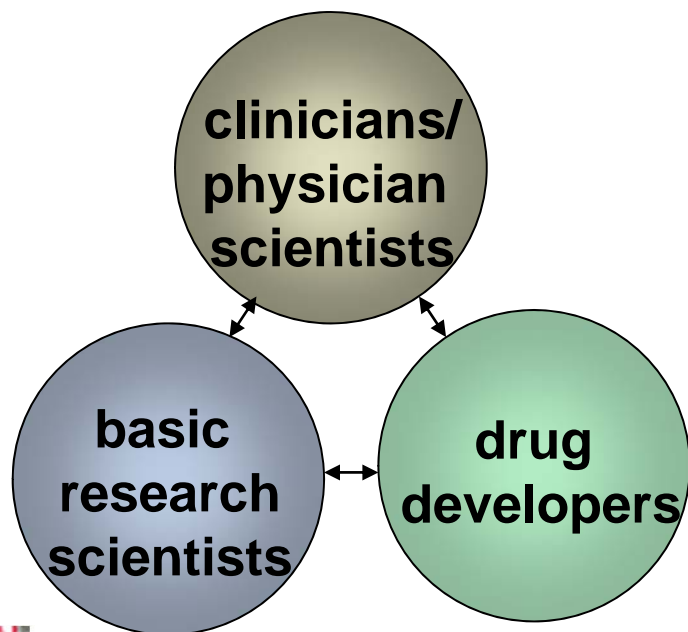
NATIONAL
CANCER
INSTITUTE

Center
for
Cancer Research

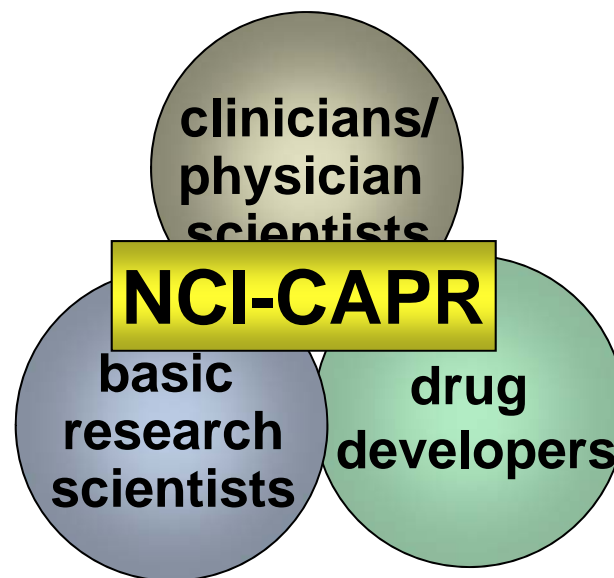
NCI-CAPR

Center for Advanced Preclinical Studies

*....to facilitate the improvement of
preclinical assessment and clinical trial design
for effective cancer diagnosis and treatment*



Current Interactome



Projected Interactome

*a new paradigm for
translational science*

NCI-CAPR

Center for Advanced Preclinical Studies

- Predict possible outcomes/patient stratification to inform clinical trial design
 - Therapeutic target discovery and validation
 - Biomarker/molecular signature identification via comparative (human, canine, murine) analyses
 - Cancer model and “tool” mouse development for UNMET needs.
 - Annotated tissue/fluids/nucleic acids banks
 - Consultation.
 - Integrated preclinical/clinical LIMS development
- Develop effective preclinical testing strategies in murine cancer models (GEM, humanized orthotopic xenografts)
- Comparative assessment of predictive power among murine cancer models
 - Develop molecular/cellular imaging strategies for therapeutic/diagnostic assessment
- Develop technologies to overcome barriers to scale up and throughput while limiting sacrifice in predictive power.

NATIONAL
CANCER
INSTITUTE

Center
for
Cancer Research

