Protocol 734: AN OPEN-LABEL, PHASE I, DOSE-ESCALATION STUDY OF AD-EGFR-CD533 AND SURGERY FOR PATIENTS WITH RESECTABLE RECURRENT HIGH GRADE GLIOMA

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Kristoffer Valerie, Ph.D.

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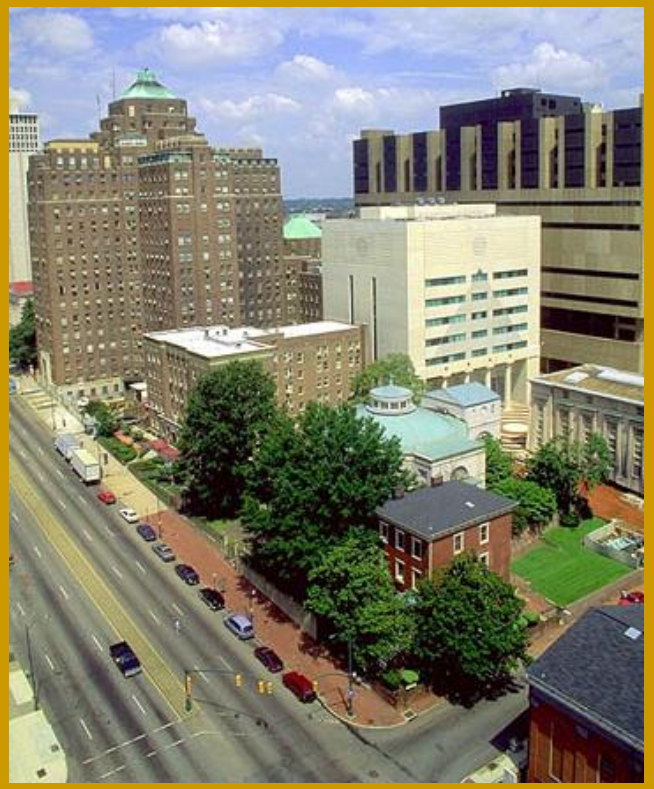

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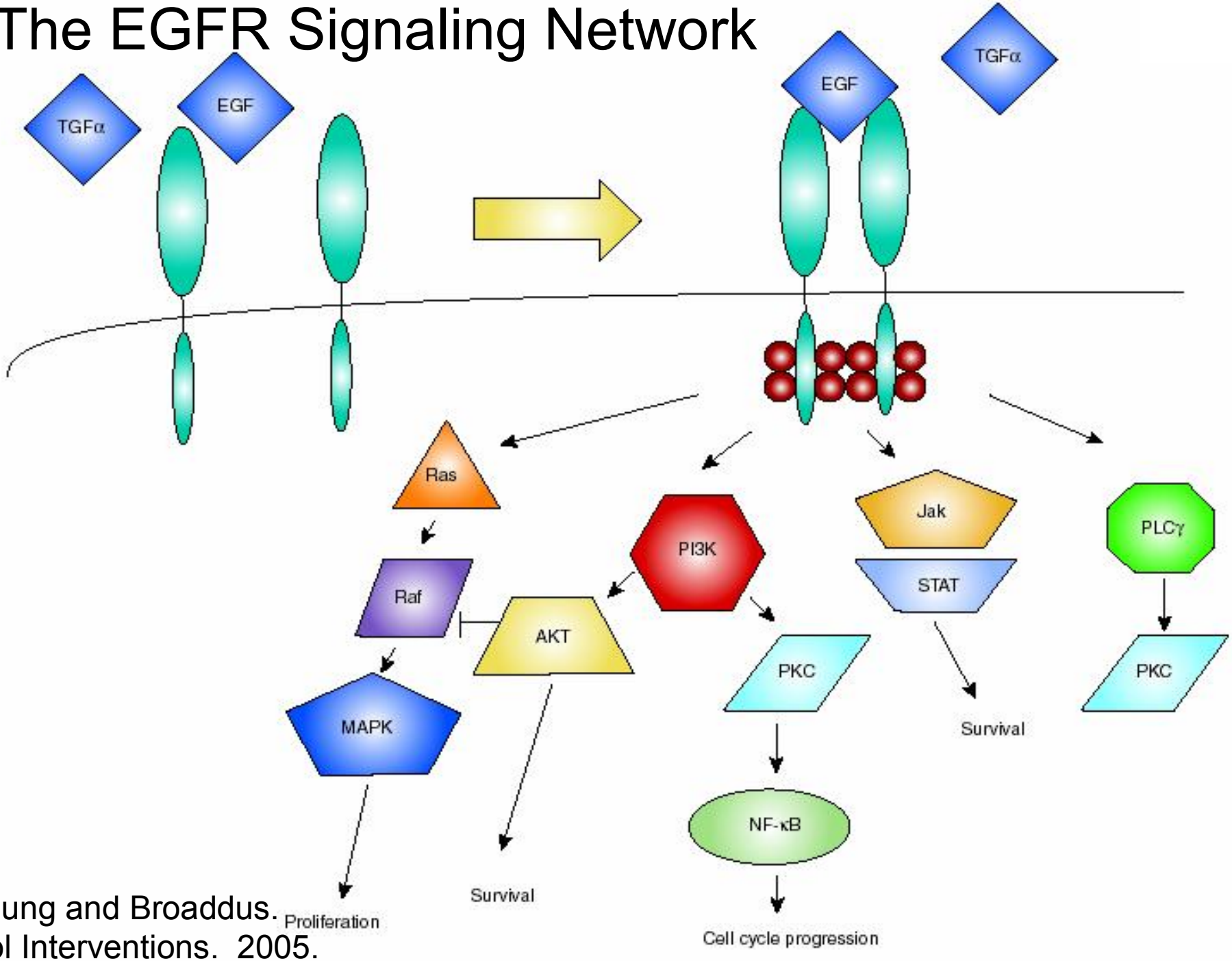
Historical Perspective

- Basic laboratory and preclinical investigation initiated by Rupert K. Schmidt-Ullrich and Kristoffer Valerie
  - 25 peer-reviewed publications
  - “Pre-pre-IND” discussion in Summer of 2004
  - Dr. Schmidt-Ullrich died in 12/2004
- Ted Chung joined faculty 7/2000 to lead the translational research effort
  - Launched institution’s first genetic transfer clinical trial (AdEGR.TNF.11D)
  - Co-PI for current proposal

GBMs and EGFR

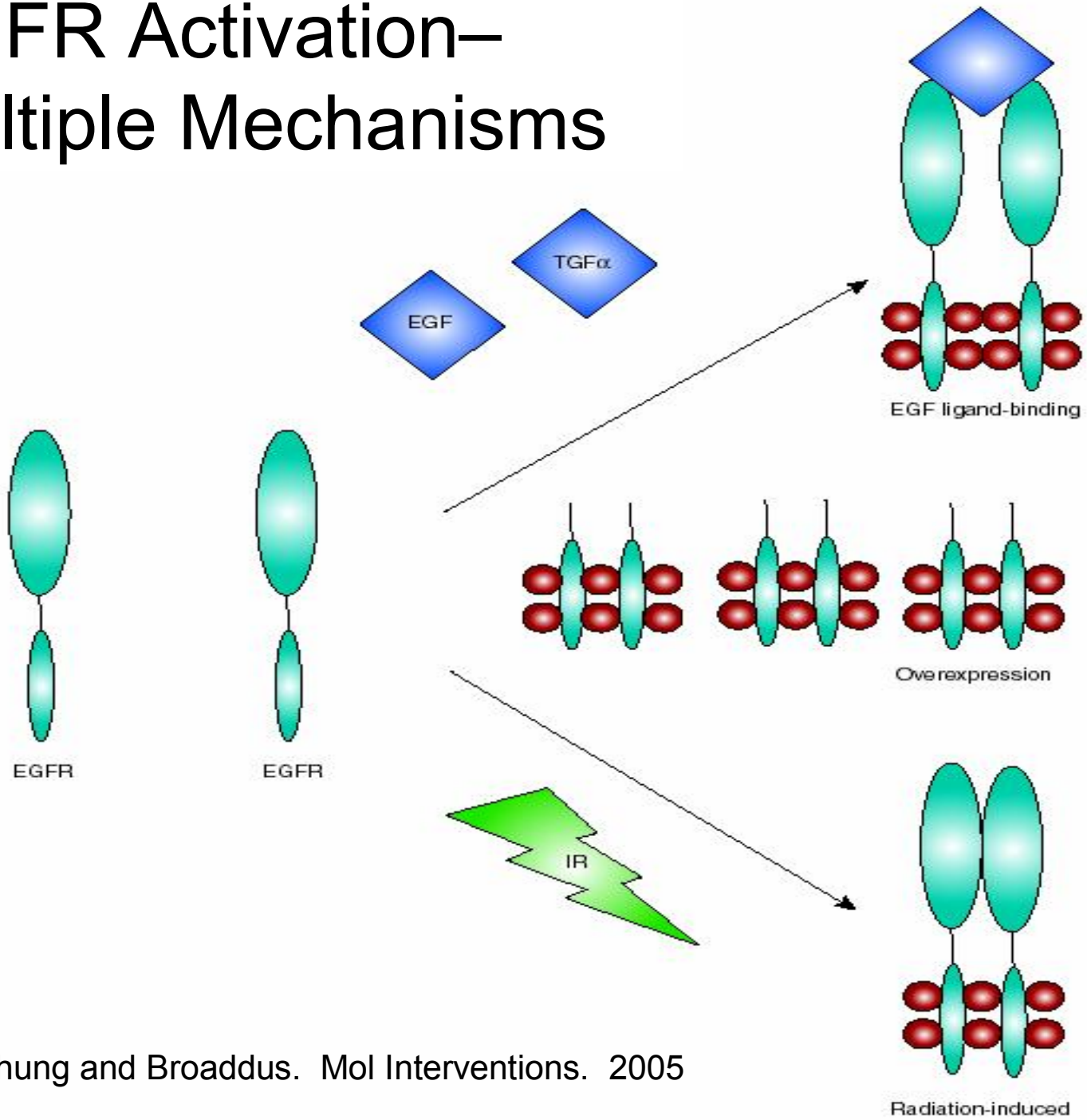
- 9 -12 month median SV
- Most prevalent molecular signature of GBMs is gene amplification of EGFR , found in greater than 40% of GBMs
- Inhibition of EGFR leads to *decreased* glioma cell proliferation and increased radiosensitivity *in vitro* and *in vivo*

The EGFR Signaling Network



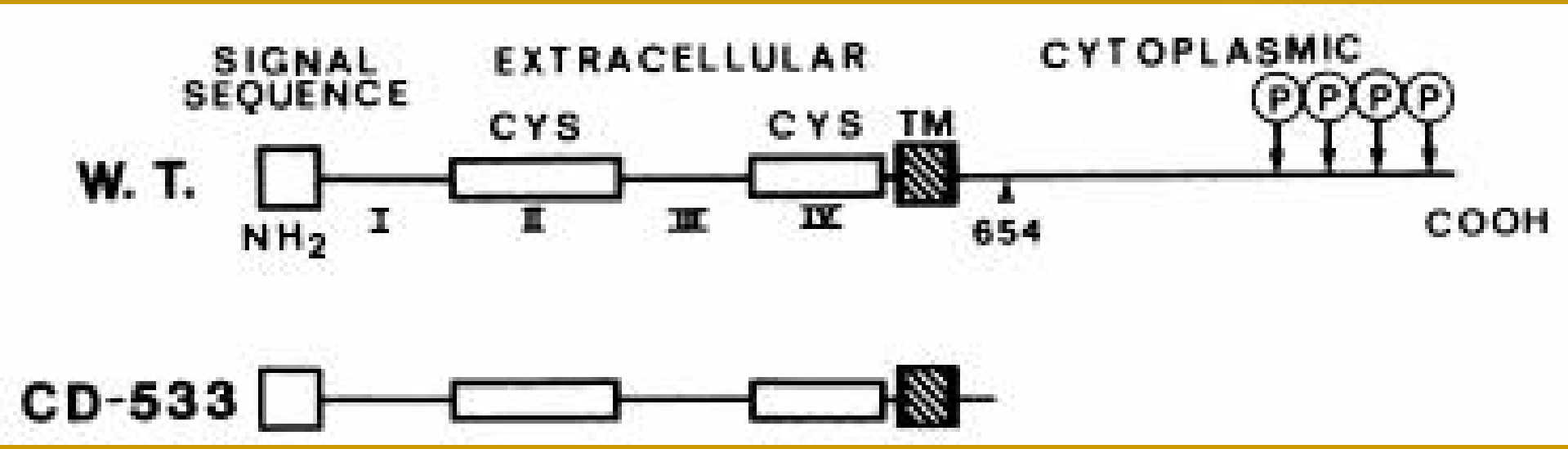
Chung and Broaddus. Mol Interventions. 2005.

EGFR Activation– Multiple Mechanisms



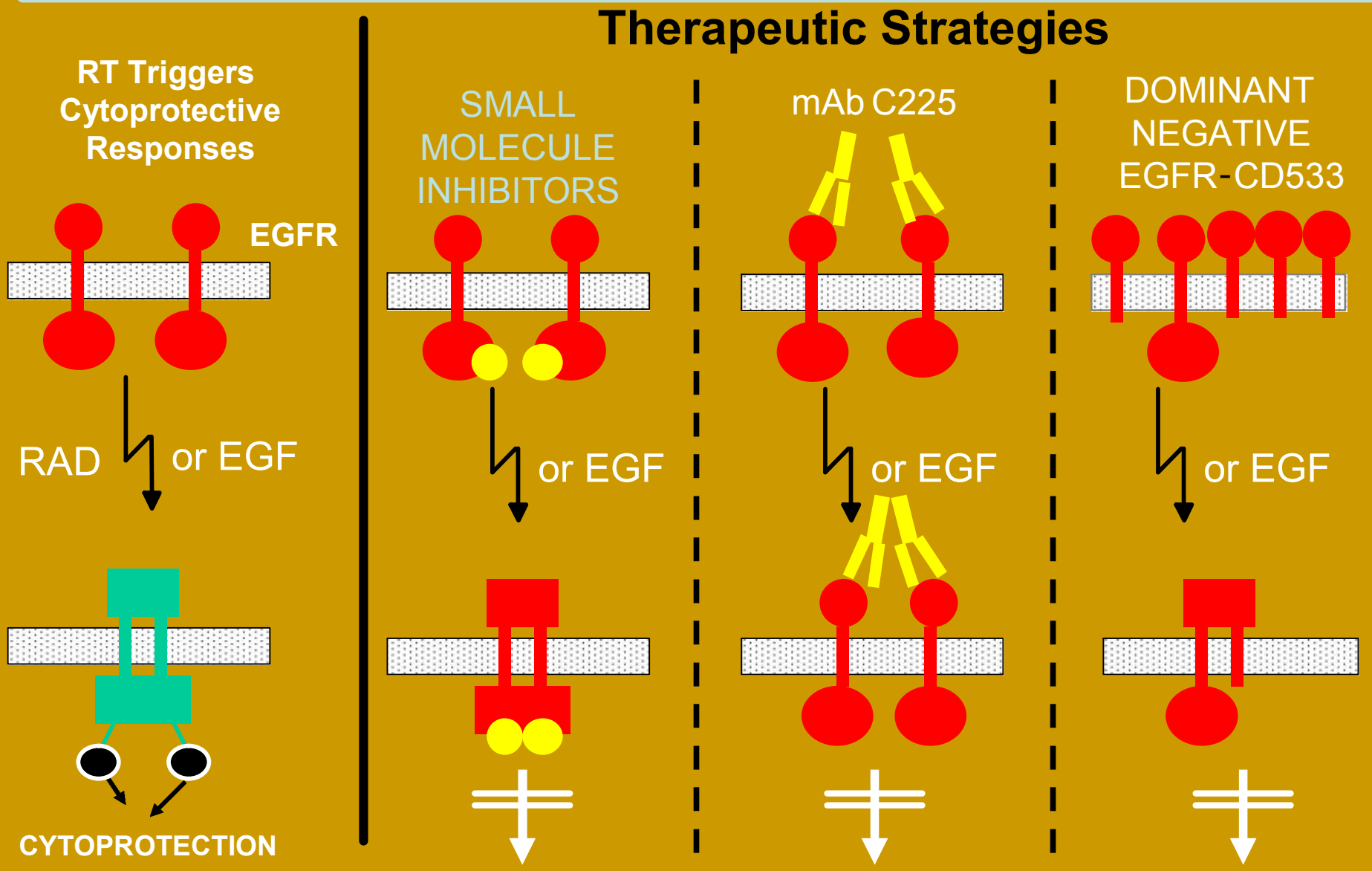
Chung and Broaddus. Mol Interventions. 2005

Dominant Negative Mutant Version of EGFR

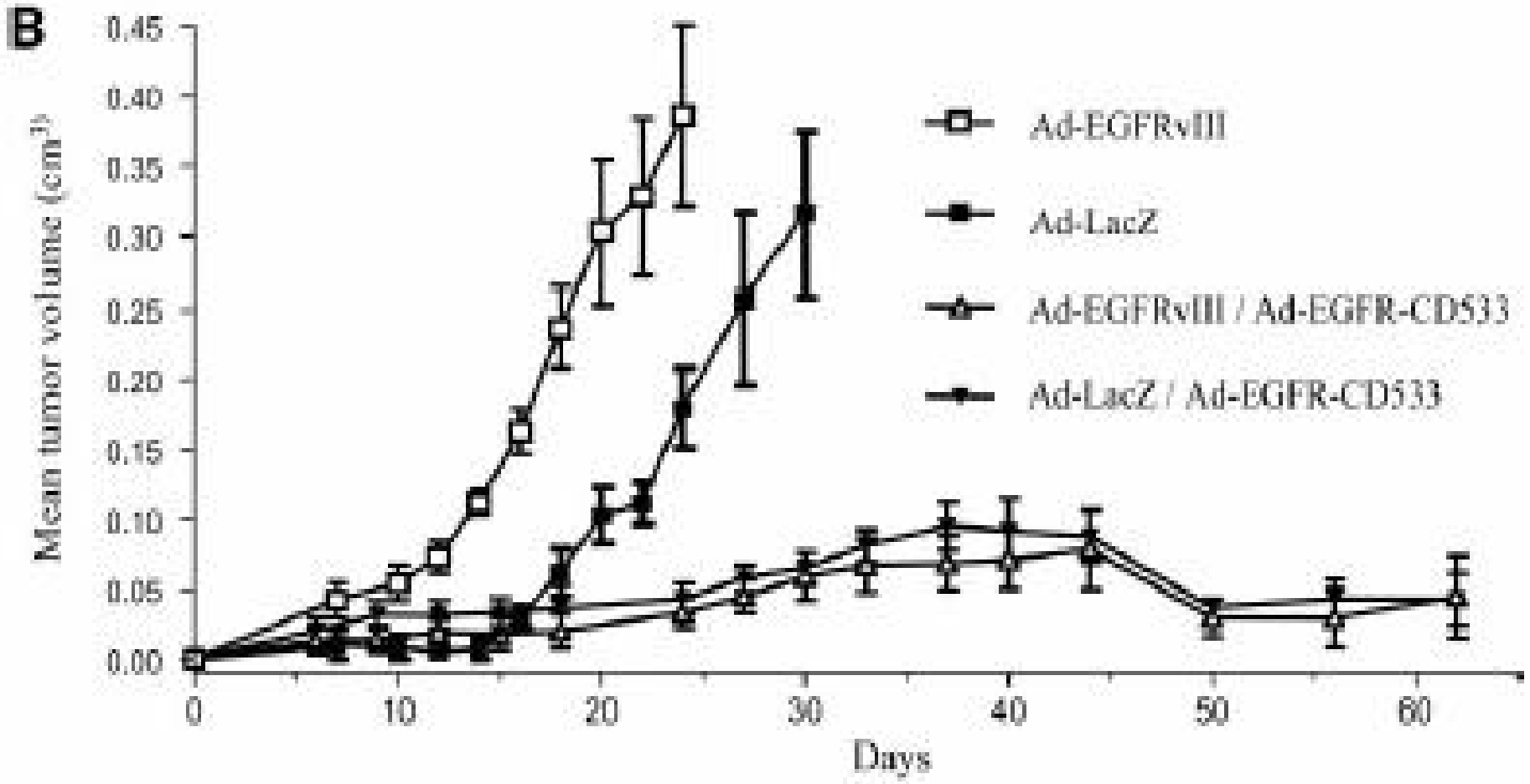


Kashles et al. Molec Cell Biol 1991

Strategies for Disrupting EGFR Function in Response to Radiation Therapy

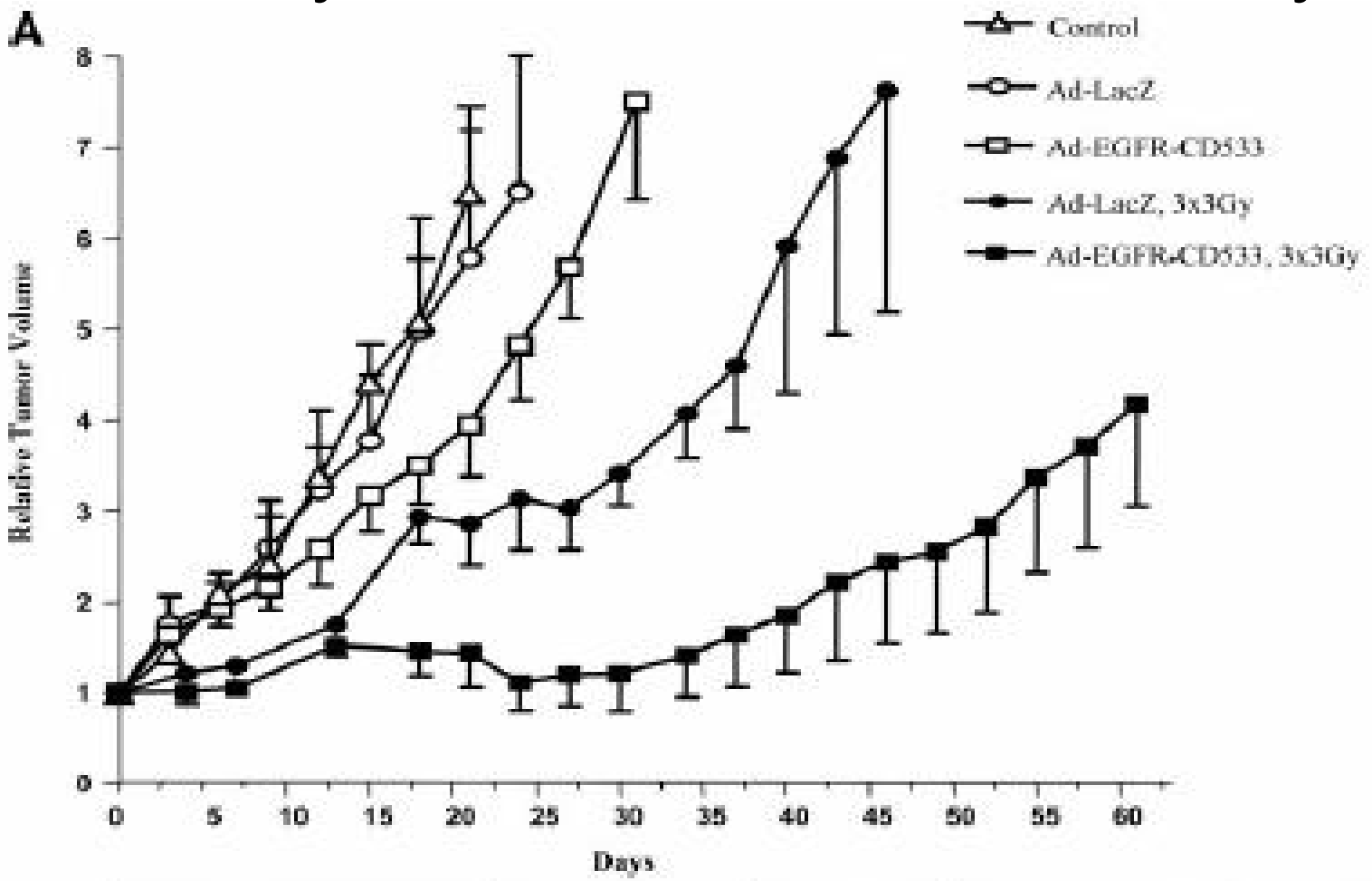


Ad-EGFR–CD533 Induces Growth Delay in U373 Xenografts



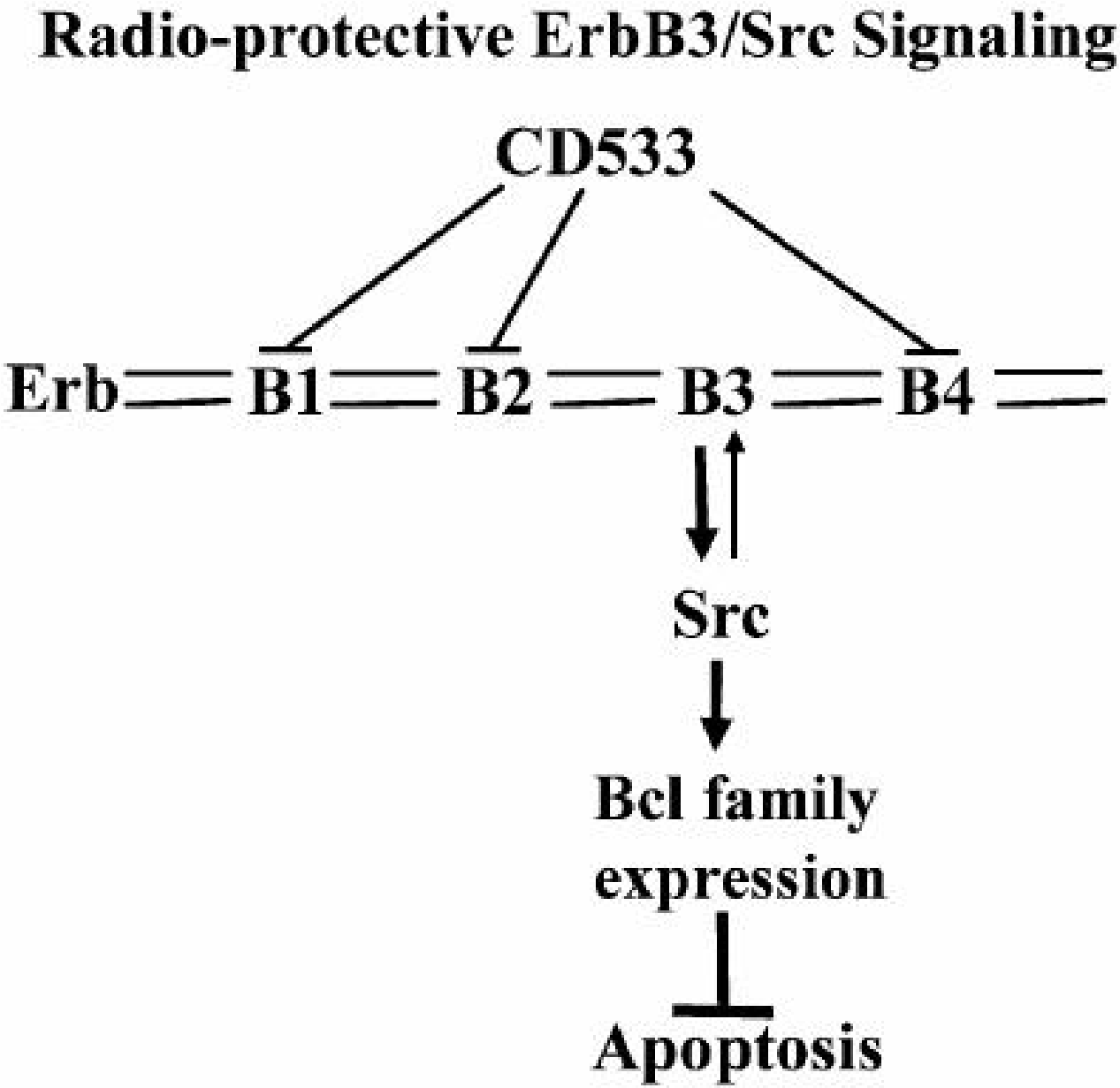
Lammering et al. 2004. Clin Cancer Res 10;6732

Growth Delay-Ad-EGFR-CD533 + 3 x 3Gy



Treatment:	Ad-EGFR-CD533	3 x 3 Gy	Ad-EGFR-CD533 + 3 x 3 Gy
Growth delay time (in days) relative to Ad-LacZ alone (to reach rel. tumor vol. 4)	5	18	44

Lammering et al. 2004. Clin Cancer Res 10;6732



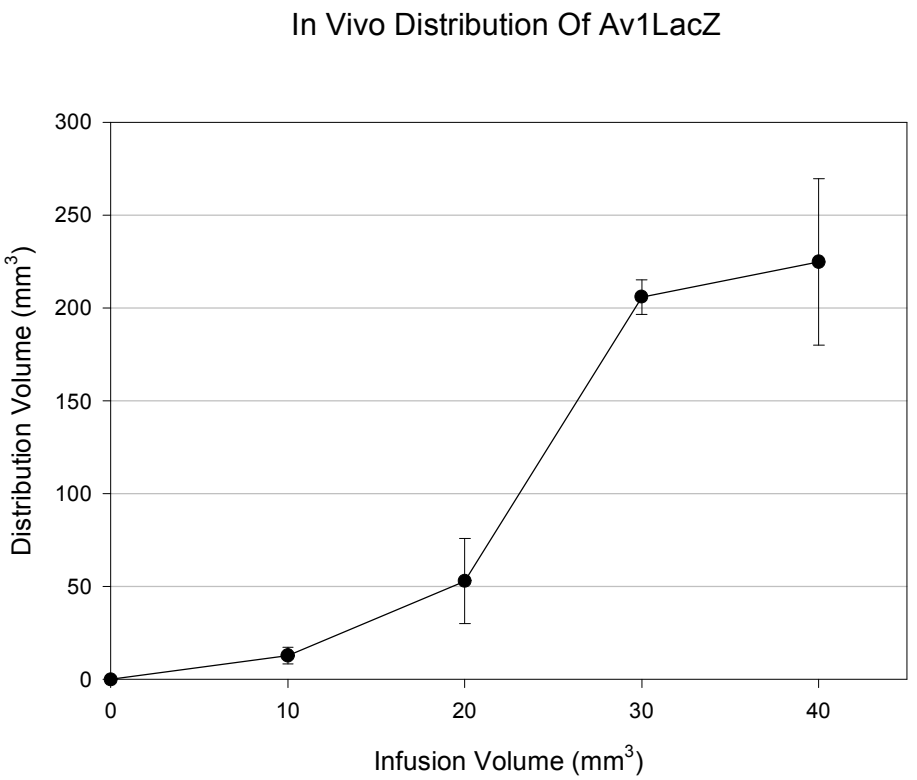
Contessa et al. 2005. Breast Cancer Res Treat. 2005 Nov 3;:1-11 [Epub ahead of print]

Selection of Viral Doses

- Lang *et al*.- Ad-p53 virus; direct intratumoral injections; reached $3x10^{12}$ pu without DLTs
- Chiocca *et al*. – ONYX-015 virus; direct peritumoral injection; reached 10^{10} pfu (based on ~20-50pu/pfu, 2-5 x 10^{12}pu) without DLTs
- 10^{11} – 10^{13} pu (typo. err., Introductory Statement)

Virus Administration into Tumor and Brain Parenchyma

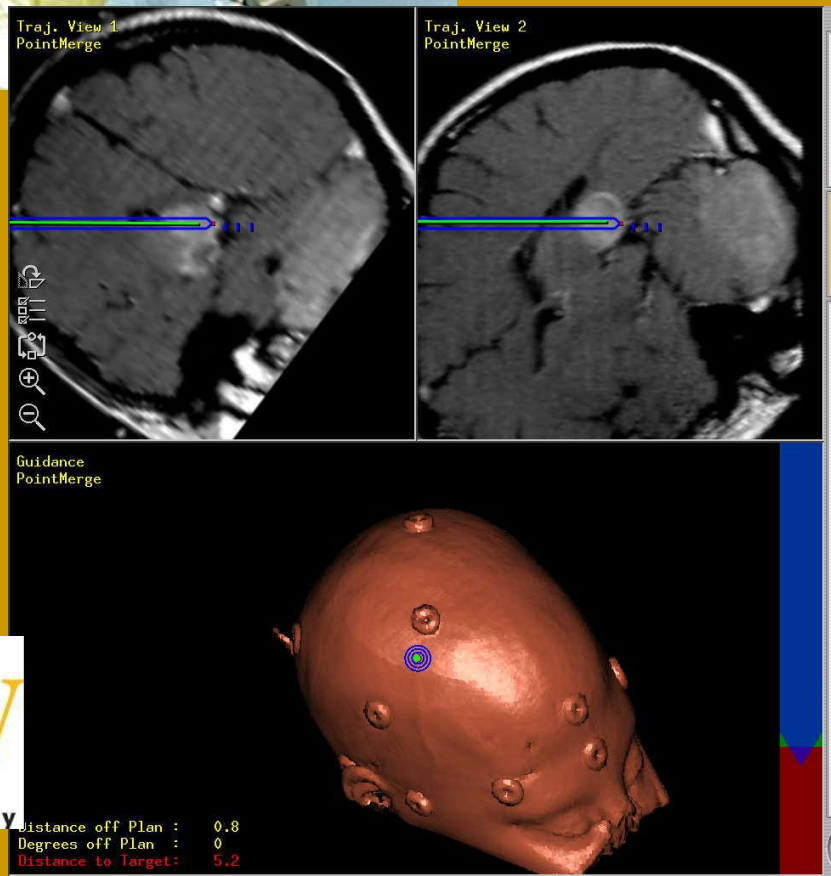
- Controlled-rate infusion improves distribution of viral particles into tissue



Viral Delivery: Pitfalls

- Avoid “sump” delivery into tumor cysts – reduces effective dose to tumor – 1 cm distance

- Avoid escape of viral vector into CSF – reduces effective dose, may raise risk
  - Escape along catheter to pial surface – 2 cm tissue track to infusion site
  - Escape into cerebral ventricle - 1 cm distance



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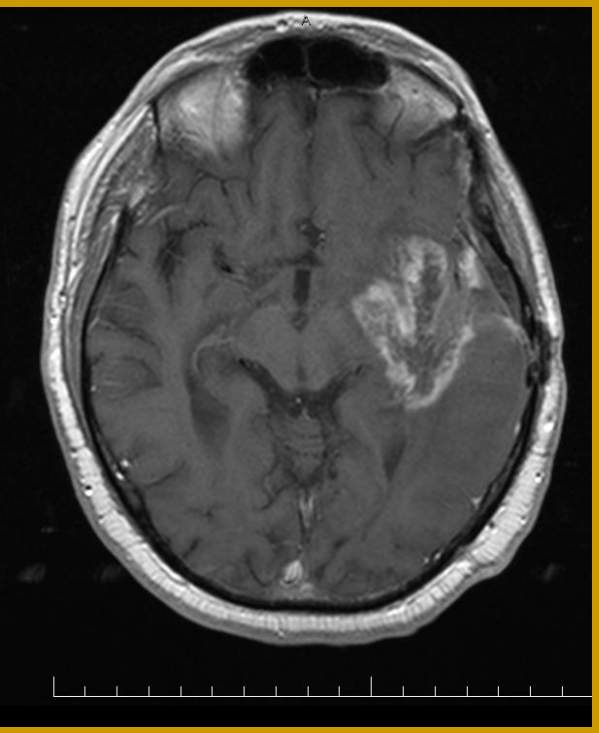
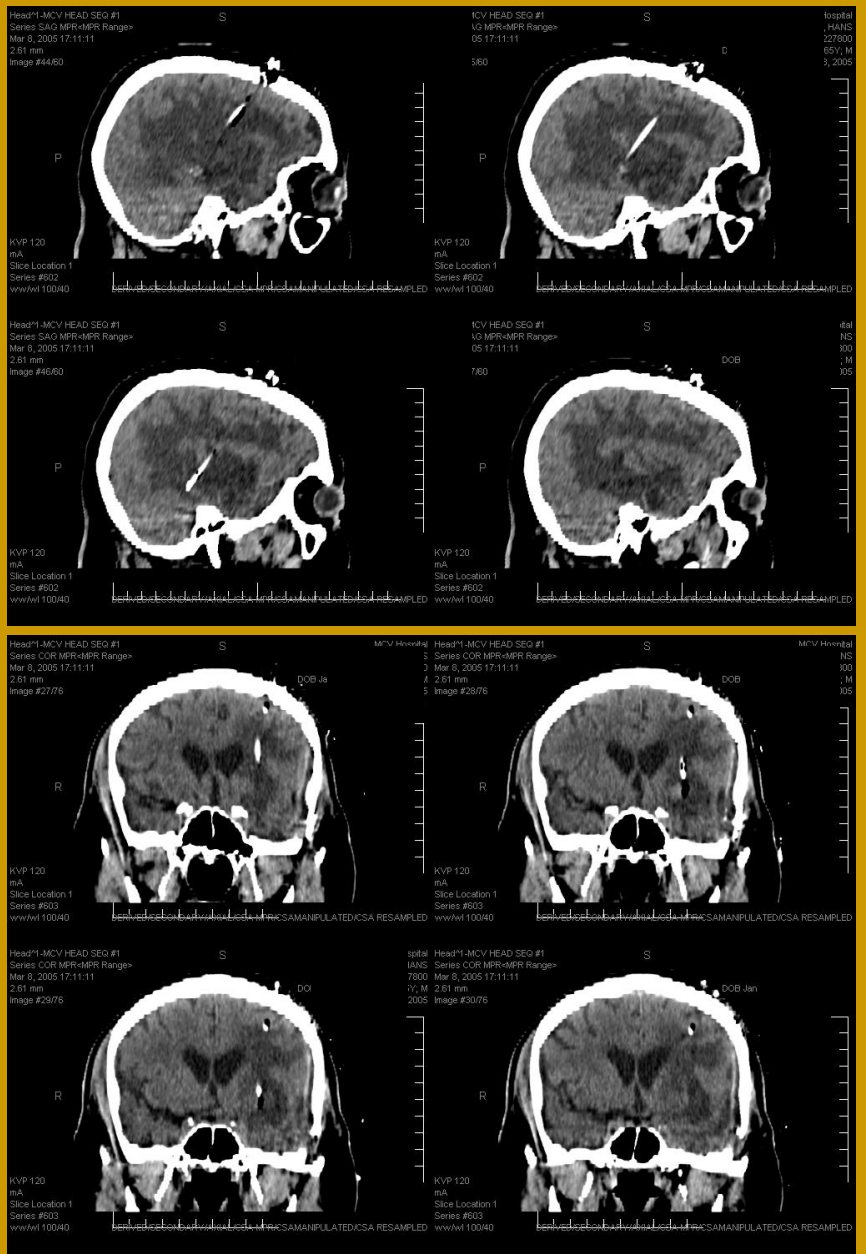
Patient Example – Intratumoral Infusion





Toxicologic Studies

- Preliminary studies
  - Mouse muscle injections
  - Rat brain infusions
- Definitive studies pending
  - Prior to proposed Phase I trial
  - Negotiations for outsourcing in progress

Summary

- Preclinical data support the proposal to test AD-EGFR-CD533 and radiotherapy in patients with GBMs.

- Prior to combining radiotherapy with Ad-EGFR-CD533 in a clinical setting, need to study the safety of the gene therapy vector, independent of radiation treatment.

Corrections/Modifications Since RAC Submission

- Preparation of lay abstract
- Correction of typographical error: pu versus pfu
- Dose escalation changes
- Clarifications and revisions of protocol
- Revisions of ICF

Acknowledgement

- We thank each the members of the RAC for your time, efforts and dedication

- In particular, we thank Dr. Albelda, Dr. K. Piantadosi, Ms T. Kwan, Dr. G. Nemerow, and Dr. H.J. Federoff their insights and help.

Data Safety and Monitoring Board

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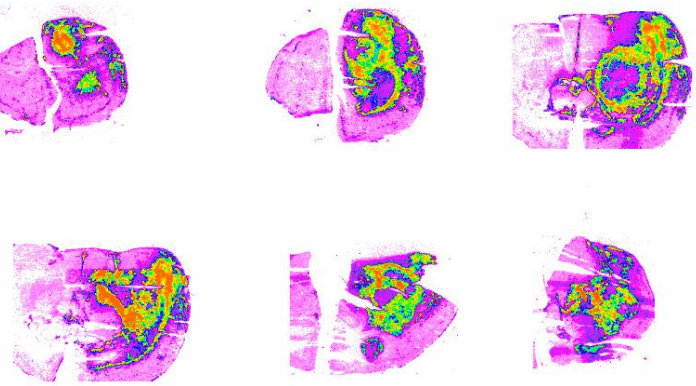
  Professor, University of Alabama Departments of Surgery, Microbiology, Cell Biology and Anatomy; Director, Brain Tumor Spore
- Ralph R. Weichselbaum, M.D.

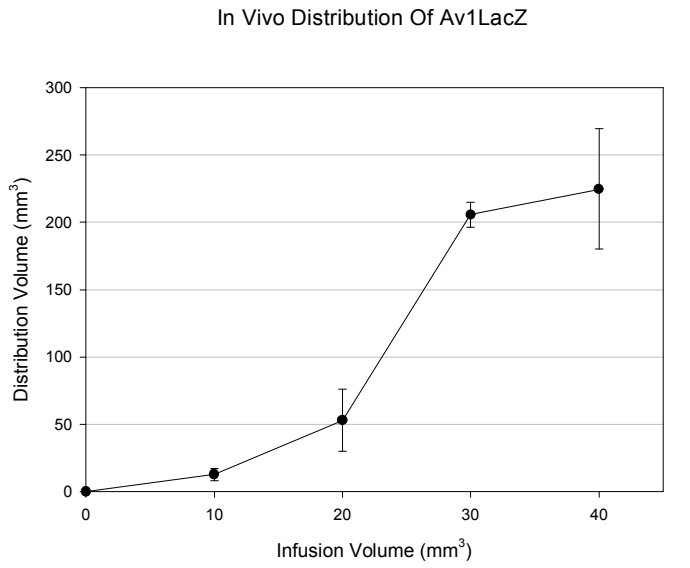
  Professor and Chairman, University of Chicago Department of Radiation and Cellular Oncology

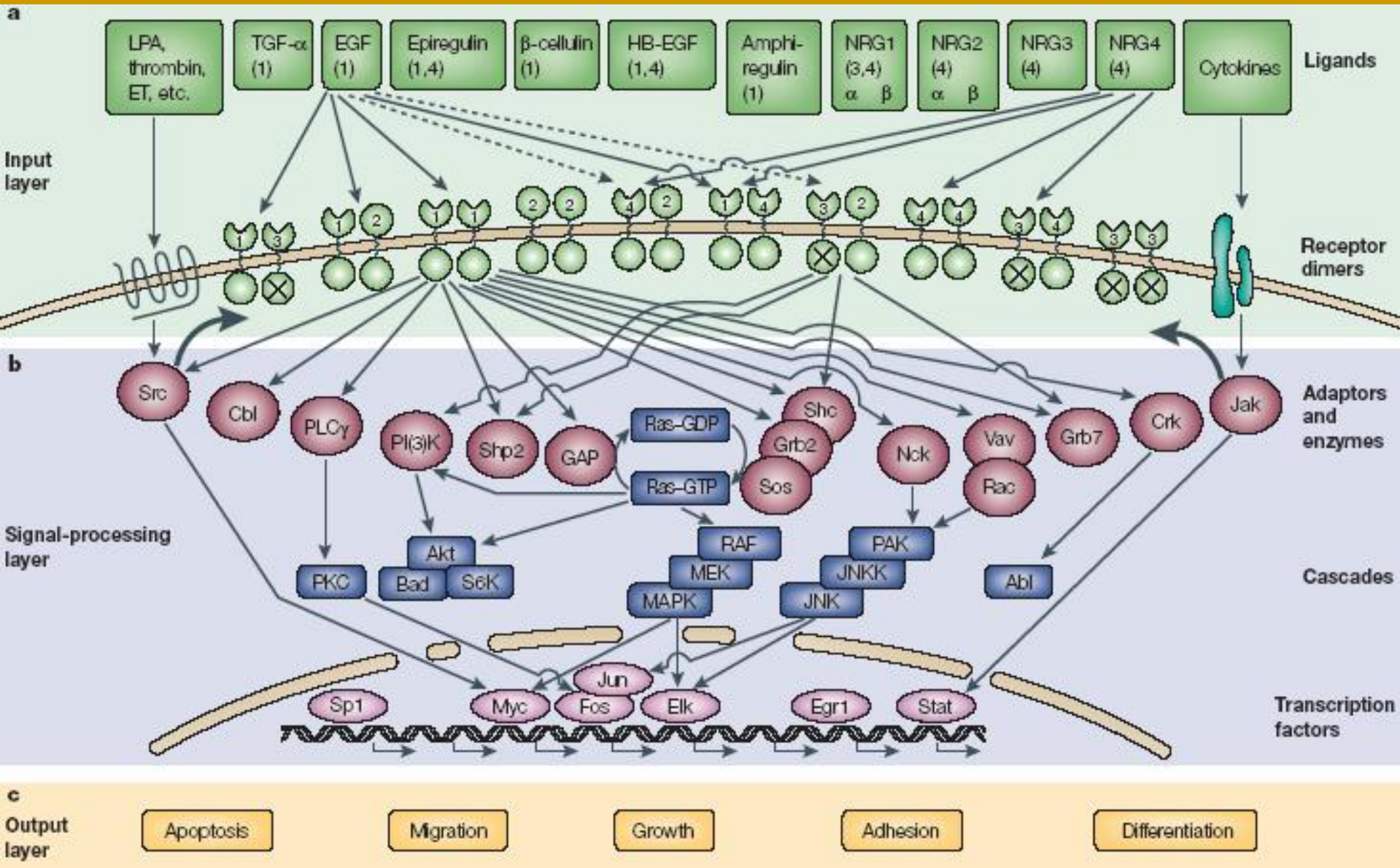
Virus Administration into Tumor and Brain Parenchyma

- Controlled-rate infusion improves distribution of viral particles into tissue

- Avoid delivery of vector suspension into fluid-filled cavities

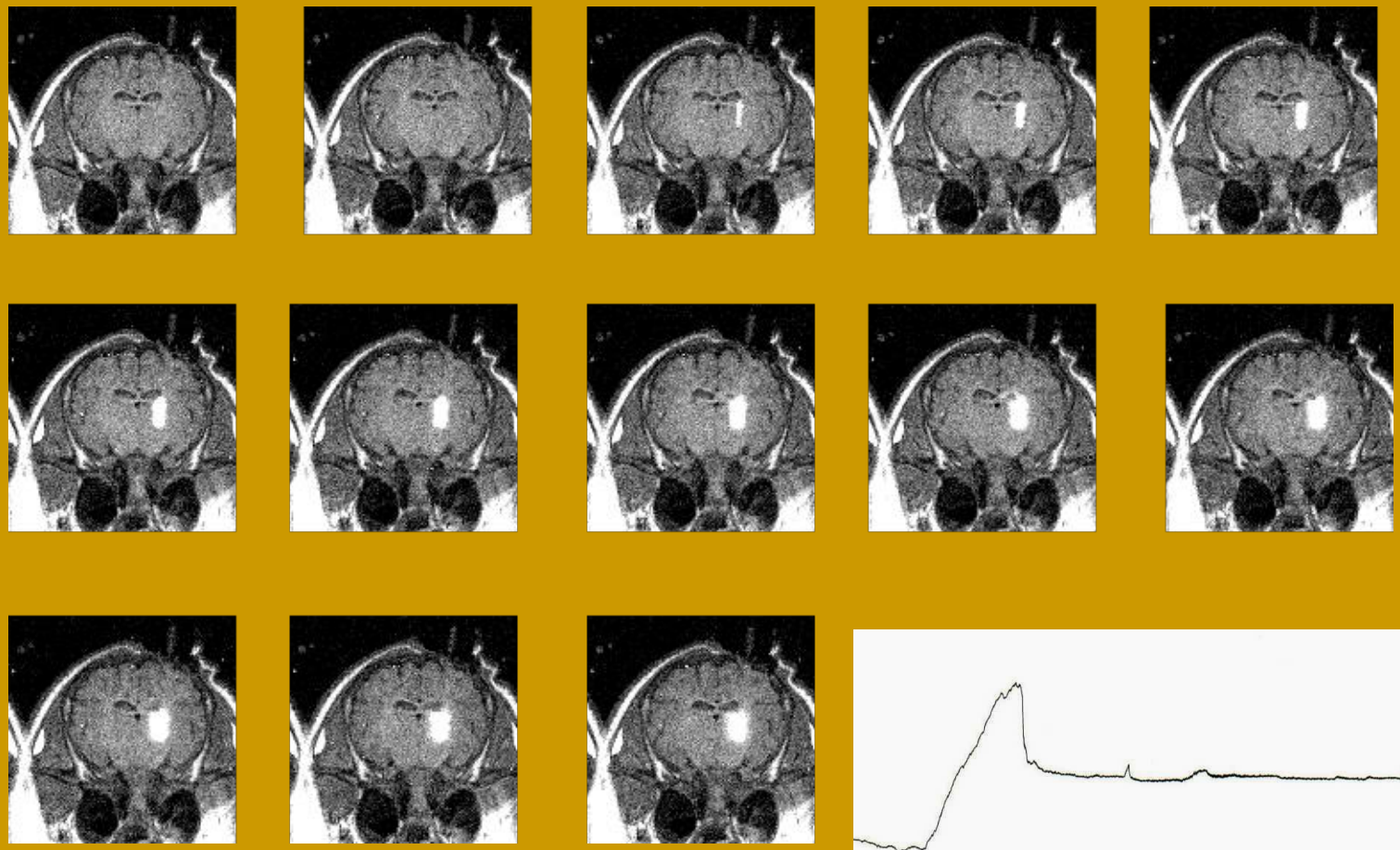






Yarden & Sliwkowski Nature Reviews Molec Cell Biol 2001

Pig Brain Infusion



Chen et al., in press, J. Neurosurg.

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