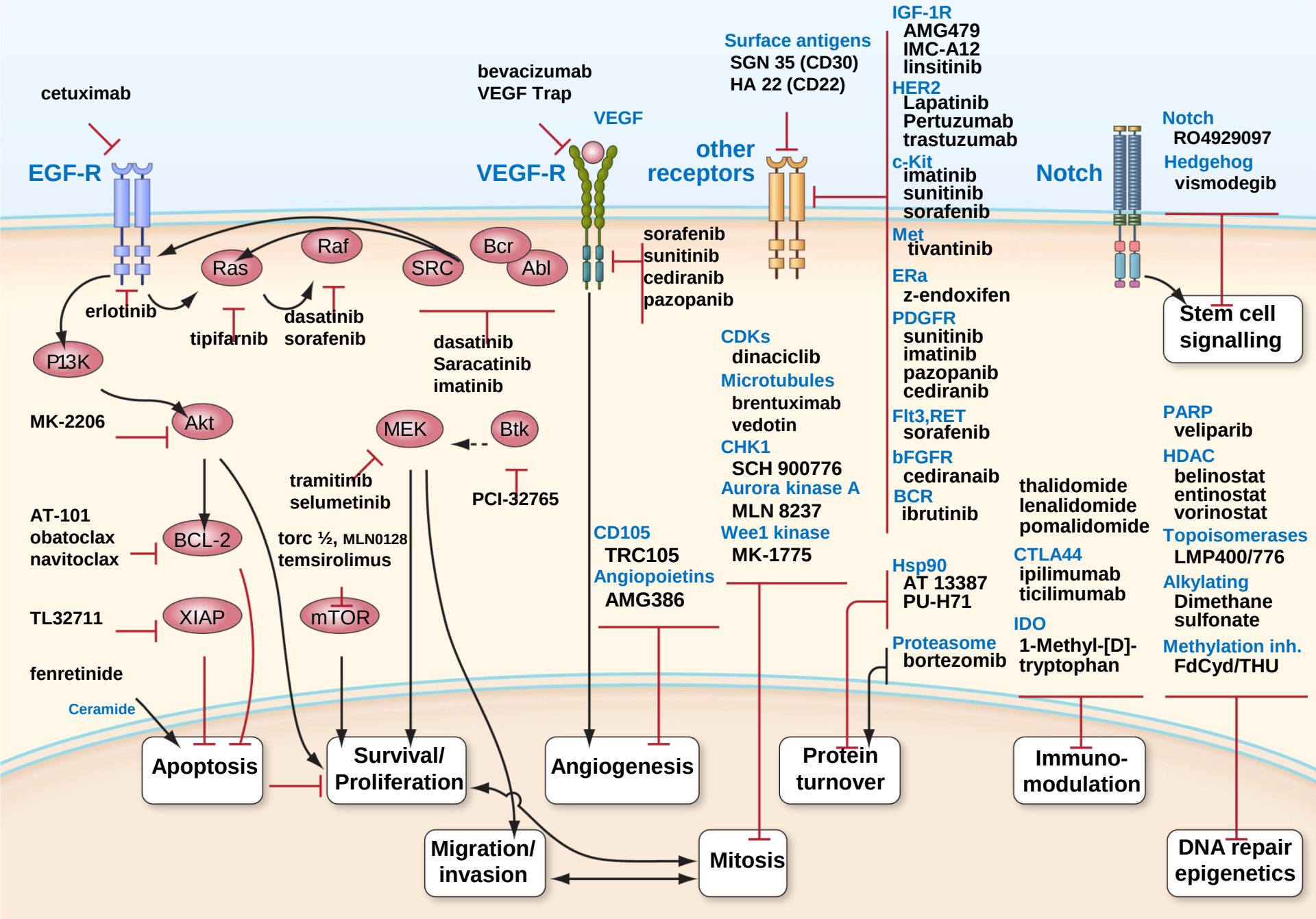
STANFORD
CANCER INSTITUTE

Clinical Challenges in Dose Selection for CombinationTherapy

12 May 2017

Mark Pegram, M.D.
Susy Yuan-Huey Hung Professor of Oncology
Associate Director for Clinical Research
Director, Stanford Breast Oncology Program
Associate Dean for Clinical Research Quality
Stanford University School of Medicine

High Priority Targets and Drugs

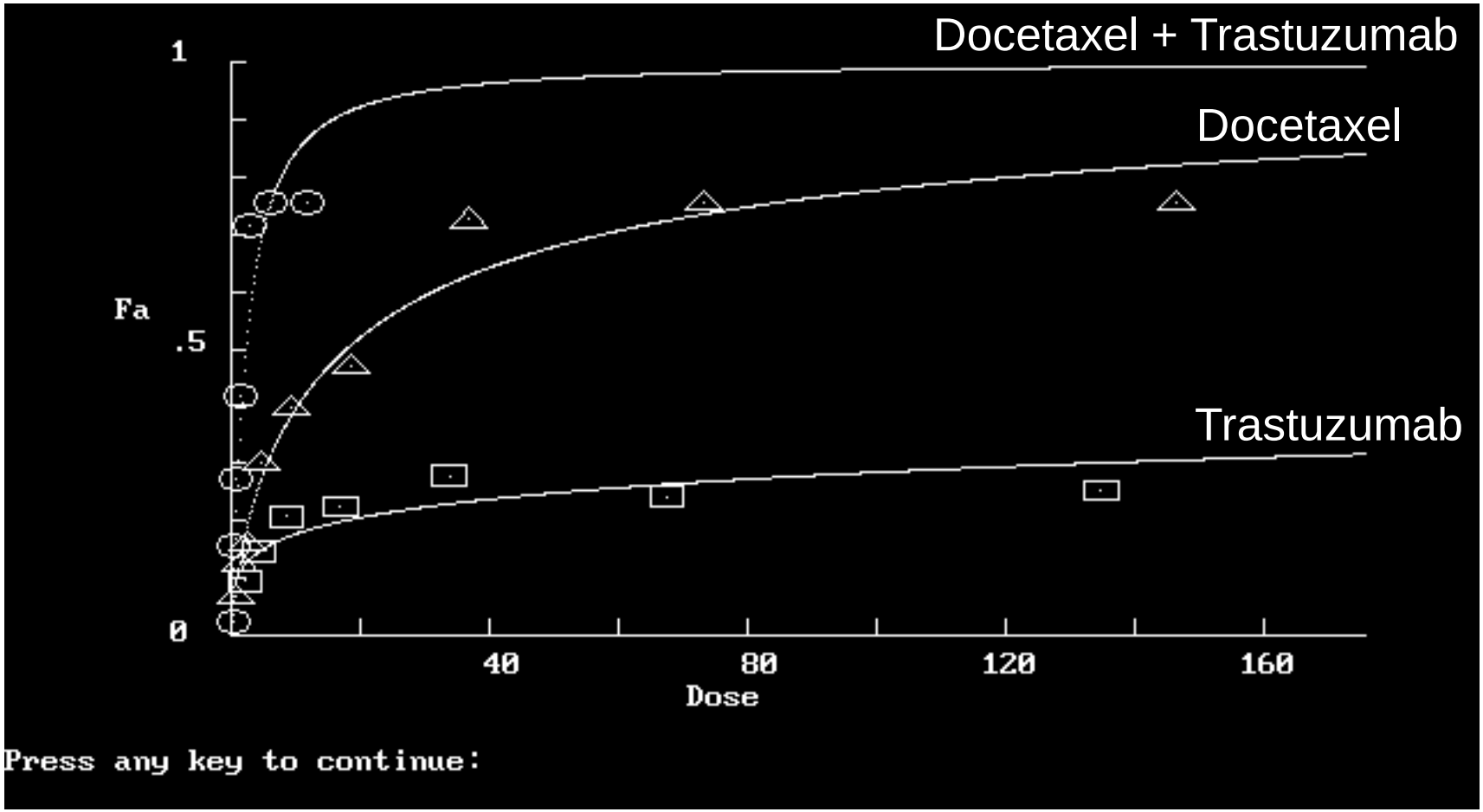


Methodologies Used to Evaluate Drug Combinations

- **Isobologram methods**
  - **Steel & Peckham (1979)**
  - **Berenbaum (1981)**
- **3D Response surface methodology**
  - **Greco, Bravo & Parsons (1995)**
- **Multiple drug effect analysis (Combination Index)**
  - **Chou & Talalay (1984)**

Dose/Response: Chemotherapy + Trastuzumab

Example: Docetaxel + Trastuzumab



The Median Effect Principle

$$fa/fu = (D/D_m)^m$$

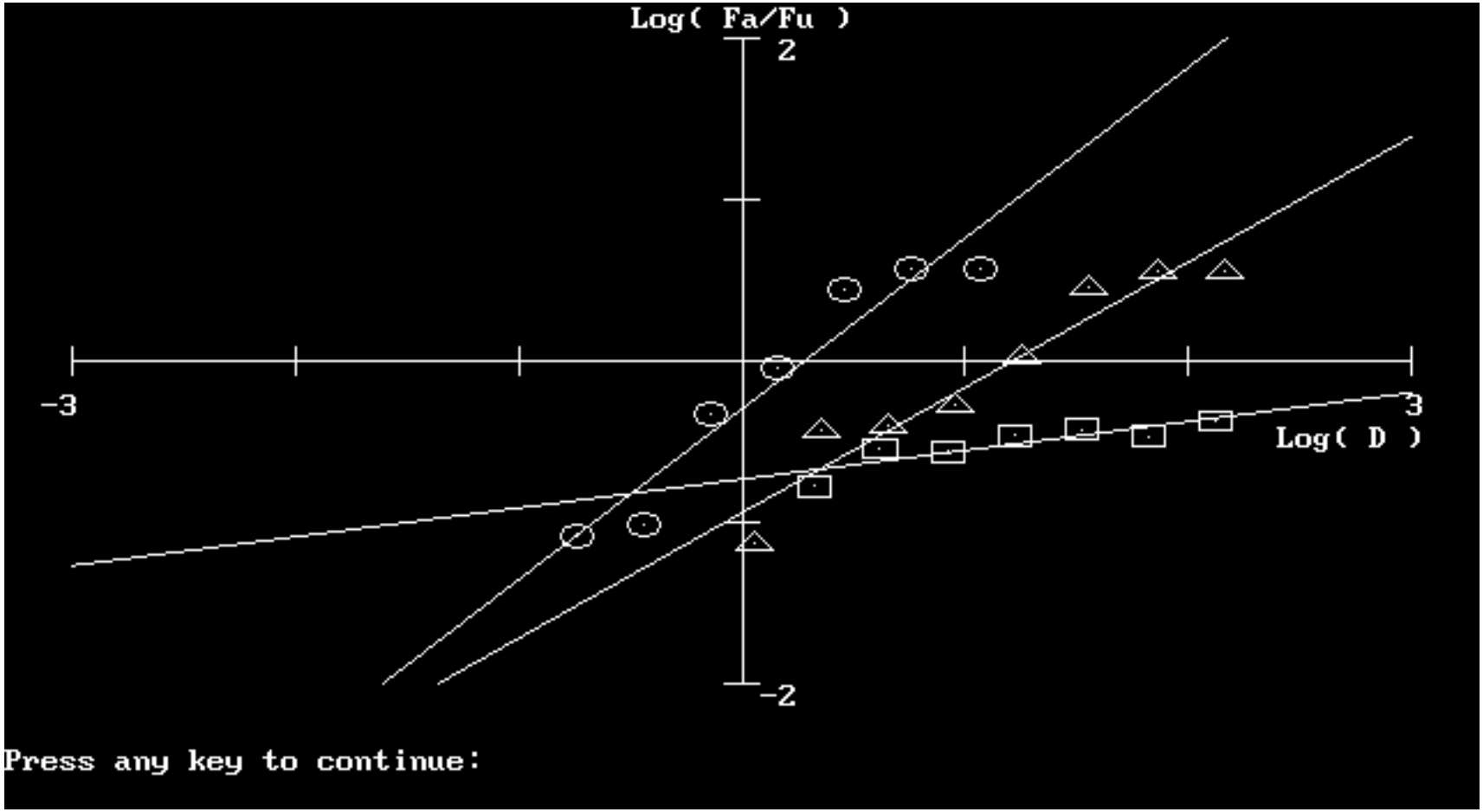
Taking the log of both sides of the equation yields:

The Median Effect Equation

$$\log(fa/fu) = m\log(D) - m\log(D_m)$$

Median Effects Plot: Chemotherapy + Trastuzumab

Docetaxel + Trasuzumab



The Median Effect Principle

Recall that: fa + fu = 1

and fu = (1 - fa)

Therefore, $fa/(1-fa) = (D/D_m)^m$

When m = 1,

$fa = [1 + (Dm/D)]^{-1}$

Looks familiar?

The Median Effect Principle

Looks familiar?

$$fa = [1 + (Dm/D)]^{-1}$$

Michaelis Menton Equation

$$v/Vmax = [1 + (Km/S)]^{-1}$$

COMBINATION INDEX (CI):

$$CI = \frac{(D)_1}{(Dx)_1} + \frac{(D)_2}{(Dx)_2} + \frac{\alpha(D)_1(D)_2}{(Dx)_1(Dx)_2}$$

CI = 1, Interaction is SUMMATION
CI < 1, Interaction is SYNERGY
CI > 1, Interaction is ANTAGONISM

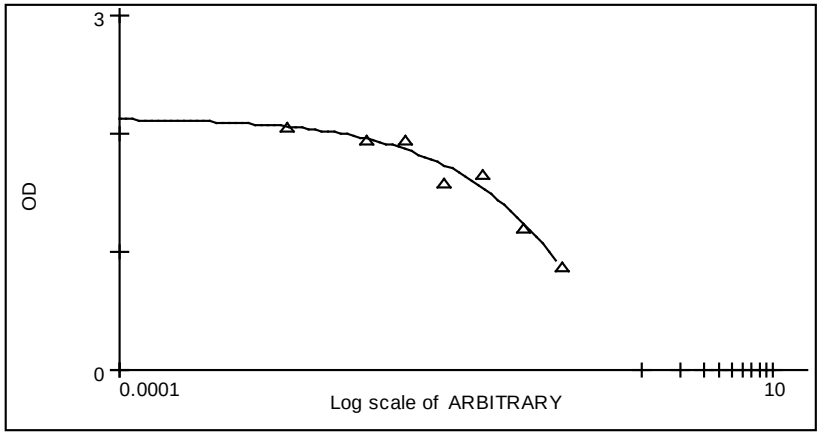
T.C. Chou and P. Talalay (1984) *Adv. Enz. Regul*. 22, 27-55.

Multiple Drug Effect Analysis: EXAMPLE

Curve Fit: 4-Parameter Corr. Coeff: 0.978

y = (A-D)/(1 + (x/C)^B) + D

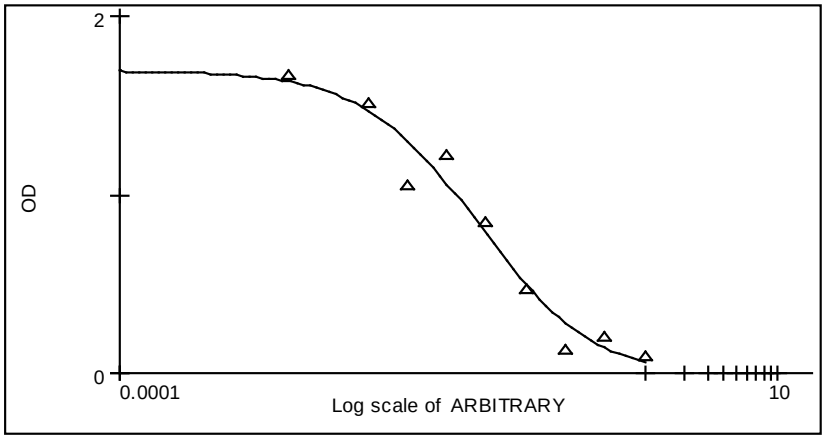
A = 2.14 B = 0.640 C = 1.86 D = -3.72



Curve Fit: 4-Parameter Corr. Coeff: 0.978

y = (A-D)/(1 + (x/C)^B) + D

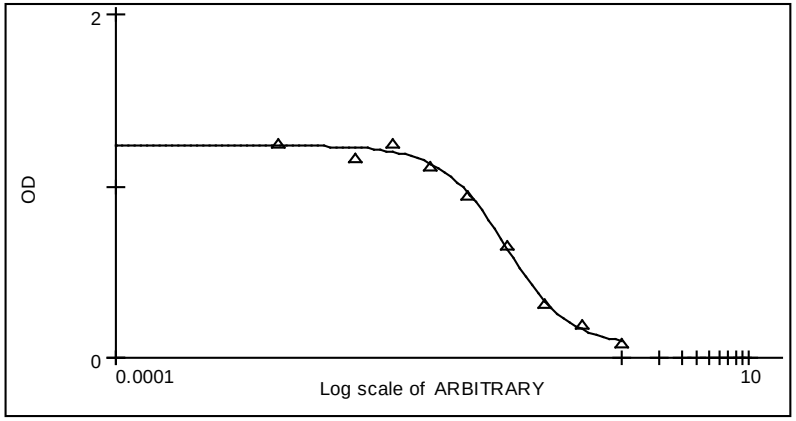
A = 1.70 B = 0.985 C = 0.0546 D = -0.0250

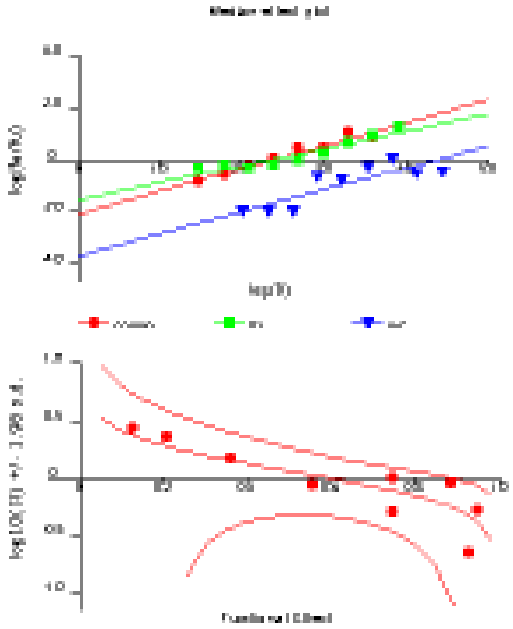


Curve Fit: 4-Parameter Corr. Coeff: 0.998

y = (A-D)/(1 + (x/C)^B) + D

A = 1.24 B = 1.70 C = 0.122 D = 0.0752





Calculated values for the Combination Index: Fractional inhibition of SK-BR-3 cell proliferation by a mixture of alkylating agent and trastuzumab

	Combination Index Values at:					Parameters:		
Drug	**IC_{30}**	**IC_{40}**	**IC_{50}**	**IC_{60}**	**IC_{70}**	**Dm**	**m**	**r**
Alkylator						**66.2uM**	**0.81**	**0.99**
MAb HER2						**675.0nM**	**0.15**	**0.96**
Alk + MAb HER2	**0.52**	**0.37**	**0.41**	**0.49**	**0.60**	**27.1uM**	**0.59**	**0.99**
Combined effect	**Synergy**	**Synergy**	**Synergy**	**Synergy**	**Synergy**			

$$CI = \frac{(D)_1}{(Dx)_1} + \frac{(D)_2}{(Dx)_2} + \frac{\alpha(D)_1(D)_2}{(Dx)_1(Dx)_2}$$

CI = 1, Interaction is SUMMATION
CI < 1, Interaction is SYNERGY
CI > 1, Interaction is ANTAGONISM

T.C. Chou and P. Talalay (1984)
Adv. Enz. Regul. 22, 27-55.

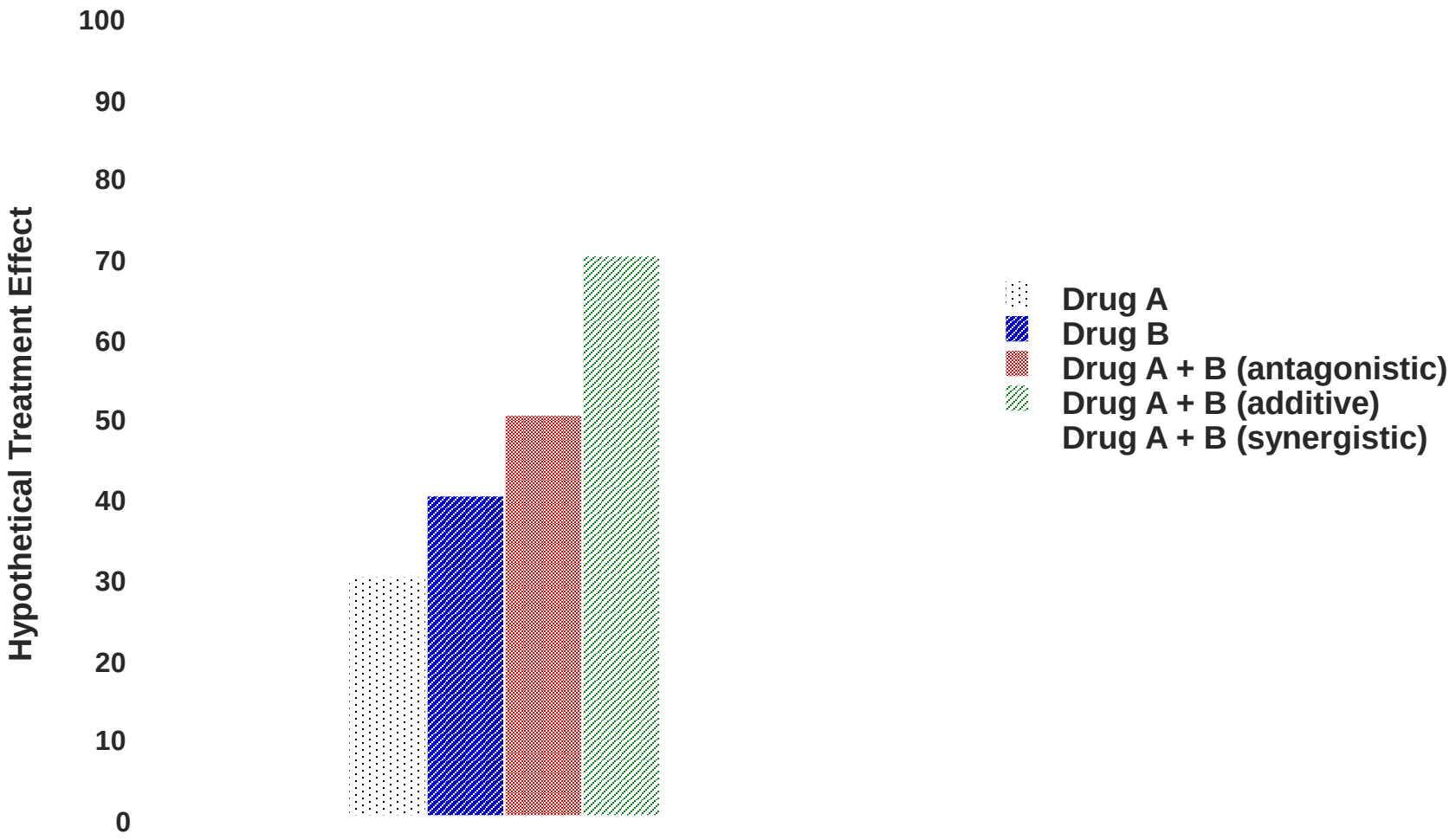
Pegram, et al., Oncogene 18: 2241-2251,1999

Combination Index Values for Chemotherapy/Trastuzumab Drug Combinations *in vitro*

Drug	Combination Index	P-value	Interaction
Cisplatin	0.56 ± 0.15	0.001	Synergy
Etoposide	0.54 ± 0.15	0.0003	Synergy
Thiotepa	0.67 ± 0.12	0.0008	Synergy
Doxorubicin	1.16 ± 0.18	0.13	Addition
Paclitaxel	0.91 ± 0.23	0.21	Addition
Methotrexate	1.36 ± 0.17	0.21	Addition
Vinblastine	1.09 ± 0.19	0.26	Addition
5-Fluorouracil	2.87 ± 0.51	0.0001	Antagonism

Pegram, et al., Oncogene 18: 2241-2251,1999

Examples of Antagonism, Addition, and Synergy



View Articles

Abstracting/ Indexing

Article Enrichments

› Genome Viewer

Related Links

› Author Stats

› Publishing Campus

› Author Services

Chou & Talalay paper from 1984 makes history

One of the most cited papers

Published in 1984, the manuscript "Quantitative analysis of dose-effect relationships: the combined effects of multiple drugs or enzyme inhibitors" by Ting-Chao Chou and Paul Talalay has become one of most cited articles in all fields. With **3,520 citations**, it is not only the most cited article in Advances in Biological Regulation, but also one of the most cited articles (being in the top 1% of most cited articles) in the field of Biochemistry, Cancer Research, Molecular Biology and Genetics (Scopus, 16thMarch 2016).

Here is what Ting-Chao Chou, first author of the manuscript tells us:

"Over 31 years ago, Prof. George Weber of Indiana University invited Prof. Paul Talalay (JHU) and me (MSKCC) to give a symposium talk sponsored by Eli Lilly, in conjunction with Advances in Enzyme Regulation. My talk was very much impressed by Professor Carl F. Cori of Harvard (Nobel Laureate of Medicine 1947). His vision has proven to be extremely insightful and accurate. The paper in Adv. Enz. Regul. 22:27-55, 1984 by Chou & Talalay has become among the most cited and the most broadly cited theoretical papers of all time in all fields."

0031-6997/95/4702-0331$03.00/0
PHARMACOLOGICAL REVIEWS

Vol. 47, No. 2
Printed in U.S.A.

The Search for Synergy: A Critical Review from a Response Surface Perspective*

WILLIAM R. GRECO, GREGORY BRAVO, AND JOHN C. PARSONS

Department of Biomathematics, Roswell Park Cancer Institute, Buffalo, New York

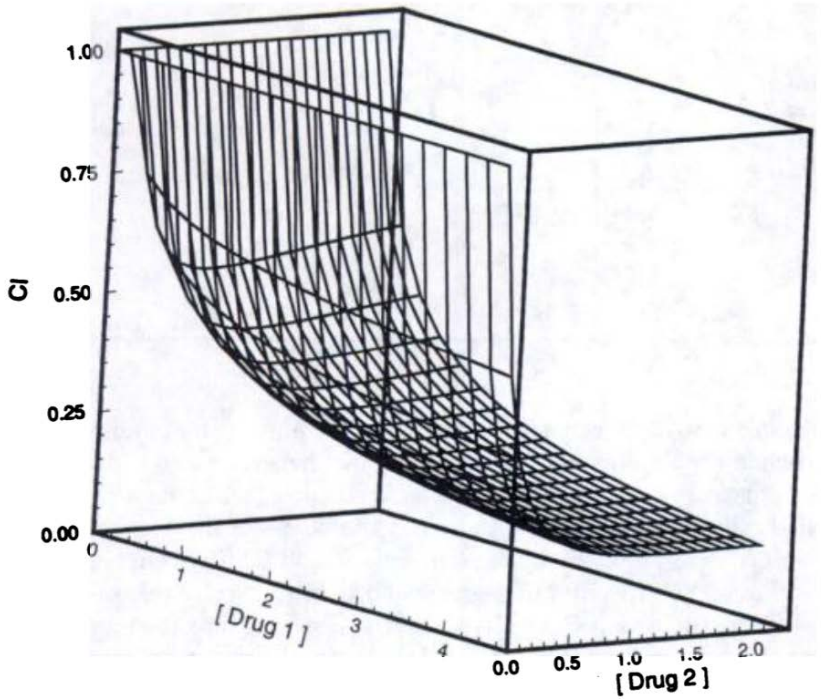
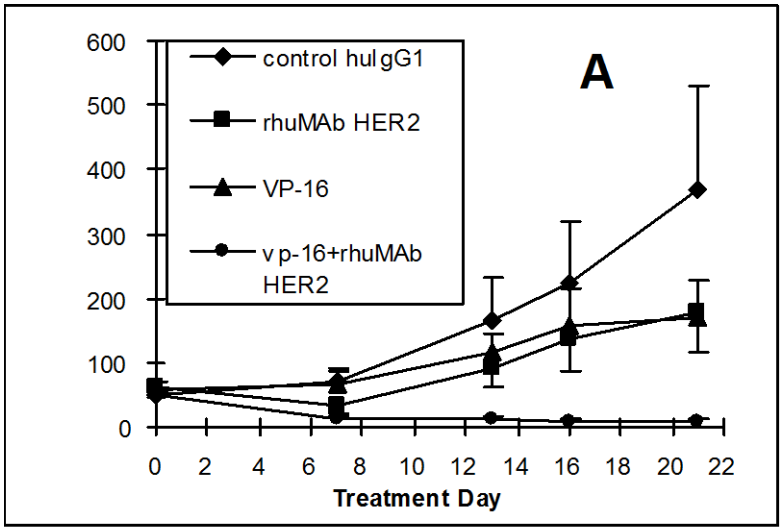
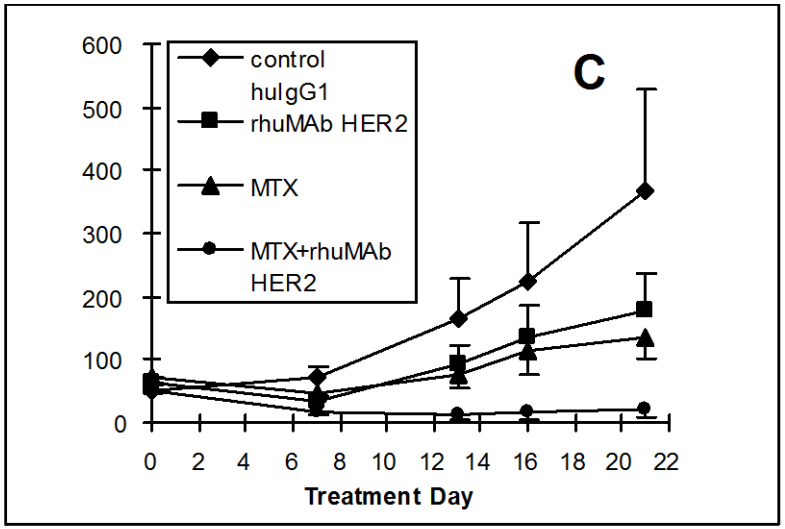
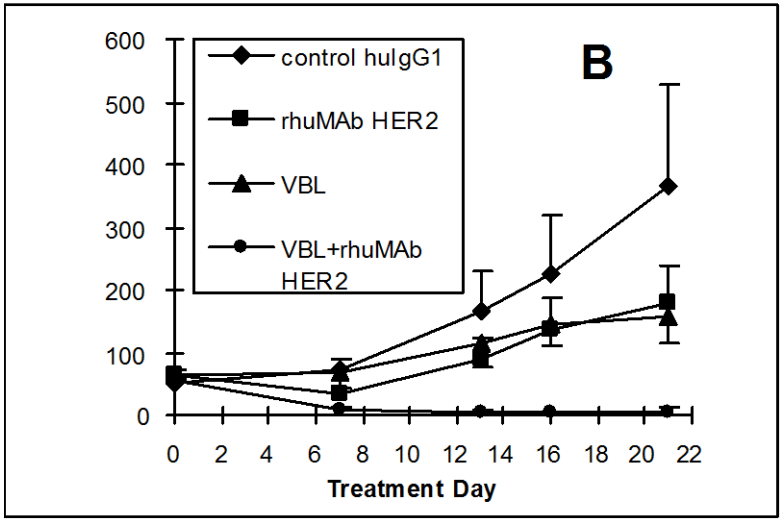


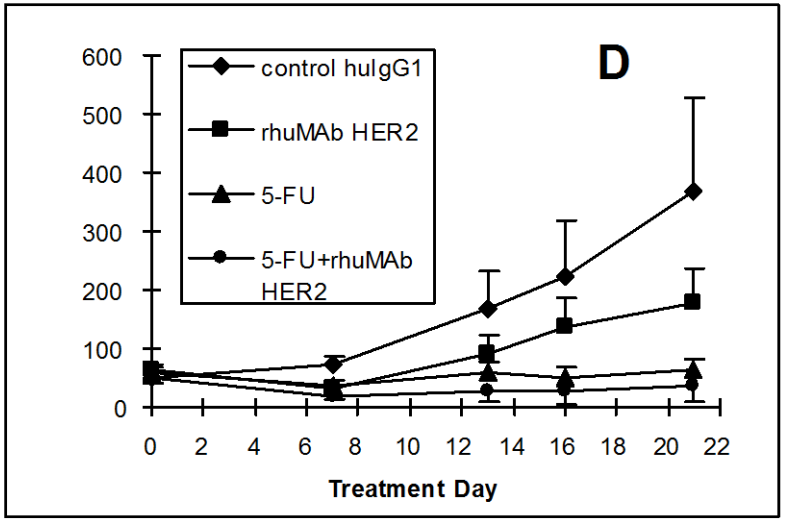
FIG. 9. A 3-D fishnet plot of the *CI* calculated from Eq. 8 for the Loewe synergistic concentration-effect surface described in Figs. 4, 5, 7, and 8.

Treatment of MCF7/HER2 xenografts with trastuzumab in combination with (A) VP-16, (B) vinblastine, (C) methotrexate, and (D) 5-fluorouracil.









Pegram, et al., Oncogene, 18: 2241-2251, 1999

Table 1. Treatment schedule

Group no.	Group code	Time of 1.0 mg/kg rhu MAb HER-2 administration, days	Time of 5.0 mg/kg doxorubicin administration, days
1	C	—	—
2	H0	0	—
3	H1	1	—
4	H4	4	—
5	D0	—	0
6	D1	—	1
7	D4	—	4
8	H0D0	0	0
9	H0D1	0	1
10	H0D4	0	4
11	H1D0	1	0
12	H4D0	4	0

Day 0 is 14 days after xenograft implantation. There were seven mice per group.

A model-based approach for assessing *in vivo* combination therapy interactions

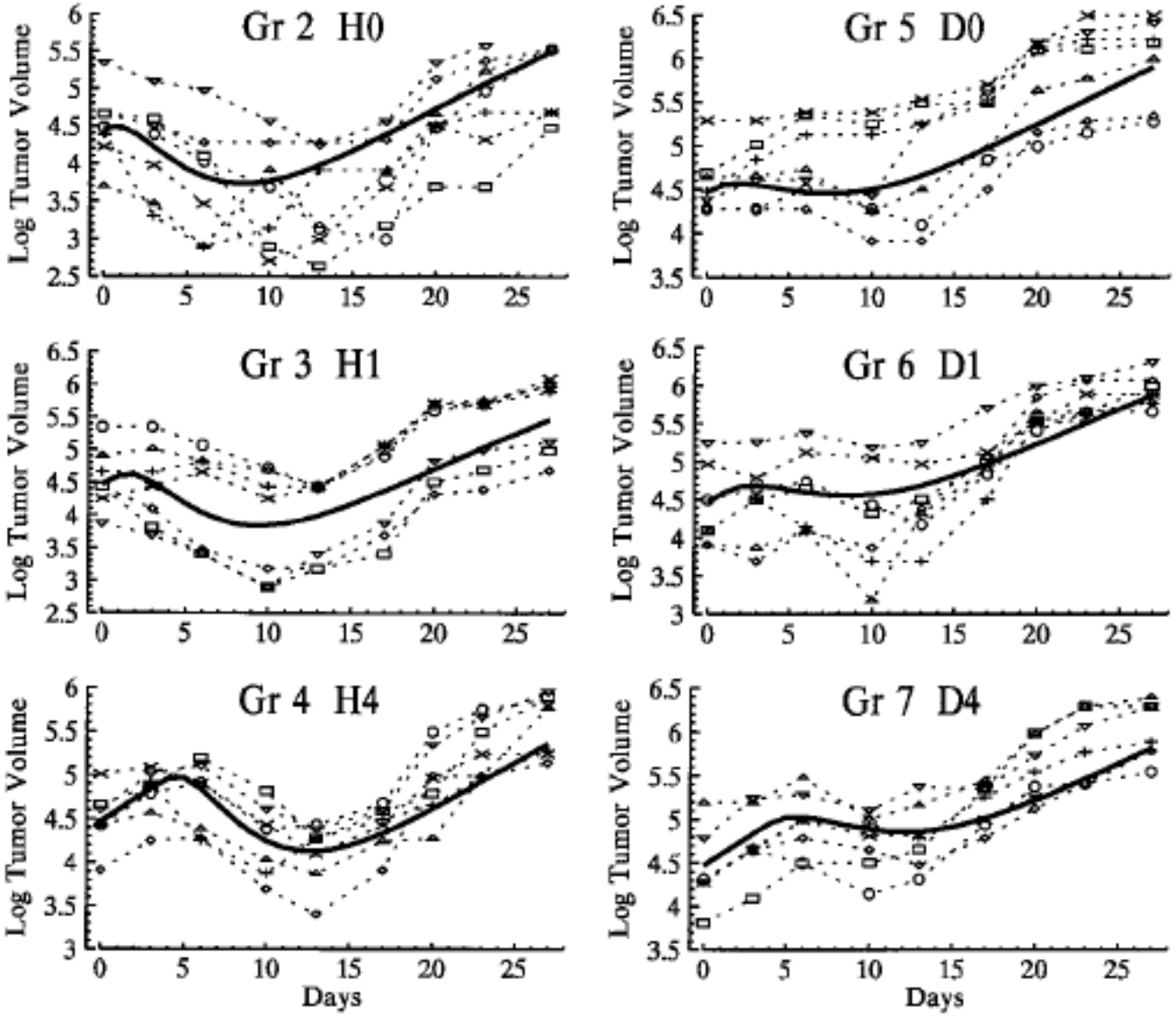
Angela M. Lopez*†, Mark D. Pegram‡, Dennis J. Slamon‡, and Elliot M. Landaw*

*Department of Biomathematics, School of Medicine, University of California, Los Angeles, CA 90095-1766; and ‡Department of Medicine, Division of Hematology/Oncology, School of Medicine, University of California, Los Angeles, CA 90095-1678

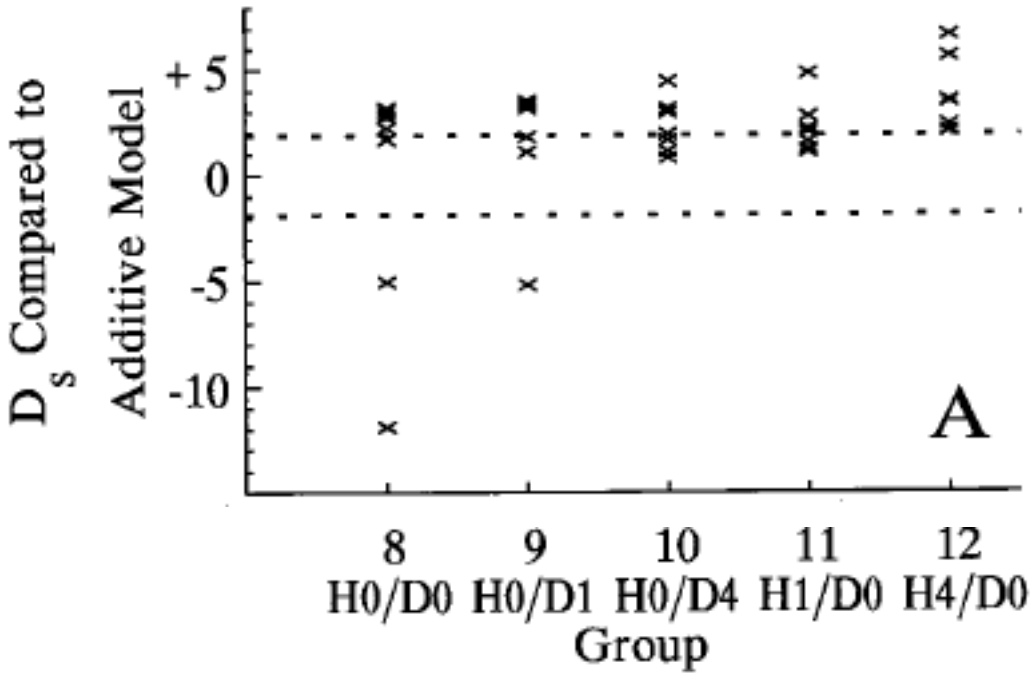
$$\frac{dL}{dt} = \alpha_1 - \alpha_2(L - L_0)$$

$$- \beta_h k_h (t - t_h)\exp(-k_h(t - t_h))I_{[t \geq t_h]}$$

$$- \beta_d k_d (t - t_d)\exp(-k_d(t - t_d))I_{[t \geq t_d]},$$

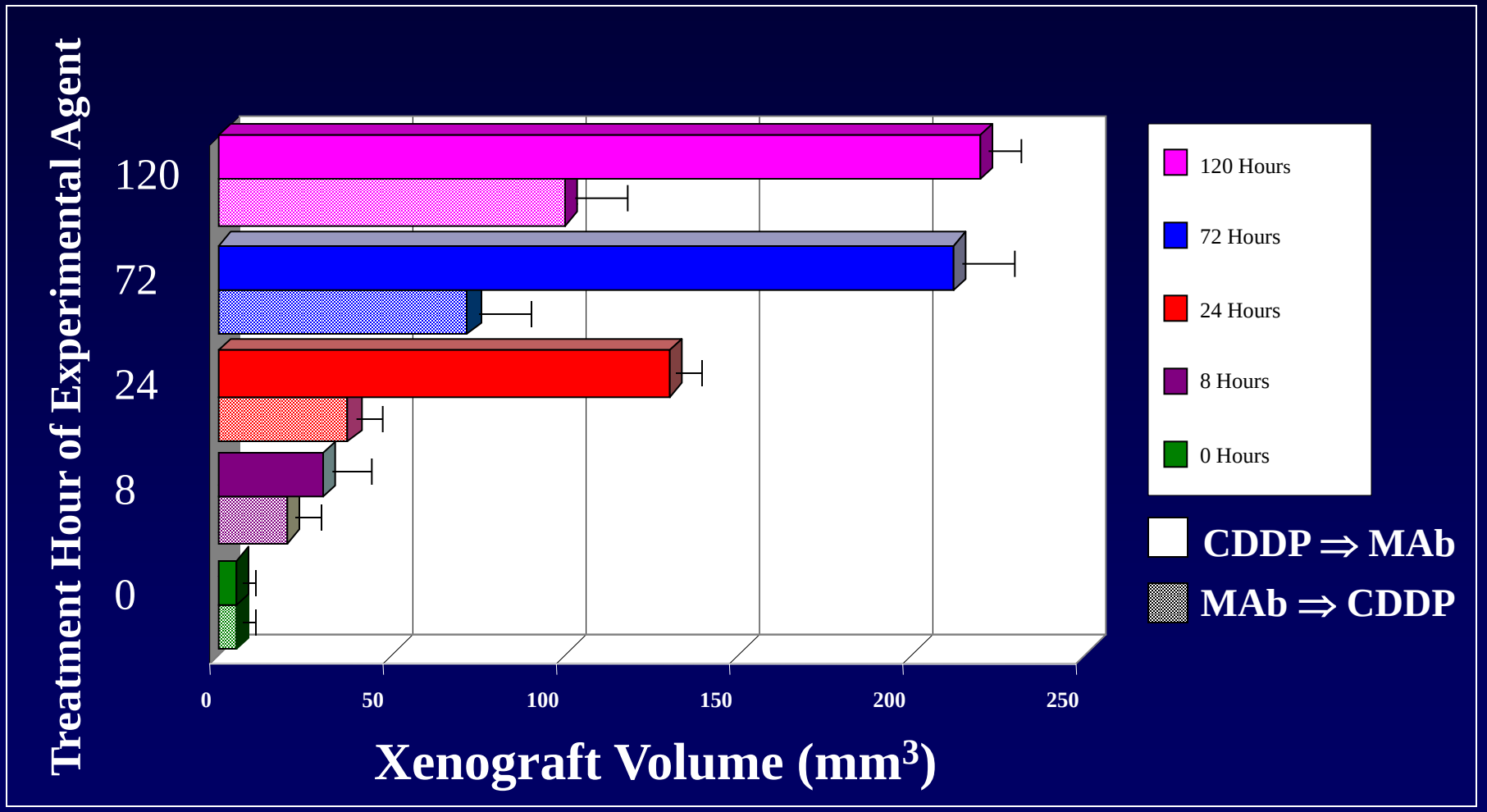

Gr 2 H0
Gr 5 D0
Gr 3 H1
Gr 6 D1
Gr 4 H4
Gr 7 D4
Log Tumor Volume
Days

Distance measures (observed vs expected)



$$D = \frac{1}{N}(\underline{z} - E(\underline{z}))^T [Cov(\underline{z})]^{-1} (\underline{z} - E(\underline{z}))$$

Effect of Order and Timing of Chemotherapy and Trastuzumab Administration on Xenograft Volume

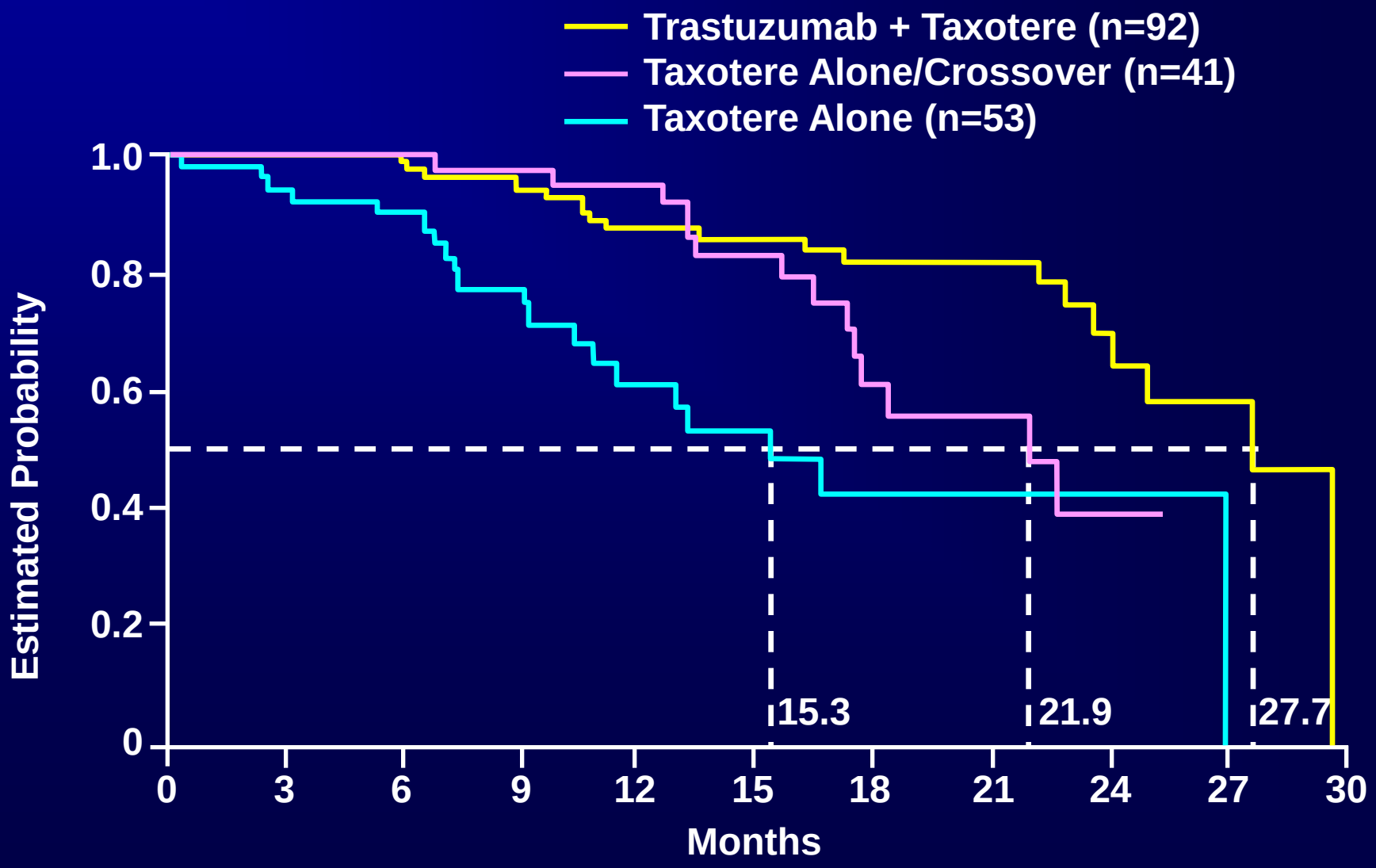


Lopez, Pegram, Slamon, Landaw *Proc Natl Acad sci USA 96: 13023-8, 1999.*

Pietras RJ, Fendly BM, Chazin VR, Pegram MD, Howell SB, and Slamon DJ. *Oncogene* 9: 1829-1838, (1994).

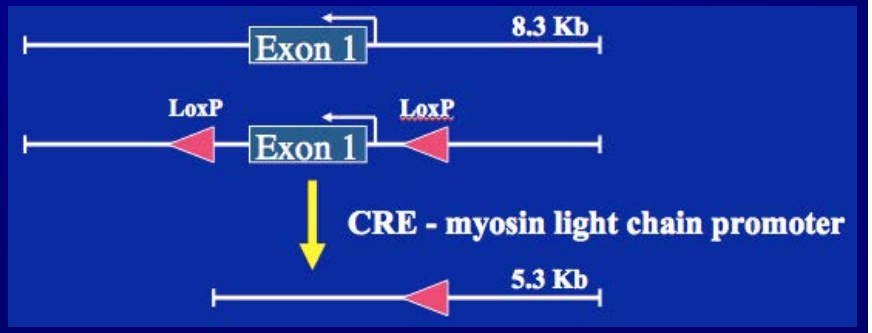
M77001

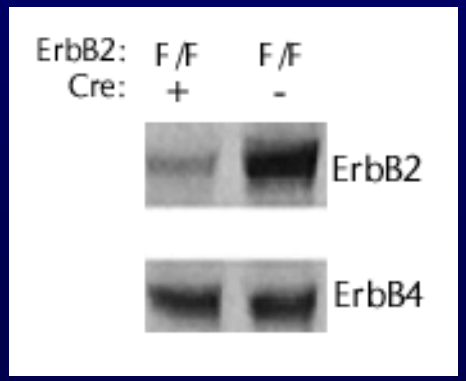
Estimated Survival



Marty, M et al., J Clin Oncol. 2005 Jul 1;23(19):4265-74.

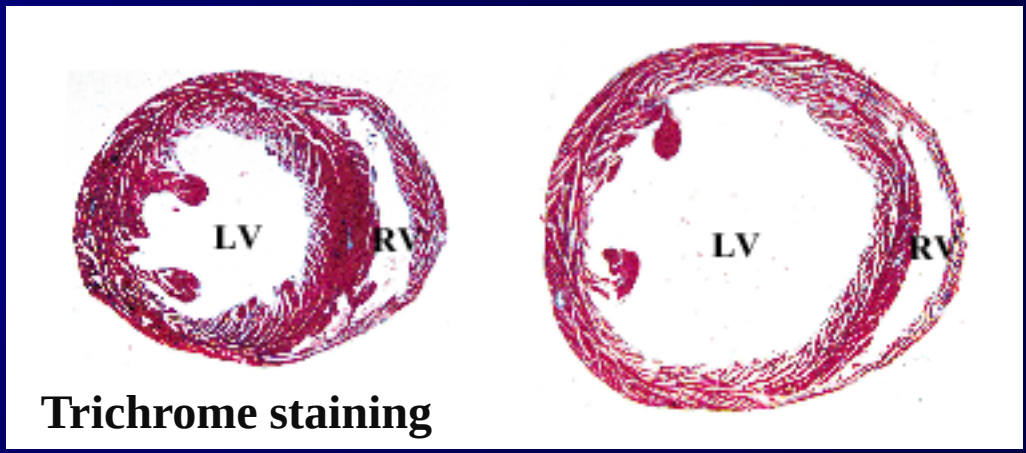
Phenotypic Analysis of erbB2 Conditional Knock-out Mouse Myocardium



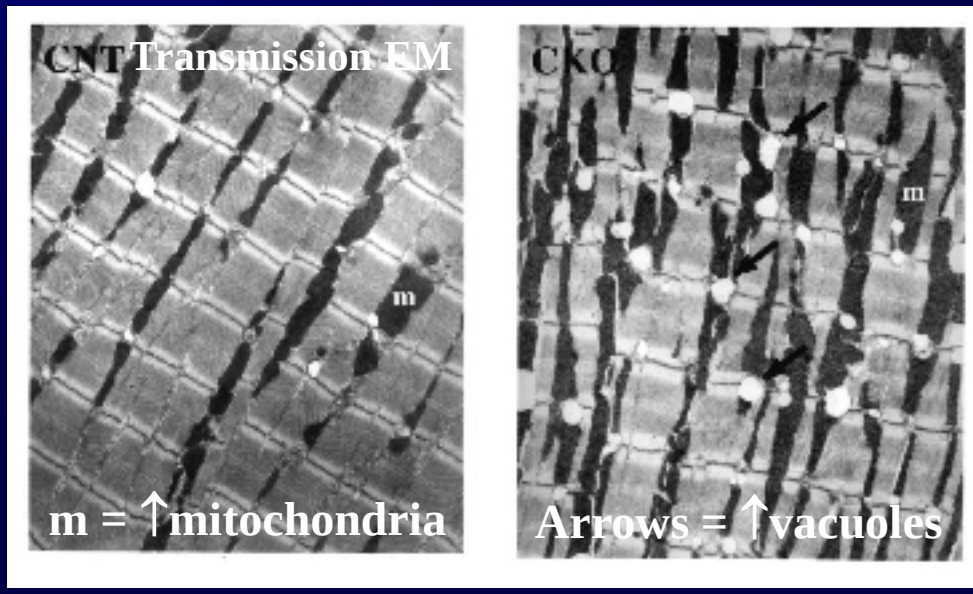


Crone SA, et al., Nature Medicine 8: 459-465 (2002)

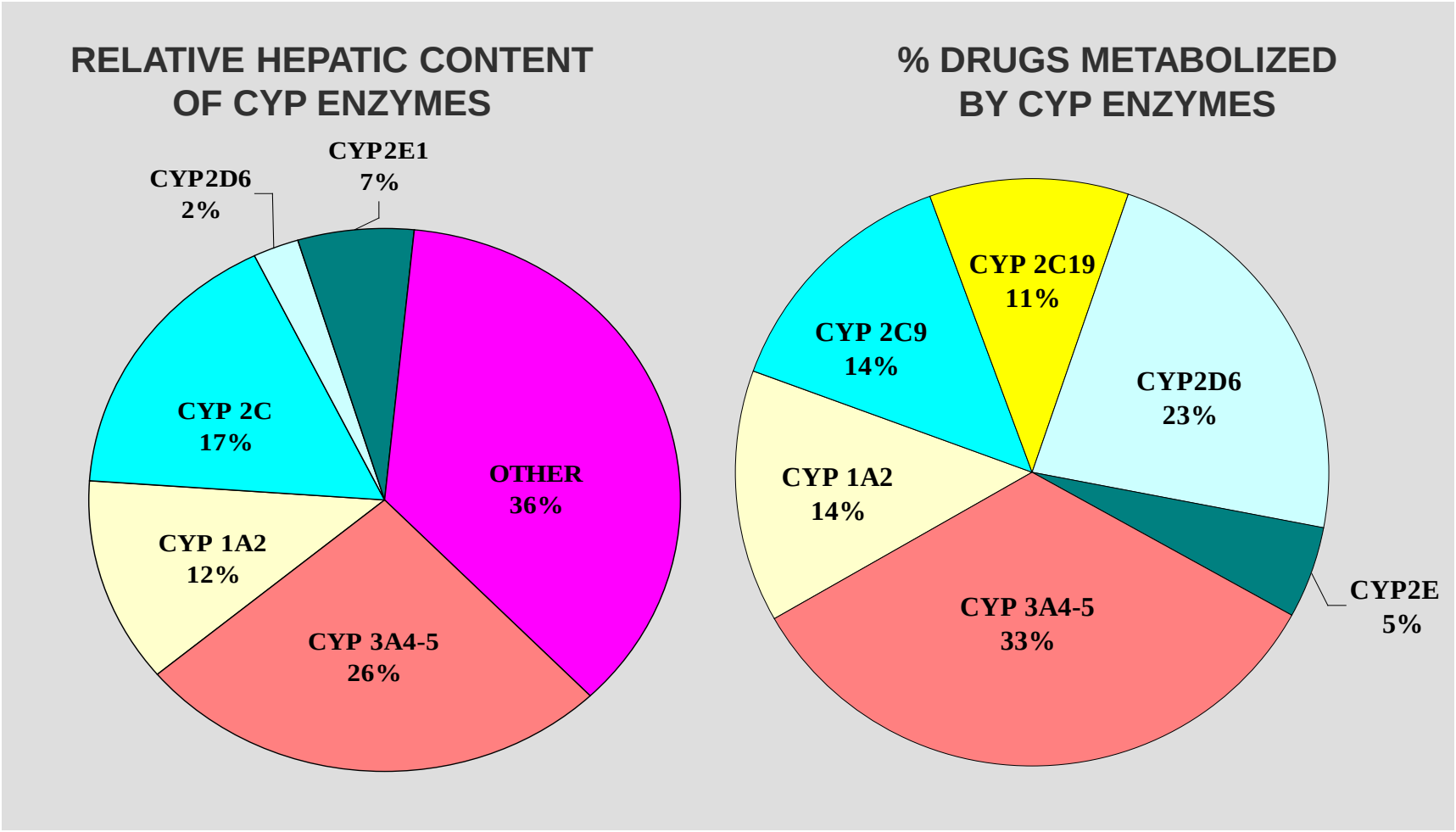
erbB2-floxed **erbB2-CKO**



Trichrome staining



ROLE OF CYP ENZYMES IN HEPATIC DRUG METABOLISM



Consider substrates, inhibition, induction and polymorphisms

Current perspective

Dose-escalation models for combination phase I trials in oncology

Paul Hamberg [a,e,*], *Mark J. Ratain* [b], *Emmanuel Lesaffre* [c,d], *Jaap Verweij* [a]

[a] *Department of Medical Oncology, Erasmus University Medical Center, Daniel den Hoed Cancer Center, Rotterdam, The Netherlands*
[b] *Department of Medicine, University of Chicago, Chicago, United States*
[c] *Department of Biostatistics, Erasmus University Medical Center, Rotterdam, The Netherlands*
[d] *L-Biostat, Catholic University of Leuven, U.Z. St. Rafael, Leuven, Belgium*

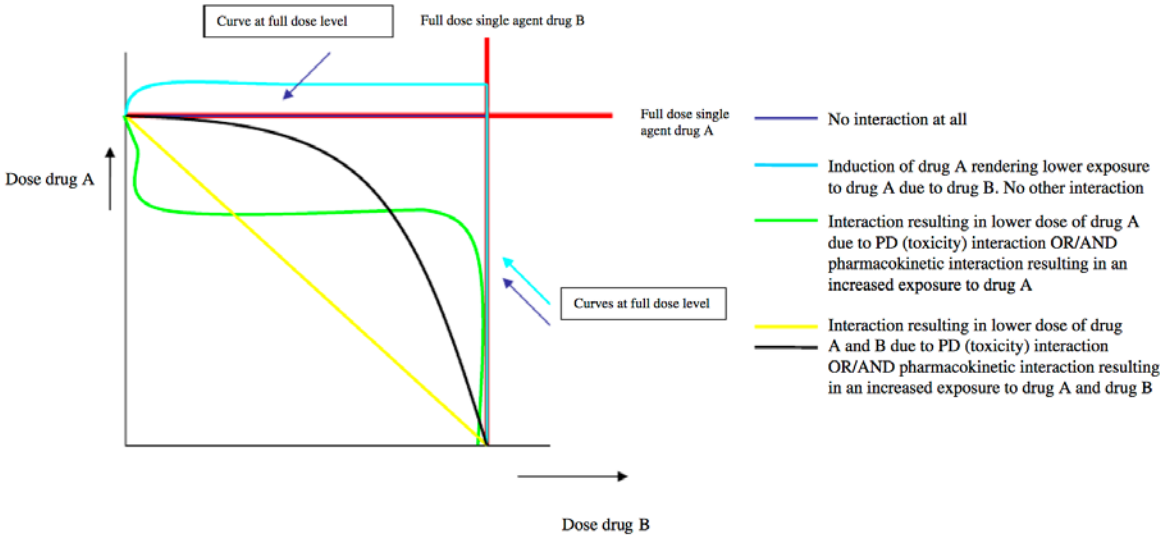


Fig. 2 – Sample of envelopes of tolerability (as types of envelopes are infinite) of a two-drug combination. An established MTD will be a single point on its curve. And although often only a single MTD is determined, many more MTDs do exist. The location of the determined MTD on its envelope is often a result of trial design.

Guidance for Industry

Codevelopment of Two or More New Investigational Drugs for Use in Combination

Additional copies are available from:
Office of Communications
Division of Drug Information, WO51, Room 2201
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993
Phone: 301-796-3400; Fax: 301-847-8714
druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

NATIONAL CANCER INSTITUTE®

Design of Phase I Combination Trials: Recommendations of the Clinical Trial Design Task Force of the NCI Investigational Drug Steering Committee

Channing J. Paller[1], Penelope A. Bradbury[2], S. Percy Ivy[3], Lesley Seymour[2], Patricia M. LoRusso[4], Laurence Baker[5], Larry Rubinstein[3], Erich Huang[3], Deborah Collyar[6], Susan Groshen[7], Steven Reeves[3], Lee M. Ellis[8], Daniel J. Sargent[9], Gary L. Rosner[1], Michael L. LeBlanc[10], and **Mark J. Ratain[11]**

Clin Cancer Res. 2014 August 15; 20(16): 4210–4217.
doi:10.1158/1078-0432.CCR-14-0521.

Combination Therapies: Opportunities and Pitfalls

Opportunities	Pitfalls
Validate novel biological hypotheses	Unreliable pre-clinical models
Synergize anti-tumor effect without synergizing toxicity	Optimal selection of drugs and targets to study in combination
Increase therapeutic index/window	Optimal sequence and dose of combination therapy
Synthetic lethality: optimize combination use of single agents with limited single agent activity	Risk overlapping toxicity
Counteract primary and secondary resistance	Lack of standard design for phase 1 / 2 for combination therapies
Develop novel indications for existing and approved drugs	Competing interests of researchers, corporations and / or institutions to combine treatments

Yap, Omlin & de Bono, JCO 2013

Developing Combination Therapies: Messages

- Developing drug combinations is arguably the most important major challenge in cancer drug development today
- Major hurdles
  - Establishing a strong hypothesis and selecting the right combinations
  - Understanding functional biology: Feedback loops, redundancies
  - Intra-tumor heterogeneity
  - Inter-patient PK-PD variability and optimizing target blockade to abrogate narrow therapeutic indices; multiple schedules?
  - Drug-Drug interactions
  - Providing early proof of concept to support Phase 3 investment
  - Combining agents from different sponsors
- But with clear thinking we can find solutions to best serve our patients

STANFORD CANCER INSTITUTE
Stanford University Medical Center
A NATIONAL CANCER INSTITUTE-DESIGNATED CANCER CENTER

Questions/Comments Discussion

- Dennis Slamon
- Richard Pietras
- Gottfried Konecny
- Angela Lopez
- Nathalie Chorn
- Richard Finn

University of California, Los Angeles

- Toby Ward
- Kazuhiro Araki
- Anna Jegg
- Ralf Landgraf
- Michelle Gallas
- Xiaofei Liu
- Rebecca Olson
- Jessica Bockhorn
- Alex Lindqwister
- Xiaosong Chen
- Greg Vidal
- Amy Zong

Pegram Lab
Grant Support:
Susan G Komen for the Cure
BCRF
US Dept of Defense
NIH – R01
Expedition Inspiration
Gateway Foundation
TNBC Foundation
Jiv Dayal Foundation
Susy Yuan-Huey Hung
Jill and John Freidenrich

James H. Clark Center
Stanford University

MILLER SCHOOL OF MEDICINE
UNIVERSITY OF MIAMI

Stanford Bio-X Program:
Biology, Medicine,Chemistry, Physics and Engineering