Cancer Pharmacogenomics Development, Science, Translation

Richard Weinshilboum, M.D.

Dasburg Professor of Cancer Genomics Research

Department of Molecular Pharmacology and Experimental Therapeutics

Mayo Clinic-Mayo Medical School

Rochester, Minnesota USA

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Cancer Pharmacogenomics

- Introduction
- Present
- Promise
- Conclusions

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Pharmacogenetics-Pharmacogenomics

Critical component of

“personalized” or “individualized”

medicine

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Pharmacogenetics-Pharmacogenomics

Clinical Goals

- Avoid adverse drug reactions
- Maximize drug efficacy
- Select responsive patients

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Pharmacogenetics-Pharmacogenomics

Scientific Goals

- Link variation in genotype to variation in phenotype
- Determine mechanisms responsible for that link
- Translate the link into enhanced understanding, treatment and prevention of disease

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Pharmacogenetics-Pharmacogenomics

FDA Hearings
Pharmacogenetics and Drug Labeling

- Thiopurines – *TPMT**
- Irinotecan – *UGT1A1**
- Warfarin – *CYP2C9* and *VKORC1**
- Tamoxifen – *CYP2D6**

germline polymorphisms

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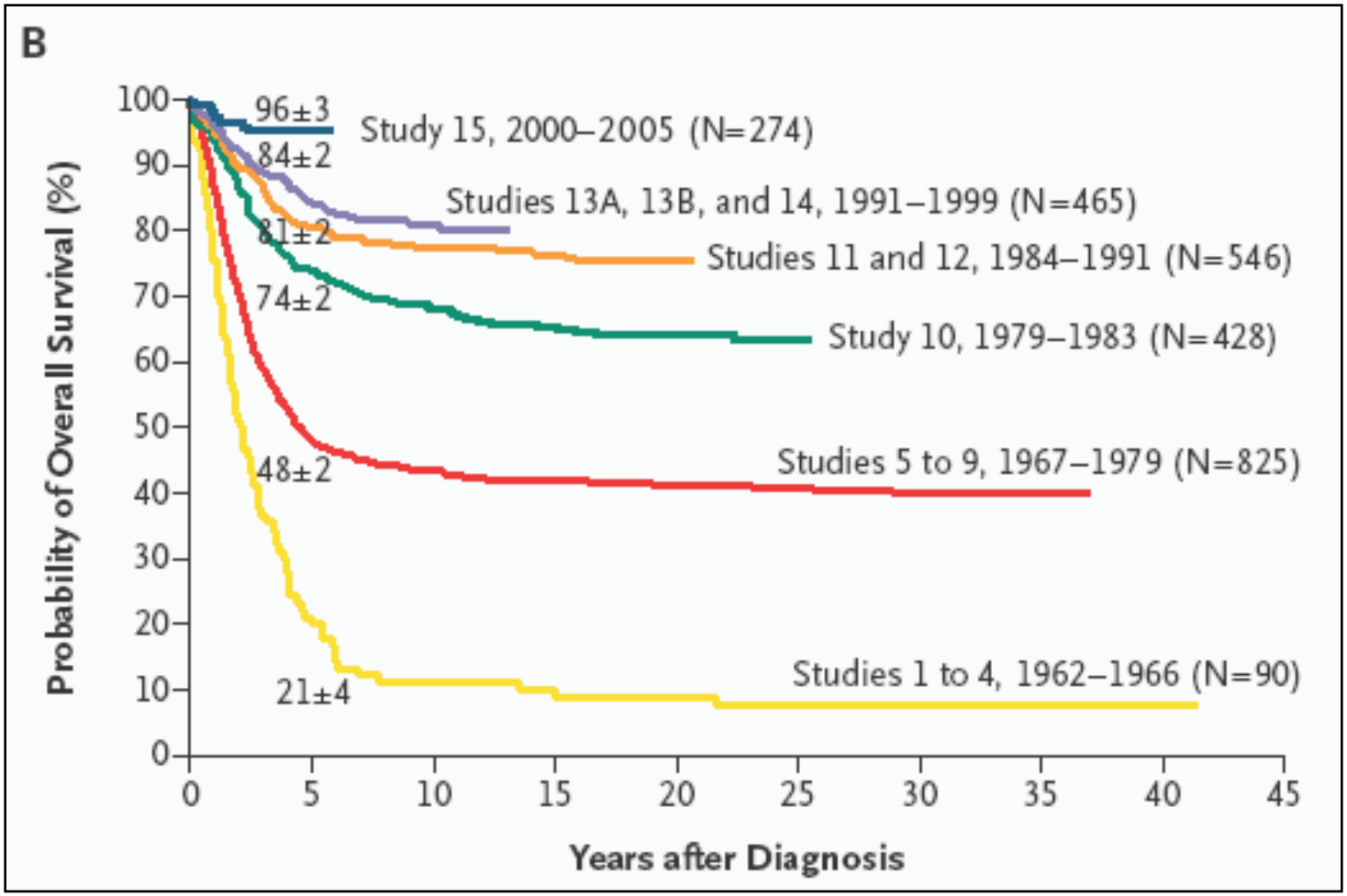
Childhood ALL Survival
St. Jude Experience



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TPMT
Genetic Polymorphism
Clinical Consequences

- **Low TPMT**
  - **Increased thiopurine toxicity**
  - **Increased risk for secondary neoplasm**
- **High TPMT**
  - **Decreased therapeutic effect**

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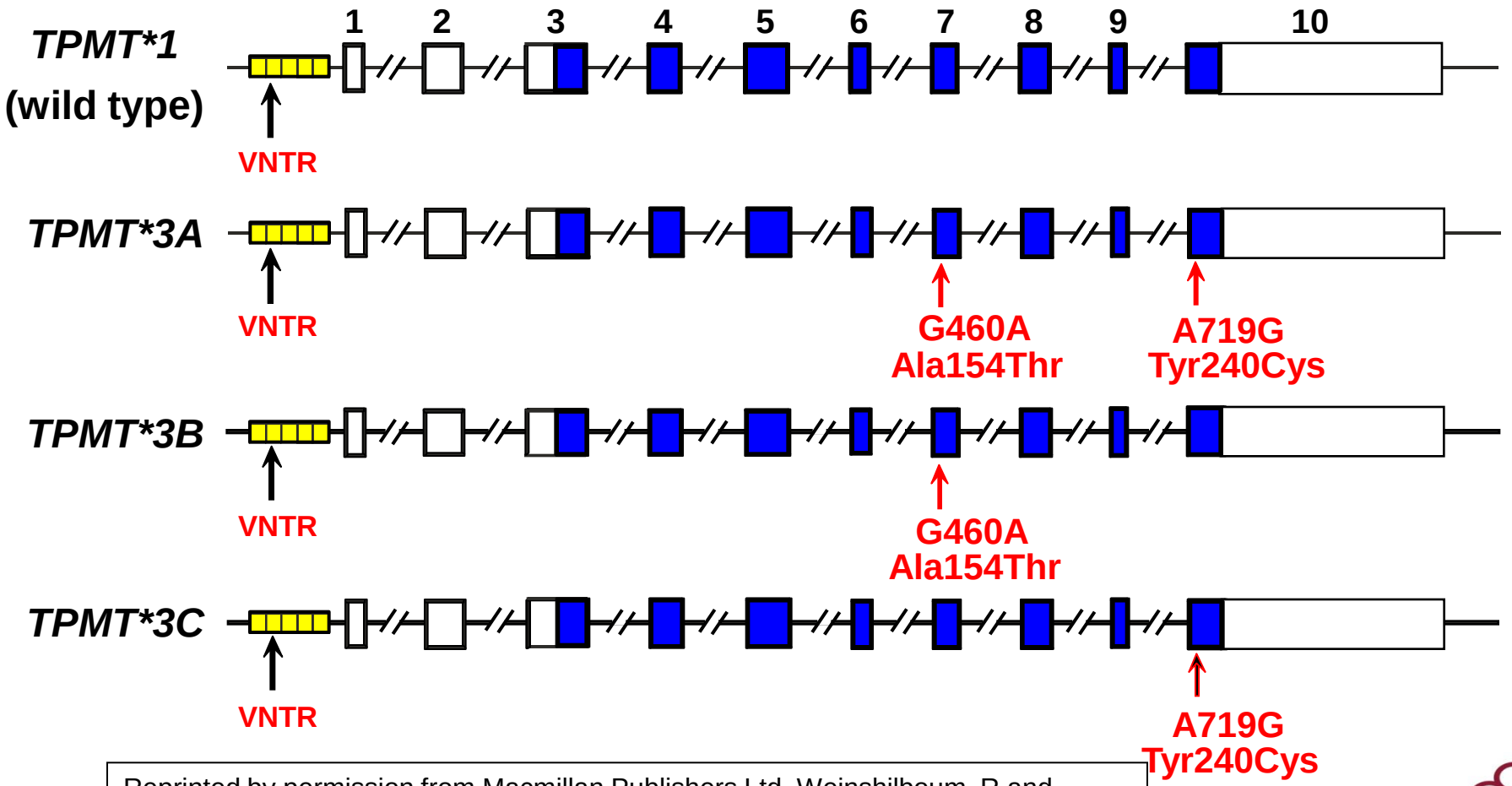
Selected Human TPMT Alleles



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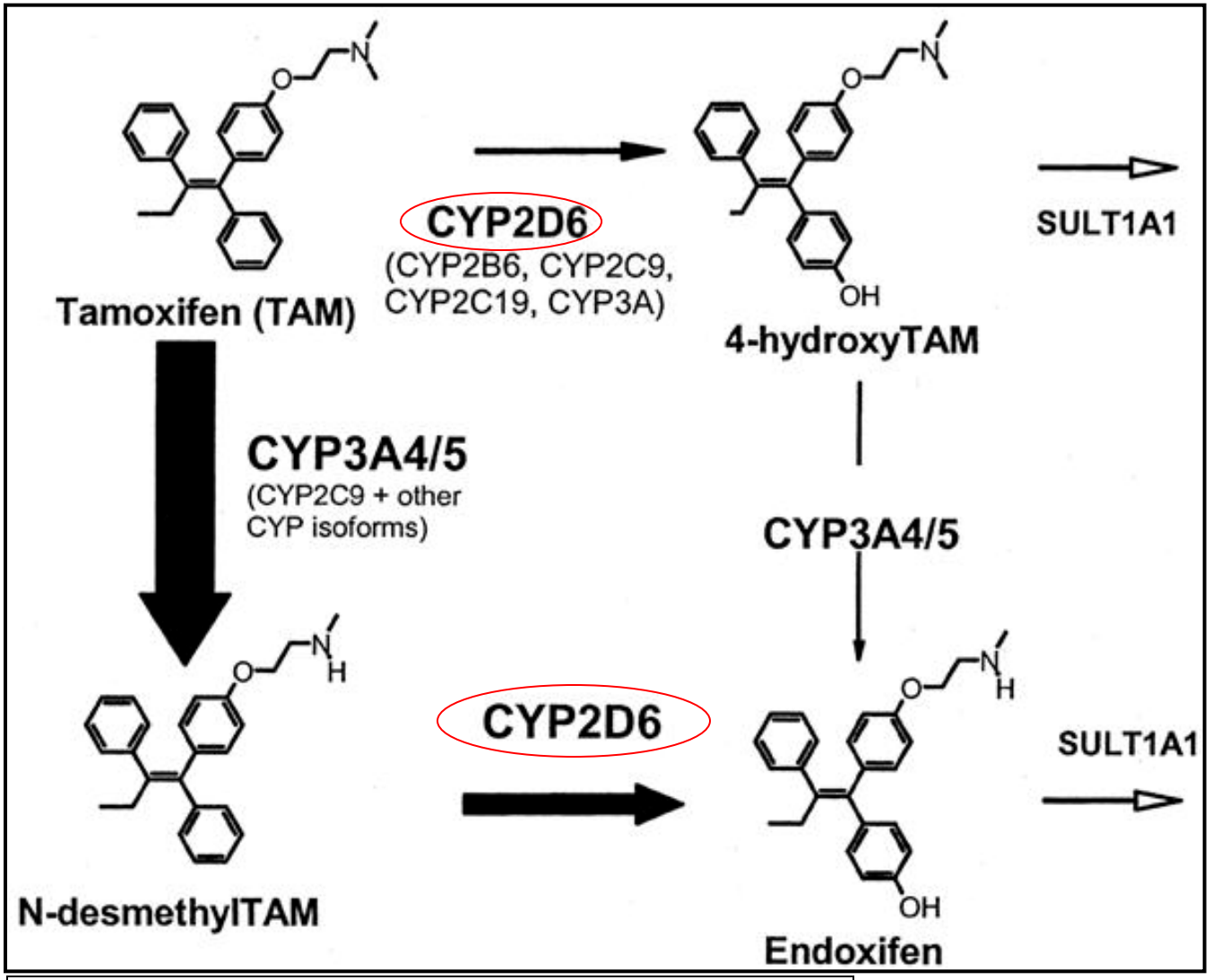
Tamoxifen Biotransformation



Jin et al., *J. Natl. Cancer Inst. 2005;* 97:20-39.
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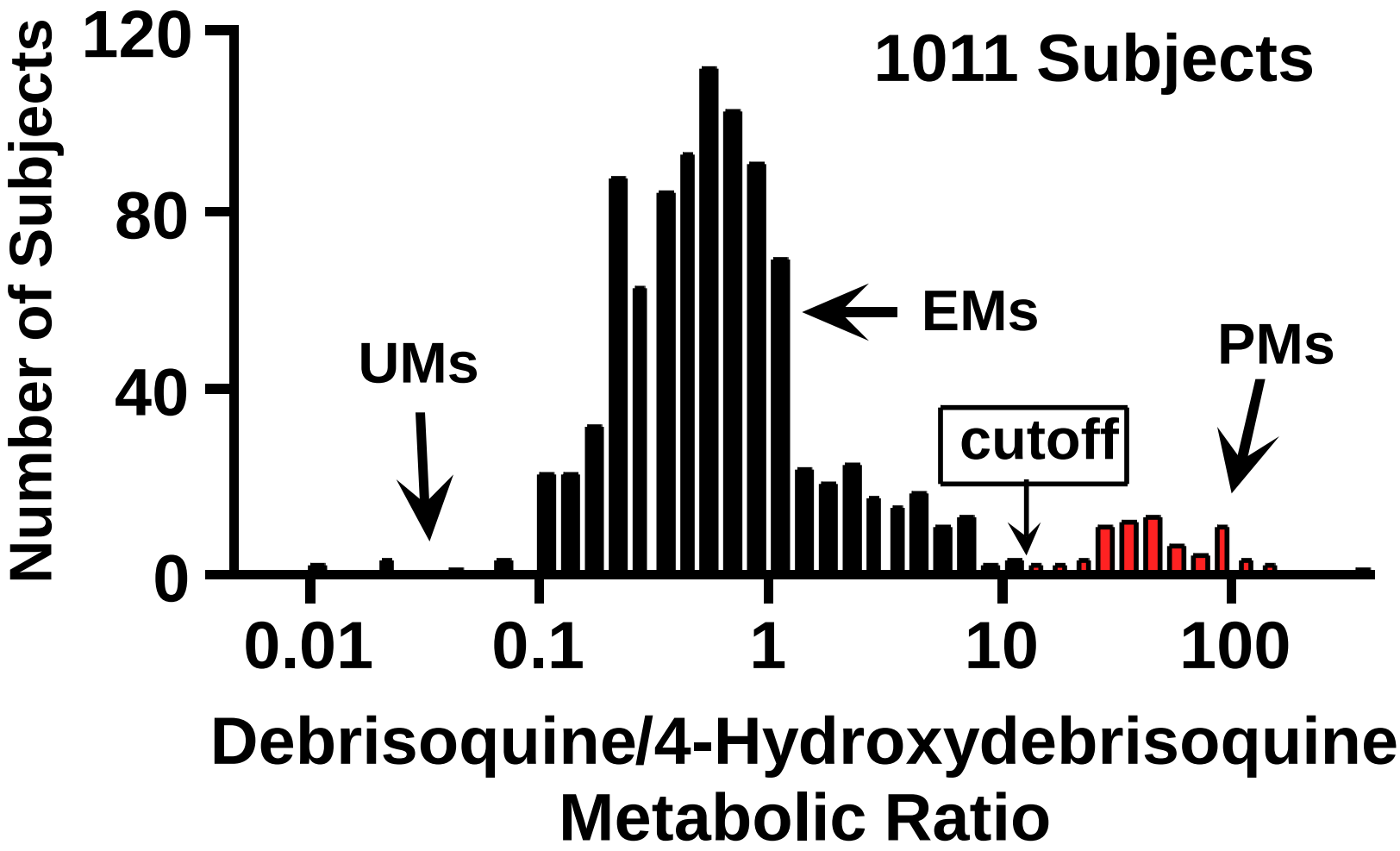
CYP2D6 Pharmacogenetics



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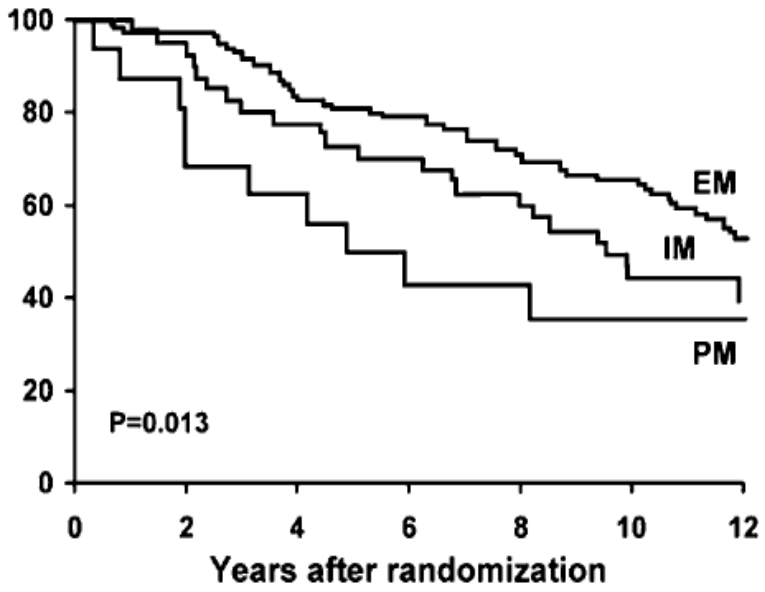
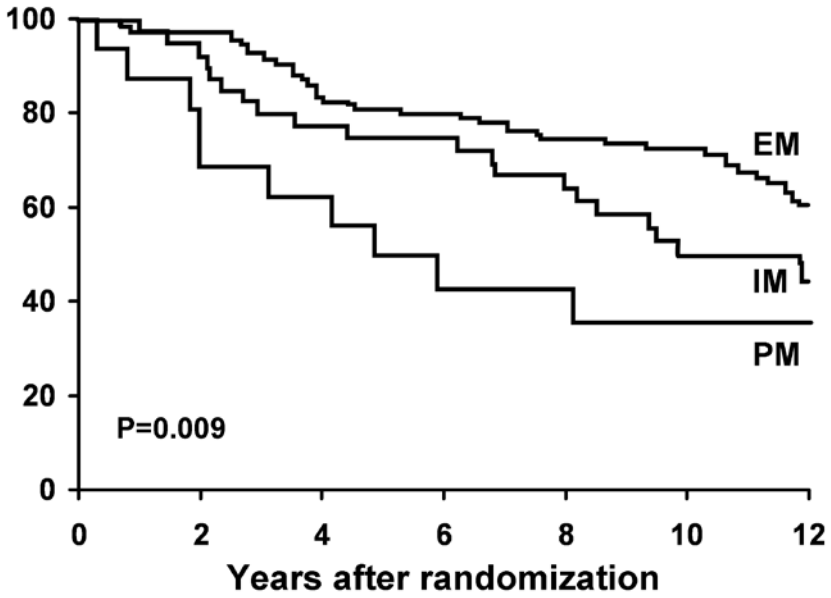
Tamoxifen Pharmacogenetics

Breast Cancer (190 Patients)

Relapse–Free Survival, %



Disease–Free Survival



Goetz et al., *Breast Cancer Res. Treat*. 2007; 101:113-121.
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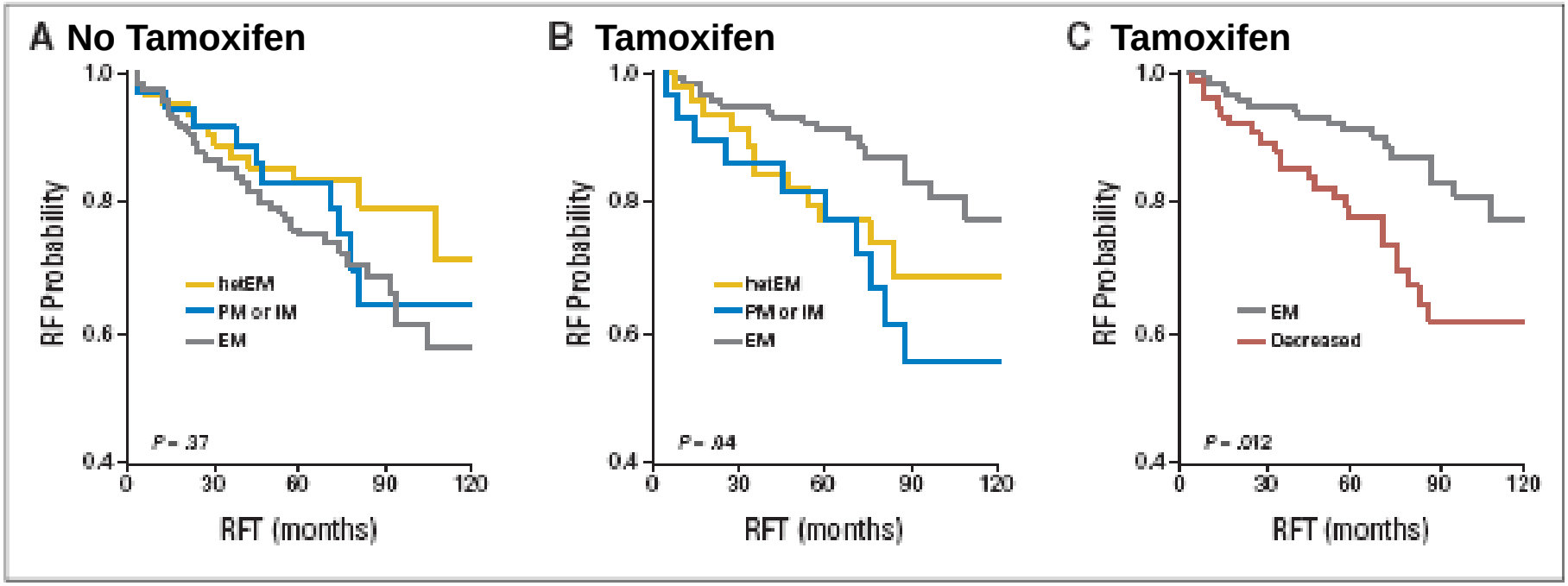
Tamoxifen Pharmacogenetics



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Pharmacogenomics

Evolution

- One gene, one or a few SNPs
- One gene, intragene haplotypes
- PK and PD pathways and haplotypes
- Genome-wide association studies

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Pharmacogenomic Genome-wide Model System

"Human Variation Panel" Cell Lines

- 96 CA, 96 AA, 96 HCA
- Illumina genome-wide SNPs
- Affymetrix 6.0 genome-wide SNPs
- Affymetrix U133 2.0 Plus expression data
- Affymetrix exon array data

Liewei Wang, M.D., Ph.D.

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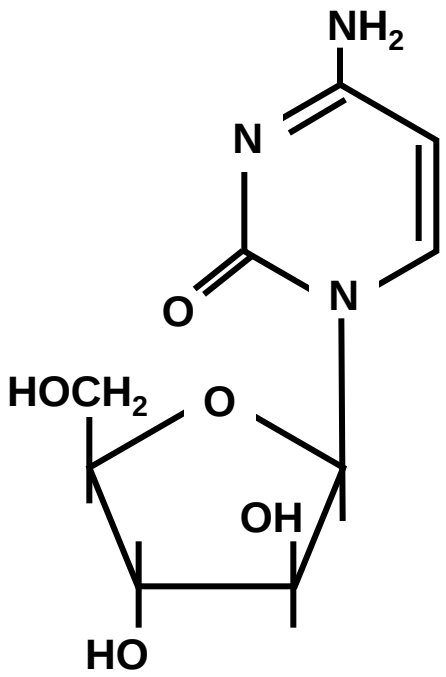
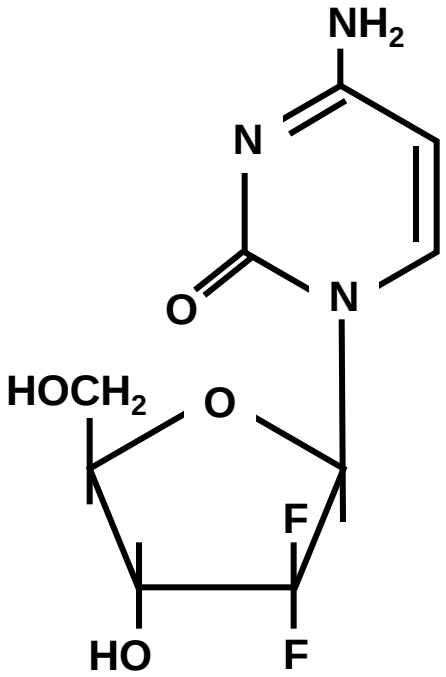
Cytidine Analogues

Ara-C



Gemcitabine



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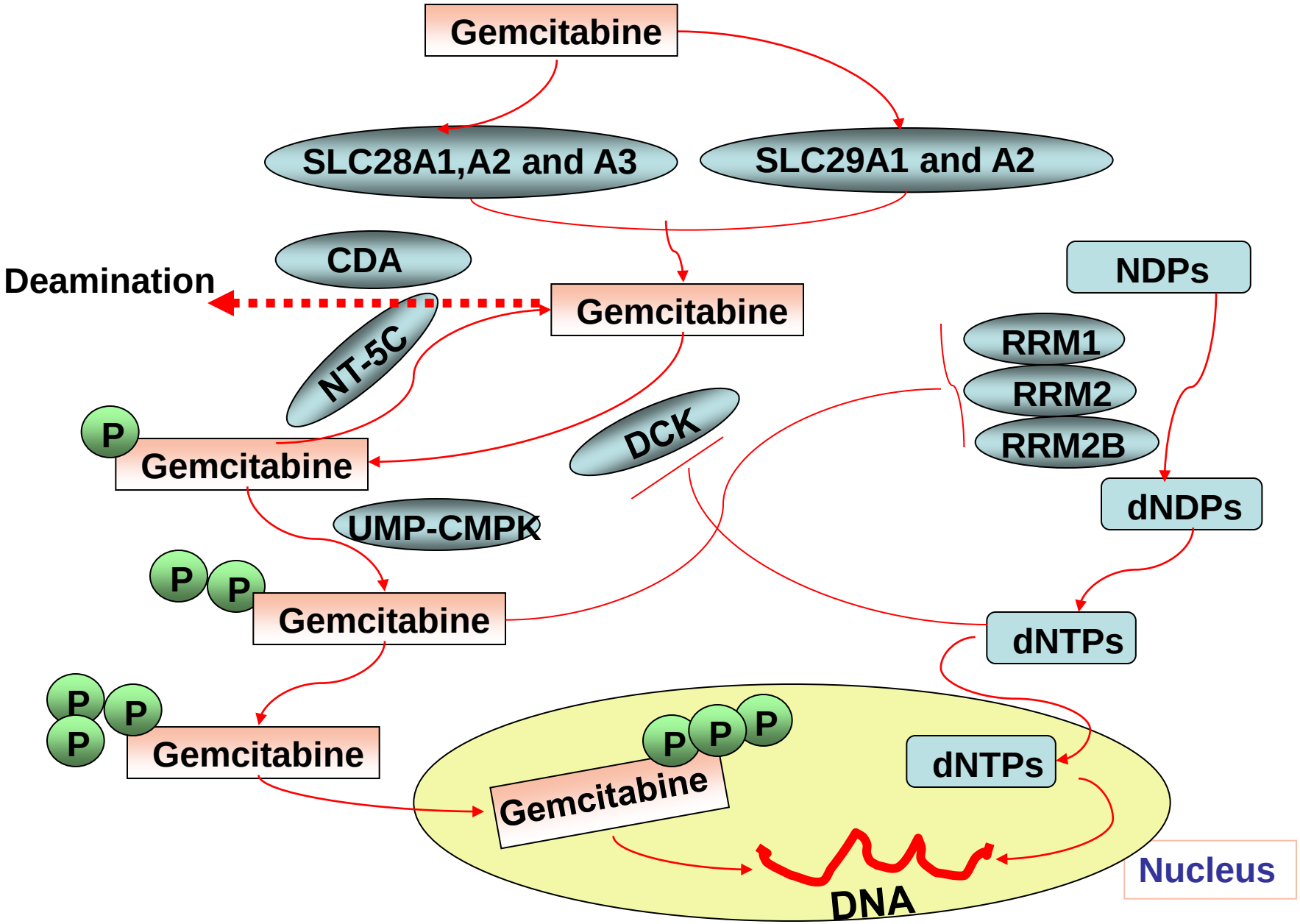
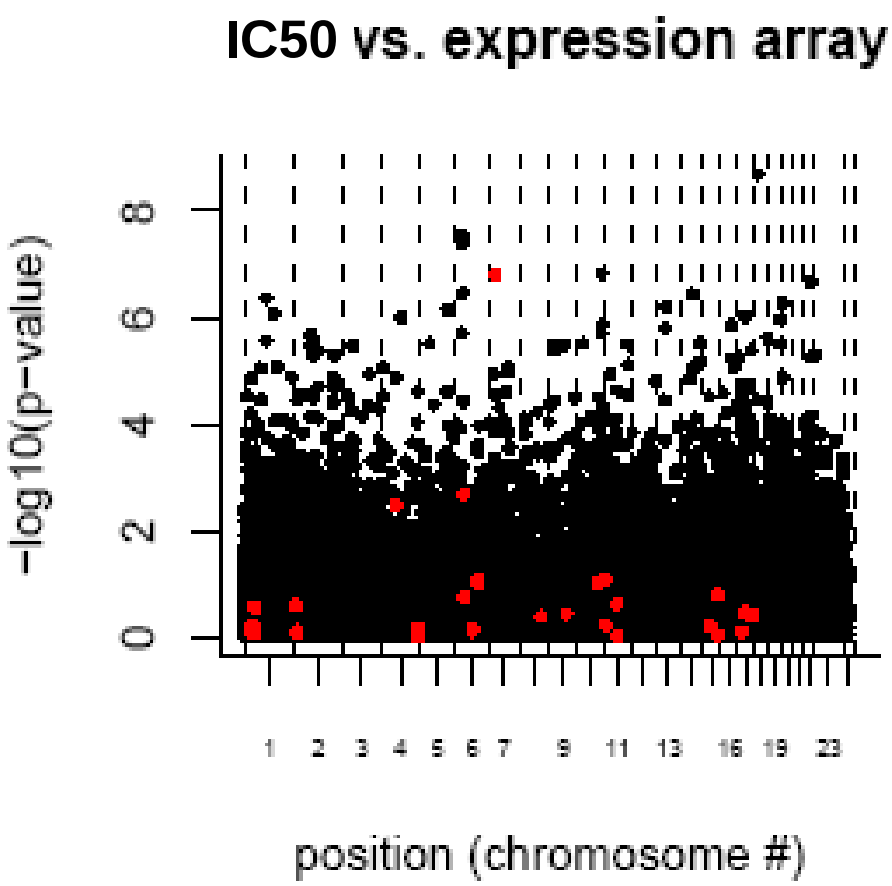
Gemcitabine “Pathway”

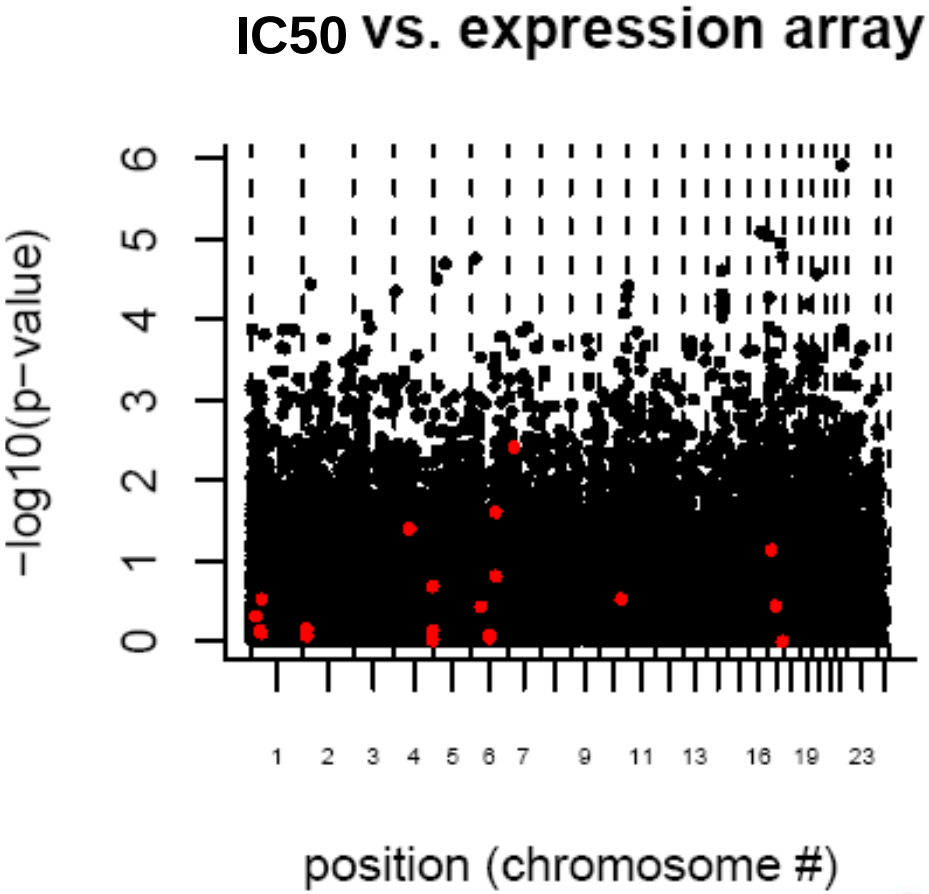


Gemcitabine-AraC
IC50 – Expression Association

Gemcitabine



AraC



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“Human Variation Panel” Strategy

- “Biased” – pathway-based
- “Unbiased” – genome-wide
- Functional validation
- ***NT5C3***, a “pathway” gene, and ***FKBP5***, a “non-pathway” gene encoding a 51 kDa immunophilin, were selected for functional study based on p values and QRT-PCR verification.

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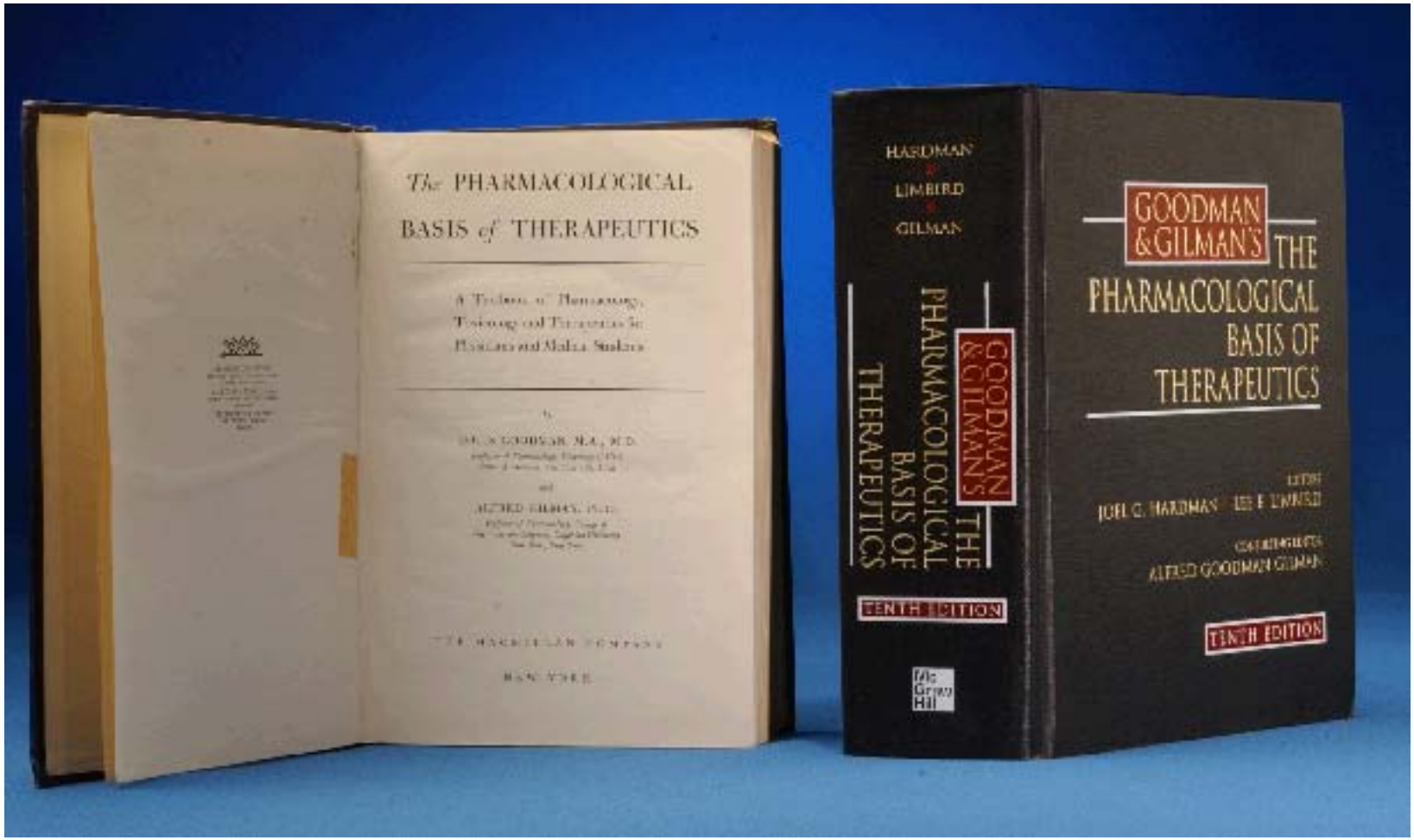
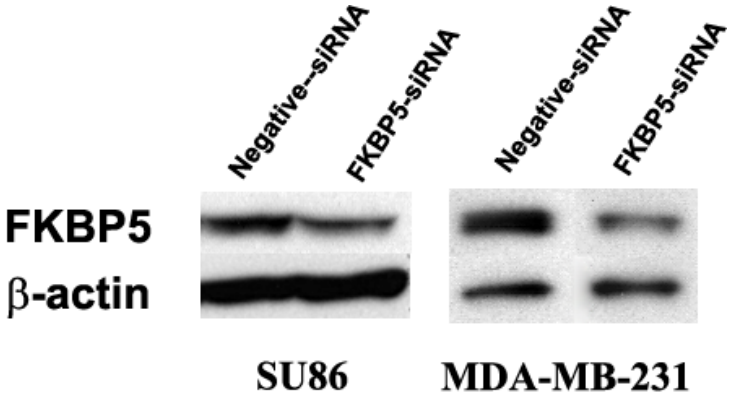
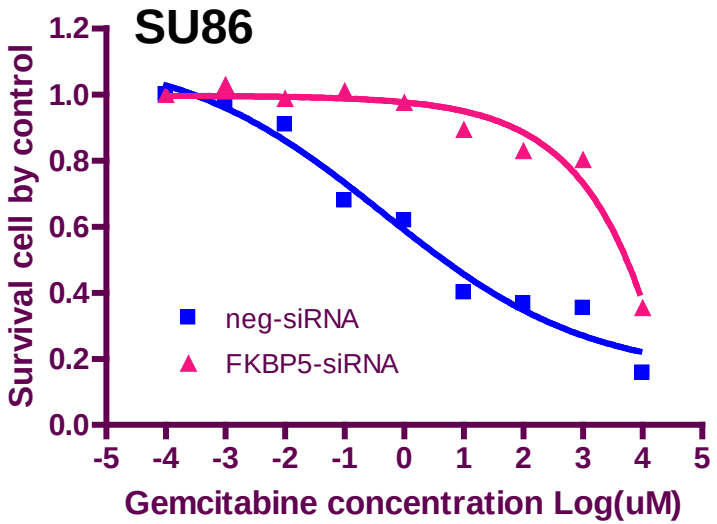
The Therapeutic Revolution

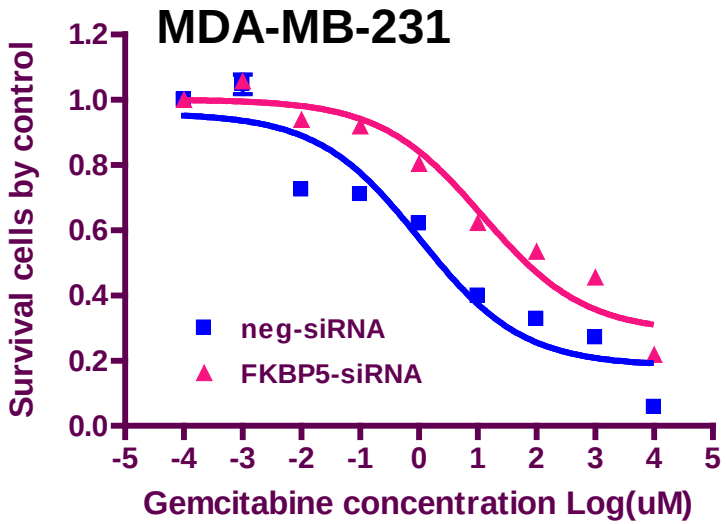


Goodman and Gilman's
"The Pharmacological Basis of Therapeutics"

Functional Characterization of FKBP5 Gemcitabine







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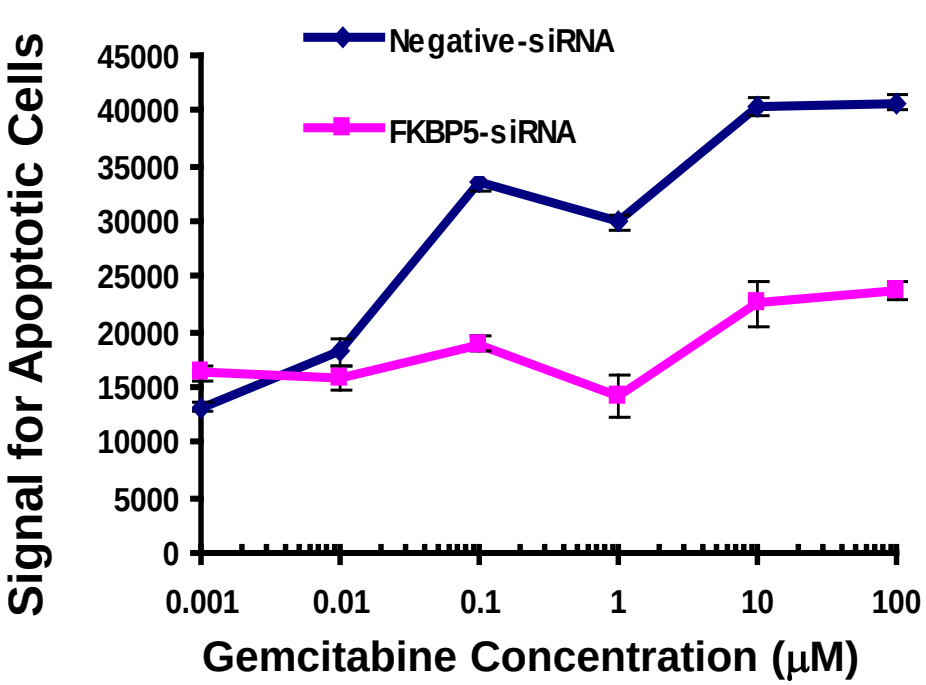
FKBP5 Functional Characterizatoin Caspace-3/7 Activity



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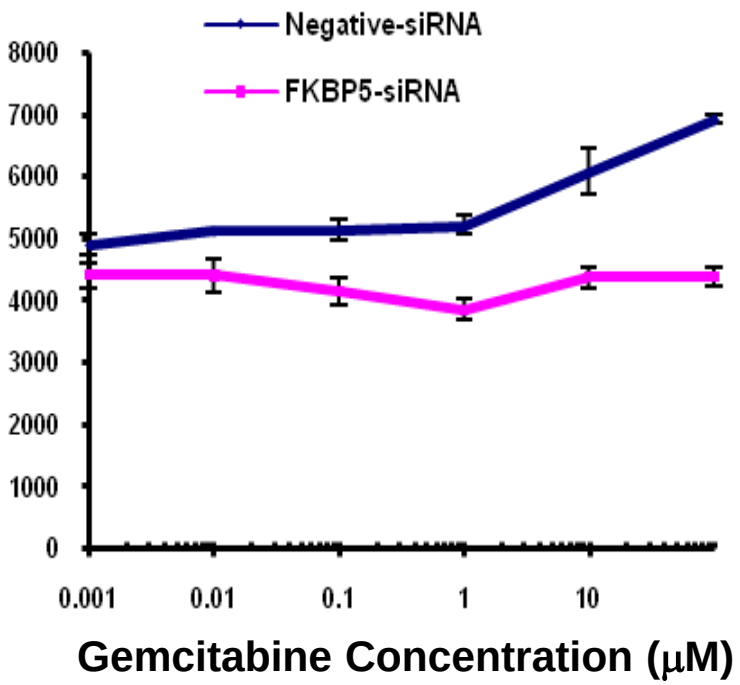

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Pharmacogenomics Genomic Era

Developments

- Next Gen DNA Sequencing
- 1000 Genomes Project
- ENCODE
- RNA-seq
- DTC Genomics

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Pharmacogenomics

Clinical Goals

- Avoid adverse drug reactions
- Maximize drug efficacy
- Select responsive patients

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Cancer Pharmacogenomics

Challenges

- Germline and/or somatic genome
- Clinical trials and/or population studies
- Translational and/or mechanistic studies
- Funding to incorporate rapidly changing, expensive technologies
- Collaboration and replication

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Acknowledgements

- Mayo PGRN – GM61388
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- RIKEN Yokohama Institute Center for Genomic Medicine (CGM)

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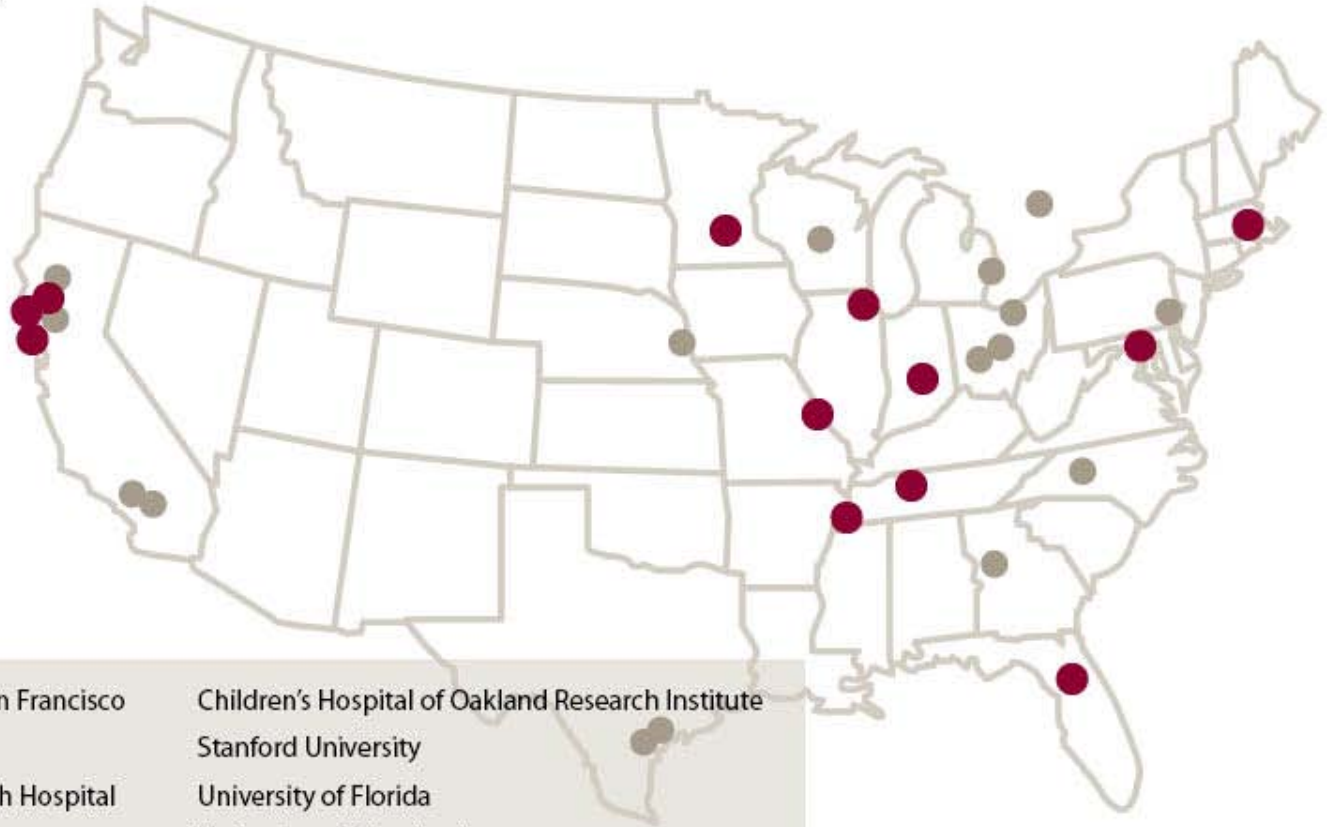
Pharmacogenetics Research Network

National Institutes of Health
U.S. Department of Health & Human Services

Research Sites

NIH Funding Institutes

NIGMS
NHLBI
NIDA
NCI
NIEHS
NIMH
NHGRI
NLM
ORWH



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University of Chicago	Stanford University
St. Jude Children's Research Hospital	University of Florida
Mayo Clinic	University of Maryland
Vanderbilt University	Indiana University
Washington University	Brigham and Women's Hospital

● Primary Investigator Site
● Co-Investigator Site

Mayo Pharmacogenomics Laboratories -- 2009

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