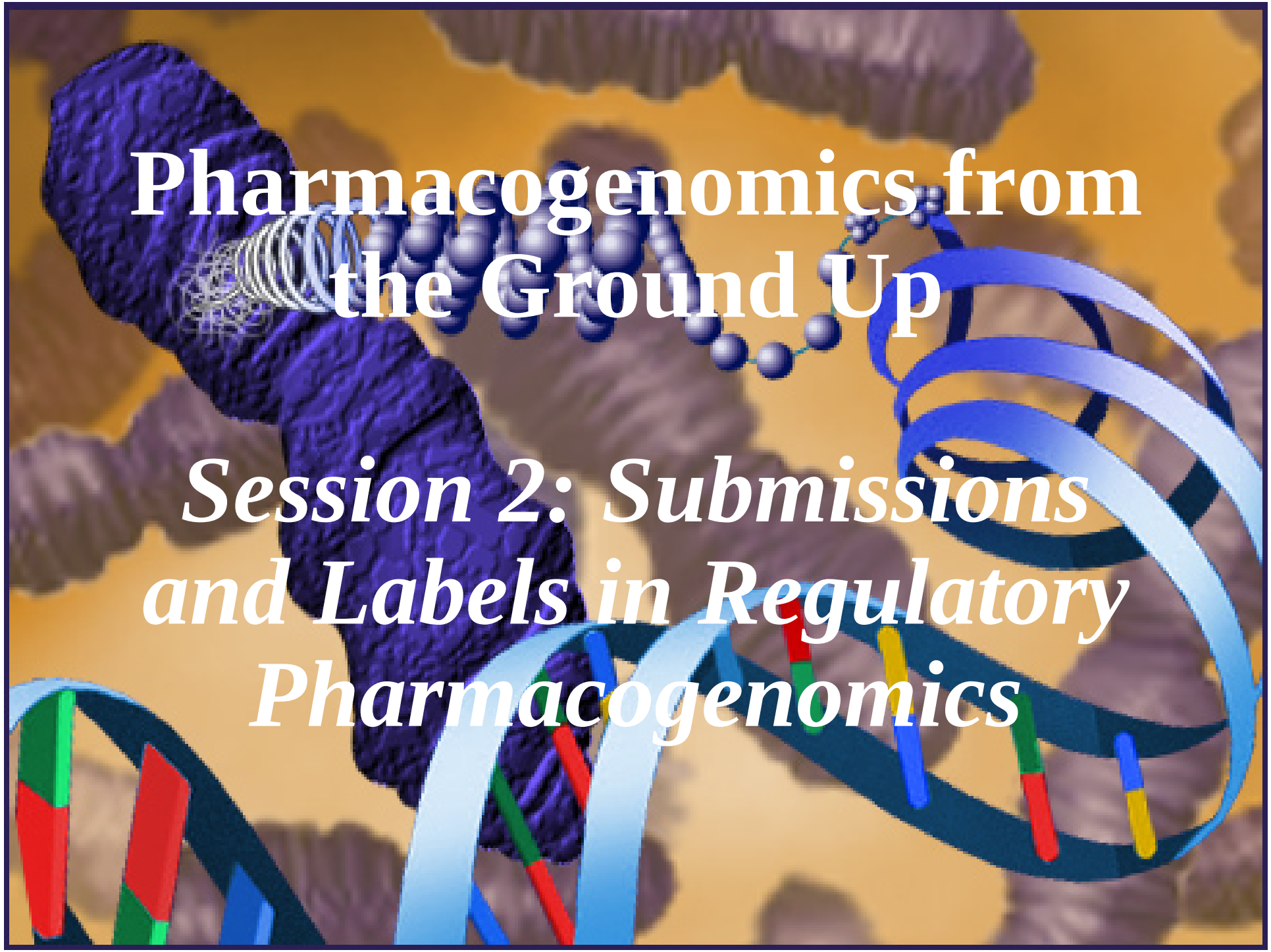

Pharmacogenomics from the Ground Up
Session 2: Submissions and Labels in Regulatory Pharmacogenomics

Labeling Regulations

"If evidence is available to support the safety and effectiveness of the drug only in selected subgroups of the larger population with a disease, the labeling shall describe the evidence and identify specific tests needed for selection and monitoring of patients who need the drug."

- 21 CFR 201.57

How Does It Read?: Examples of Pharmacogenomic Information in the Drug Label

Brand Name (generic name)	Labeling section	Labeling Statement
HERCEPTIN® (trastuzumab) August 2002	INDICATIONS AND USAGE	HERCEPTIN should be used in patients whose tumors have been evaluated with an assay validated to predict HER2 protein overexpression (see PRECAUTIONS : HER2 Testing and CLINICAL STUDIES : HER2 Detection).
Purinethol (6-Mercapto-purine) July 2004	WARNINGS DOSAGE and ADMINISTRATIONS	Individuals who are homozygours for an inherited defect in the TPMT (thiopurint-S-methyltransferase) gene may be unusually sensitive to the myelosuppressive effects of mercaptopurine and prone to developing rapid bone marrow suppression following the initiation of treatment. …….. (see DOSAGE AND ADMINITRATION). Patients with inherited little or no thiopurine S-methyltransferase (TPMT) activity are at increased risk for severe PURINETHOL toxicity from conventional doses of mercaptopurine and generally require substantial dose reduction. The optimal starting dose for homozygous deficient patients has not been established (see CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS sections)
(thioridazine) July 2003	CONTRA-INDICATIONS	thioridazine is contraindicated ….. in patients, comprising about 7% of the normal population, who are known to have a genetic defect leading to reduced levels of activity of P450 2D6 (see WARNINGS and PRECAUTIONS).
STRATTERA (atomoxetine) March 2003	Drug-Drug Interactions Laboratory Tests	In EMs, inhibitors of CYP2D6 increase atomoxetine steady-state plasma concentrations to exposures similar to those observed in PMs. Dosage adjustment of STRATTERA in EMs may be necessary when coadministered with CYP2D6 inhibitors, e.g., paroxetine, fluoxetine, and quinidine (*see* Drug Interactions *under* PRECAUTIONS). In vitro studies suggest that coadministration of cytochrome P450 inhibitors to PMs will not increase the plasma concentrations of atomoxetine. CYP2D6 metabolism --Poor metabolizers (PMs) of CYP2D6 have a 10-fold higher AUC and a 5-fold higher peak concentration to a given dose of STRATTERA compared with extensive metabolizers (EMs). Approximately 7% of a Caucasian population are PMs. Laboratory tests are available to identify CYP2D6 PMs. The blood levels in PMs are similar to those attained by taking strong inhibitors of CYP2D6. The higher blood levels in PMs lead to a higher rate of some adverse effects of STRATTERA (*see* ADVERSE REACTIONS).

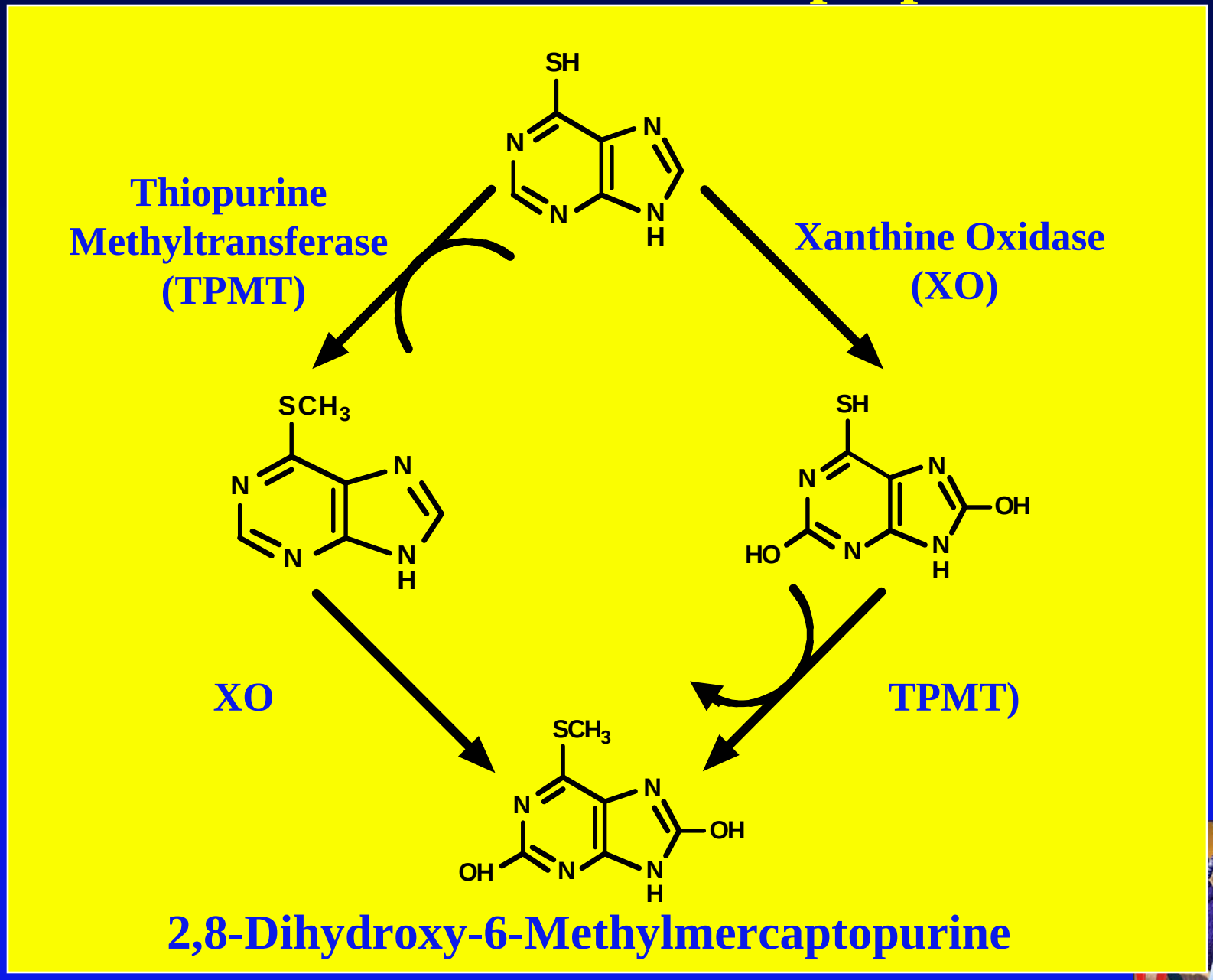
Mercaptopurines

- **Leukemia indication**
  - **Converted to nucleotides for incorporation into DNA by hypoxyxanthine phosphoribosyl transferase (HPRT).**
  - **Mercaptopurine-derived products block DNA replication and lead to tumor cell death.**
- **Mercaptopurine metabolism**
  - **Thiopurine methyltransferase (TPMT) converts mercaptopurine into an inactive metabolite called methylmercaptopurine.**
    - **90% homozygous for wild type allele and metabolize product normally**
      - **Toxicity is low, but relapse is high.**
    - **Some are poor metabolizers**
      - **Toxicity is high.**
    - **0.3% are homozygous for these variants**
    - **High risk of myelosuppression and secondary tumors.**
- ***Label:* "Recommendation to use pharmacogenetic testing to guide dosing".**

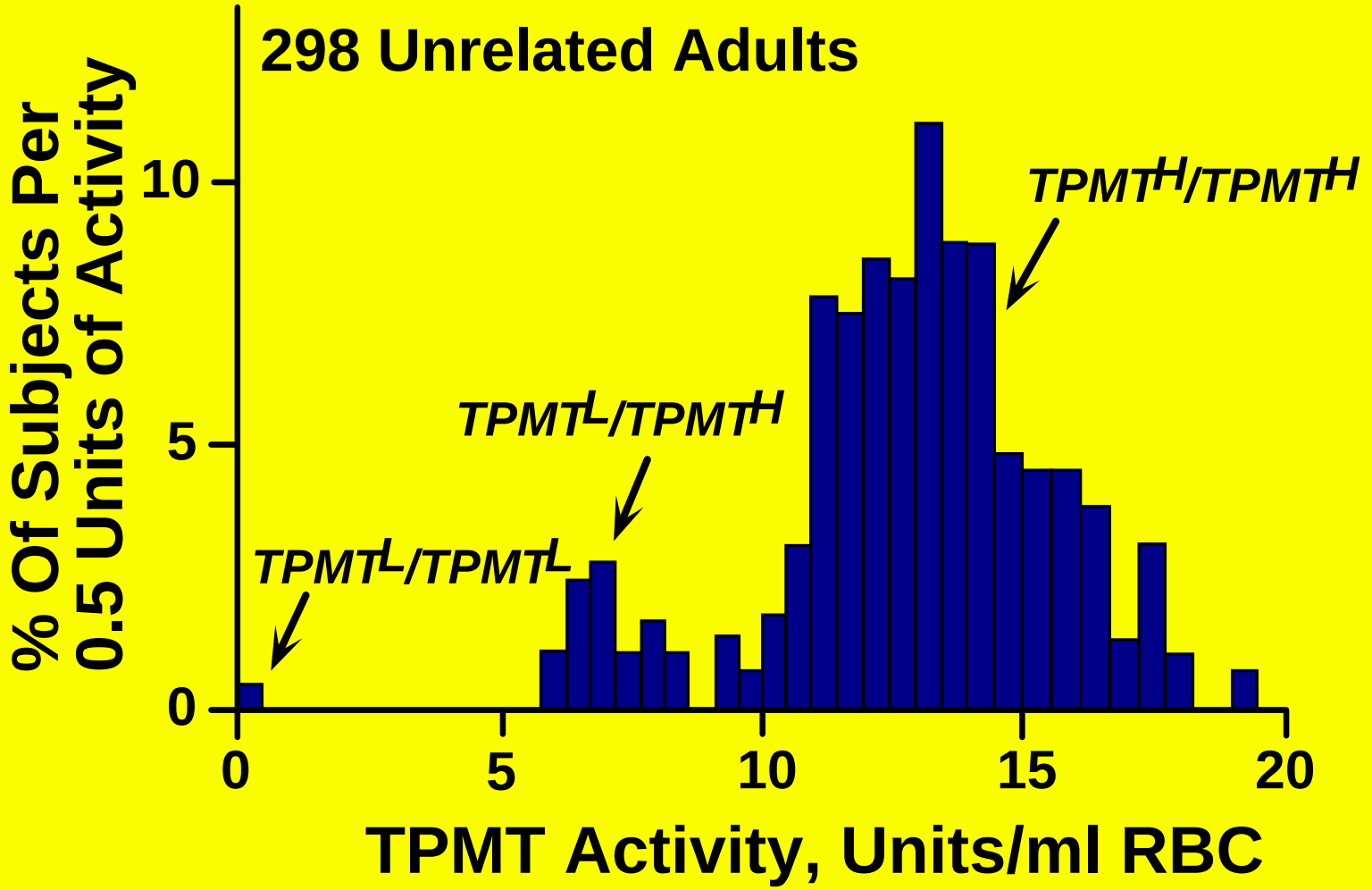
2005 FDA Pharmacogenomic Guidance *Valid Biomarkers*

- **Cytochrome P450 2D6 (CYP2D6)**
- **Thiopurine S-methyltransferase (TPMT)**

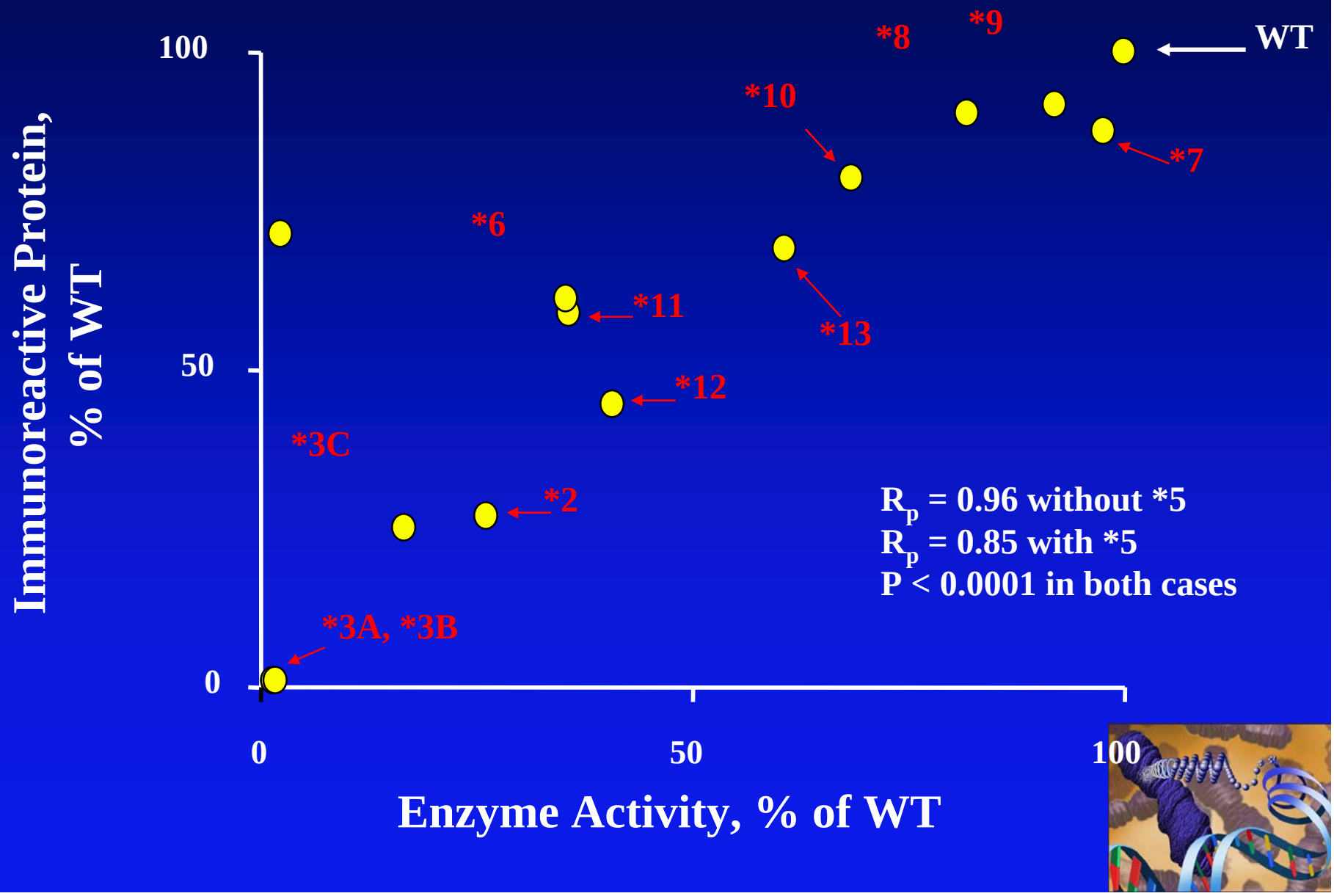
Metabolism of 6-Mercaptopurine



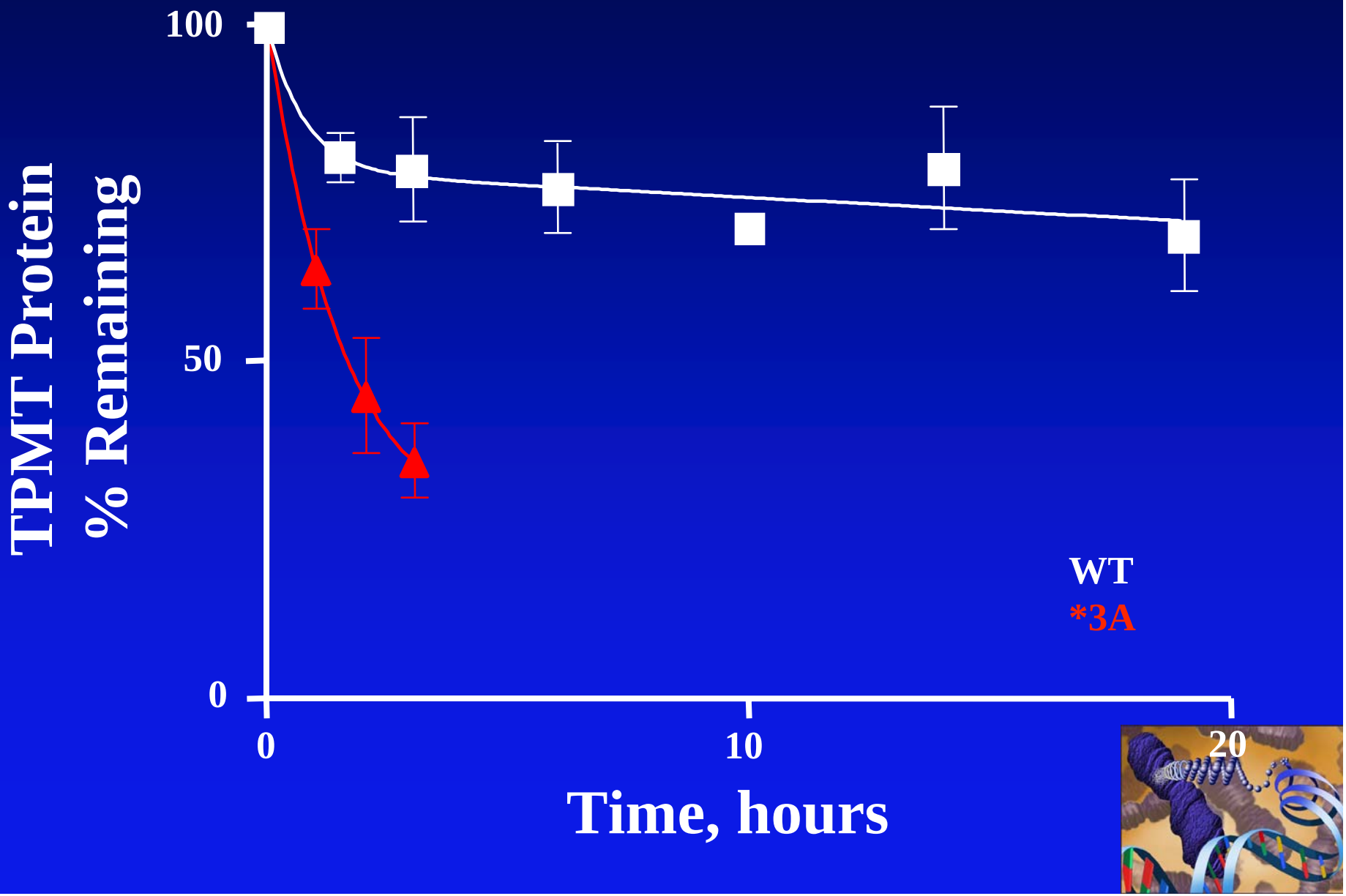
Human RBC TPMT



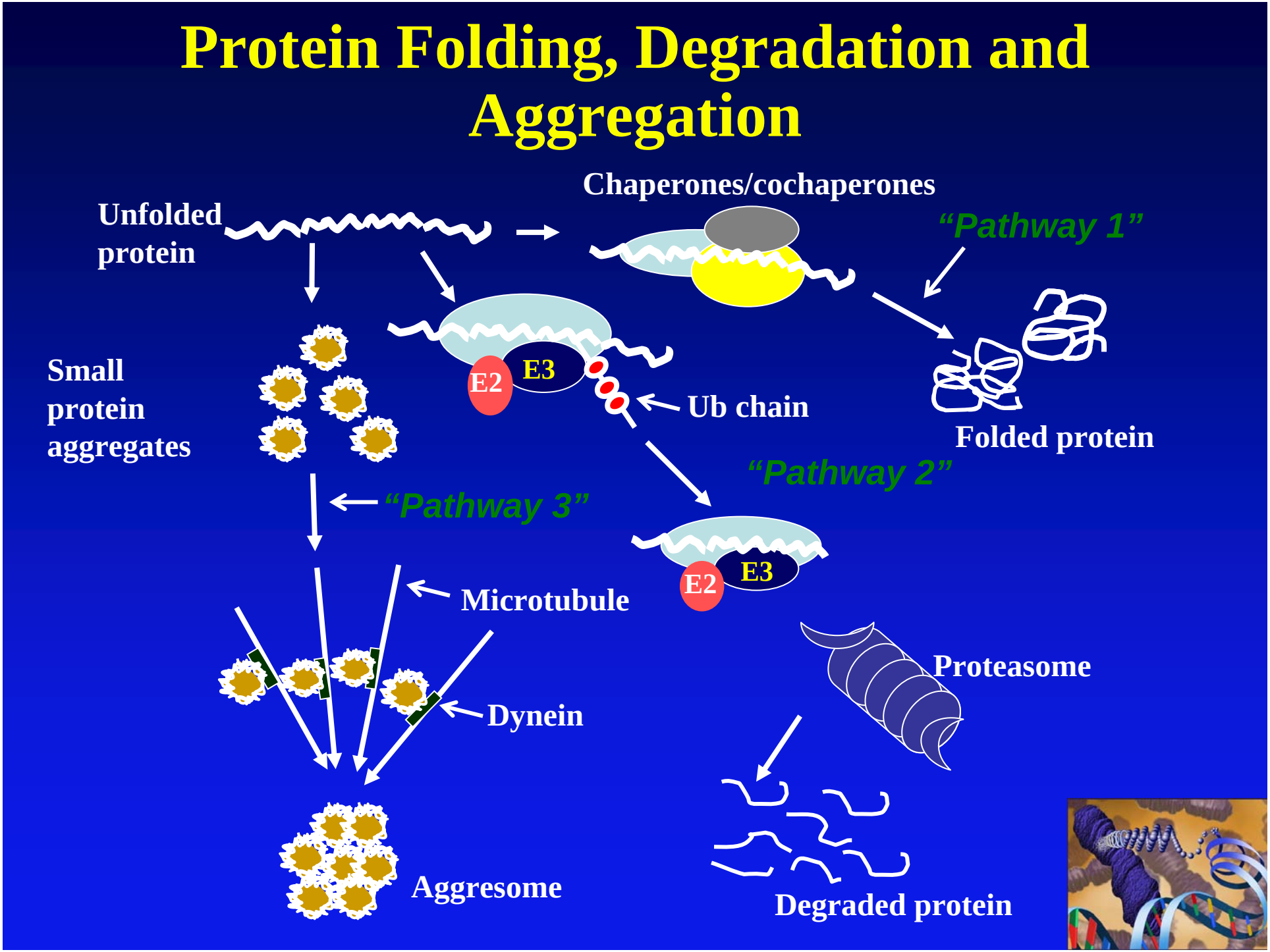
Human Recombinant TPMT Allozymes



Human TPMT Protein Degradation



Protein Folding, Degradation and Aggregation



TPMT Genetic Polymorphism Clinical Consequences

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

6-Mercaptopurine and TPMT Polymorphism

- ***Labeling*** **– absence of PGx information in label discussed at CPSC and Pediatric Oncology Subcommittee in 4/03 and 7/03**

- ***New labeling*** **- revised by sponsors in consultation with FDA- includes data on increased risk of severe myelosuppression for TPMT activity-deficient genotypes**

- **Informs clinicians about option of using TPMT testing to guide treatment with 6MP**

General Process for Updating Labels with PGx Information

- Develop the appropriate questions
- Capture the relevant evidence
- Abstract and summarize the evidence
- Evaluate the quality of studies
- Assess the overall strength of evidence
- Consider other factors in relabeling decision
- Determine specific language for label

Goals of This Session

- **Aftermarket**
  - **–Irinotecan**
- **The Epidermal Growth Factor (EGFR) Story**
  - **–Iressa**
  - **–Tarceva**
  - **–Erbitux**

Irinotecan

Irinotecan is a semi-synthetic derivative of camptothecin, an alkaloid extract from *camptotheca acuminate*. Camptothecin and its analogue belong to the class of Topoisomerase I inhibitors. Topoisomerase I is a DNA enzyme responsible for controlling and modifying DNA during replication and translation of genetic materials. Irinotecan and its active metabolite, SN-38, bind to the topoisomerase DNA complex, preventing religation of the single-strand breaks in the DNA molecule. Advancing replication enzymes collide with the camptothecin-topoisomerase I-DNA complex, causing double stranded DNA breaks, which can lead to apoptosis. The drug and its active metabolite are believed to exert their cytotoxic effects during the S-phase of cell cycle.

Irinotecan is one of many FDA-approved choices for metastatic CRC

- 1st line therapy
  - 5-FU + leucovorin
  - Irinotecan
  - Oxaliplatin
  - Capecitabine
  - Bevacizumab
- 2nd line therapy
  - Irinotecan
  - Oxaliplatin
  - 5-FU + leucovorin
  - Cetuximab

Irinotecan

- Camptosar (Irinotecan hydrochloride injection)
  - accelerated approval on June 14, 1996
  - patients with metastatic carcinoma of the colon or rectum
    - » disease has recurred or progressed following initial fluorouracil based therapy
  - subsequently approved as a component of first-line therapy in combination with 5-fluorouracil and leucovorin for patients with metastatic colon or rectal cancer
  - administered as weekly, biweekly, or once every 3-week dosage schedules

Irinotecan

- Clinical Trials
  - irinotecan treatment in combination with 5-fluorouracil and leucovorin significantly increased in patients with metastatic carcinoma of the colon or rectum
    - » median survival
    - » objective tumor response rates
    - » time to tumor progression
  - single-agent irinotecan given once-every-three-week dosage schedule significantly increased
    - » survival of patients with metastatic colorectal cancer
      - disease has recurred or progressed following prior 5-flurouracil therapy

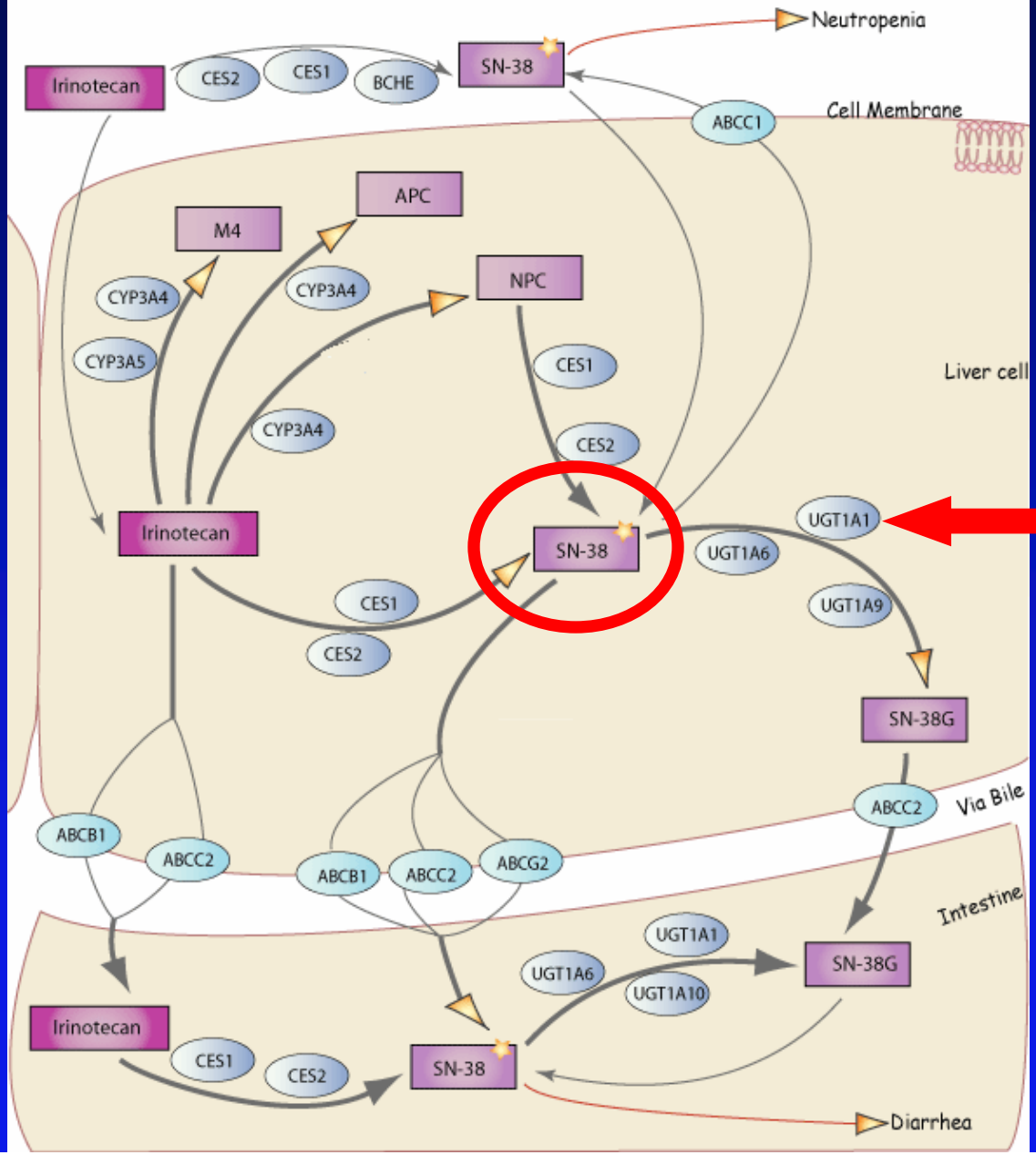
Irinotecan

- **Adverse Events**
  - **Diarrhea**
    - » **early and late forms**
    - » **requires dose adjustment based on severity of diarrhea**
  - **Neutropenia**
    - » **Sepsis related death.**
    - » **Dose adjustment based on neutrophil count is recommend in the label.**
  - **Nausea**
  - **Vomiting**
  - **Alopecia**

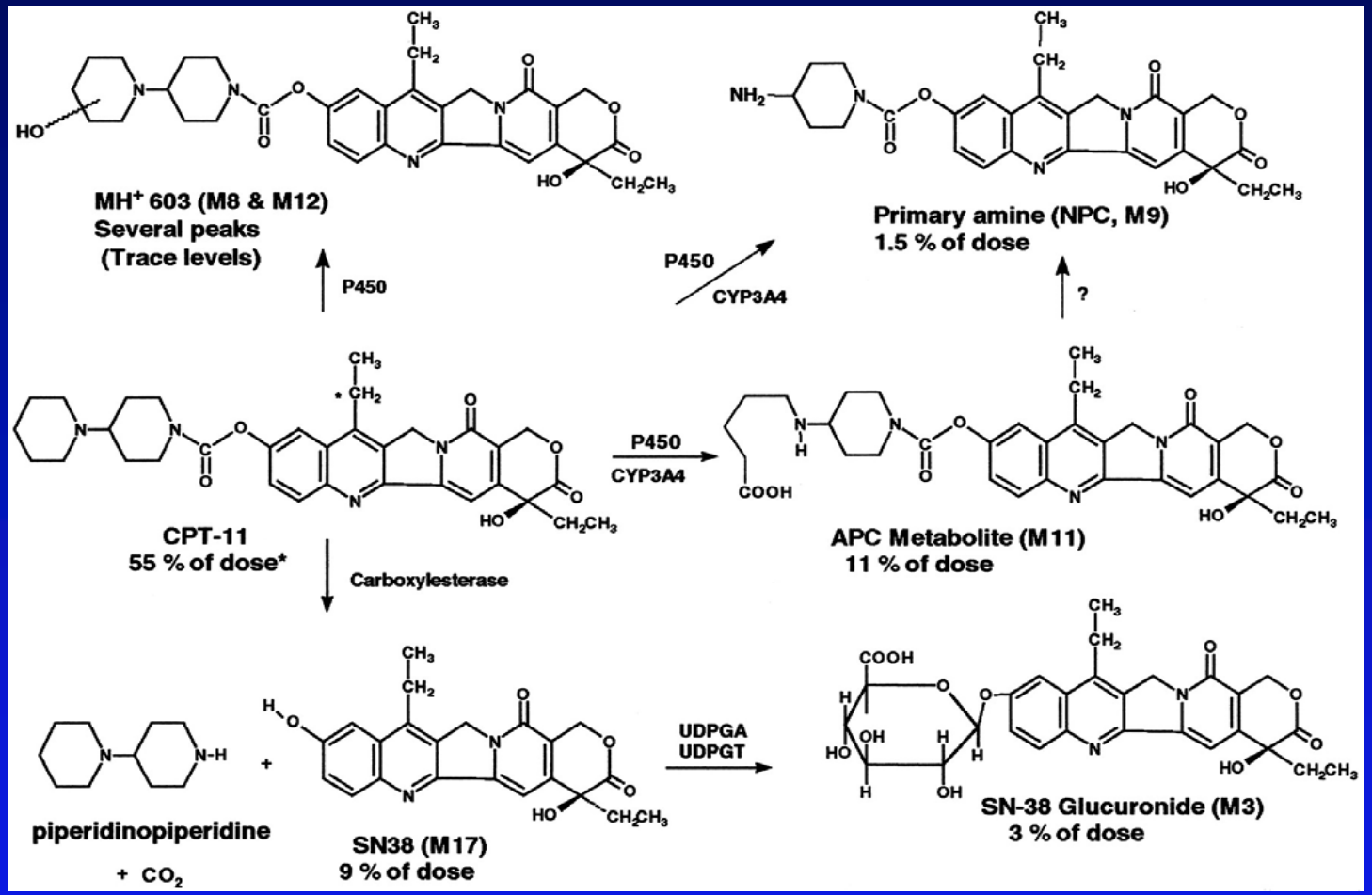
Irinotecan Pathway

Liver cell: Model human liver cell showing blood, bile and intestinal compartments, indicating tissue specific involvement of genes in the irinotecan pathway.

Legend



Mass Balance of Irinotecan



SN-38 is the active metabolite and acts as a DNA topoisomerase I poison

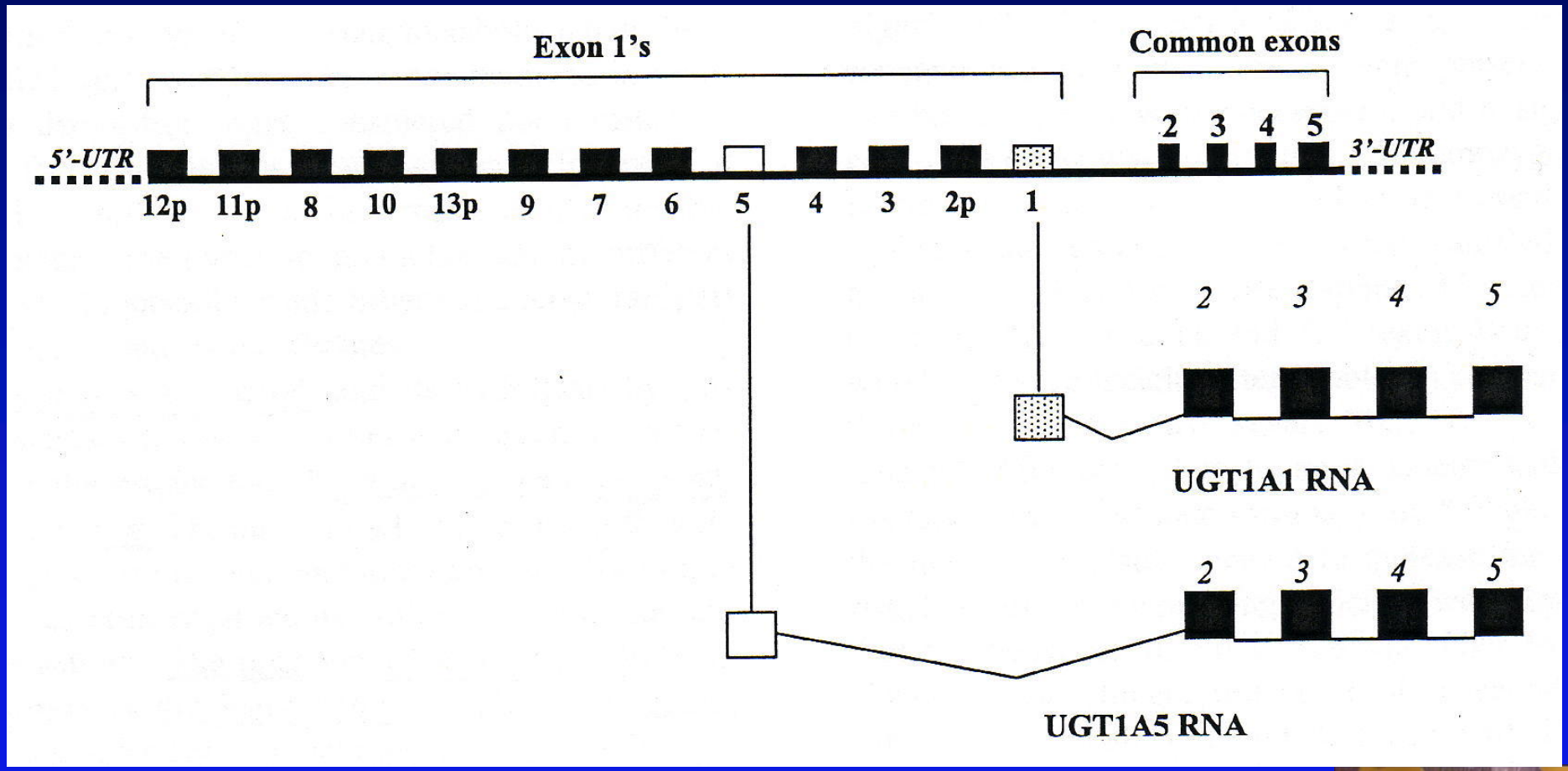
SN-38 exposure

- **Large inter-individual variability.**
- **SN-38 is an active metabolite of irinotecan and is responsible for the pharmacological and toxic effect of irinotecan.**
- **SN-38 is glucuronidated by Uridine diphosphate-glucuronyl transferase enzymes (UGT)**
  - **predominantly by UGT1A1 isoenzyme**
  - **UGT1A1 is a polymorphic enzyme**
    - » **TA repeats (5, 6, 7, or 8) in the TATA box of the UGT1A1 promoter region is inversely correlated with gene transcription efficiency and overall enzyme activity.**
    - » **Presence of seven repeats (TA7) compared to the normal genotype of six (TA6) repeats results in the variant allele UGT1A1*28.**
    - » **Allele is associated with reduced gene expression and reduced glucuronidation in human liver microsomes.**
    - » **10% of the North American population carry the two deficient alleles (homozygous). In the European population, the allele frequencies for TA6 and TA7 are 0.613 and 0.387.**

UDP-glucuronosyl-transferase (UGT)

- **Catalyzes the conversion of hydrophobic substrates to more hydrophilic glucuronides (glucuronidation).**
- **Found in hepatic and extrahepatic tissues.**
- **Superfamily of UGT proteins is divided into 2 families (UGT1A, UGT2B) based upon sequence homologies. 5 exons.**
- **The UGT2B genes have been mapped to chromosome 4 and consist of individual structural genes.**
- **The UGT1A gene locus has been identified on chromosome 2. At least 9 functional UGT1A genes and 3 pseudogenes are encoded. Four exons are located at the 3' end of the UGT1A locus and are combined with one of a consecutively numbered array of first exon cassettes towards the 5' end of the gene locus. The aminoterminal 280 amino acids of UGT1A proteins are encoded by the unique exon 1 sequences.**

UGT1A Gene Structure



Glossary Review

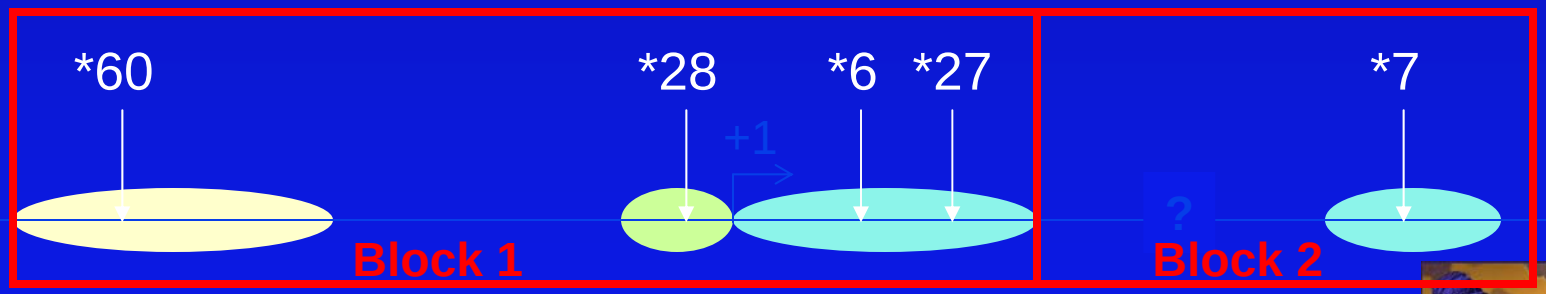
- **Enhancer**
  - **A DNA control element 5’ of the start codon. When bound by transcription factor(s), it enhances the level of transcription of the gene. The effect by itself is not sufficient to cause expression.**
- **Promoter**
  - **A DNA control element 5’ of the start codon. When bound by RNA polymerase, it causes the transcription of DNA into RNA (gene expression). Expression can be additionally regulated by enhancer(s).**
- **Exon**
  - **The sequence of the primary RNA transcript (or the DNA that encodes them) that exit the nucleus as part of a messenger RNA molecule. Separated by introns.**
- **Intron**
  - **Noncoding DNA sequence transcribed into heterogeneous RNA (hnRNA). Removed by splicing process, leaving mature mRNA (exons only), which is transcribed in the cytoplasm.**

Glossary Review

- **Untranslated Region (UTR)**
  - **Region of mRNA, typically those 5' to the initiation (ATG) site and 3' to the stop site, which are not translated into a peptide.**
- **Haplotype**
  - **A set of closely linked genetic markers present on one chromosome which tend to be inherited together. Some haplotypes may be in linkage disequilibrium.**
- **Diplotype**
  - **The combination of haplotypes in the genome of diploid (2n) autosomal cells**
- **Linkage Disequilibrium (LD)**
  - **Observed frequencies of two or more genetic markers in a population do not agree with predicted frequencies, i.e. the markers are observed together more often than expected.**

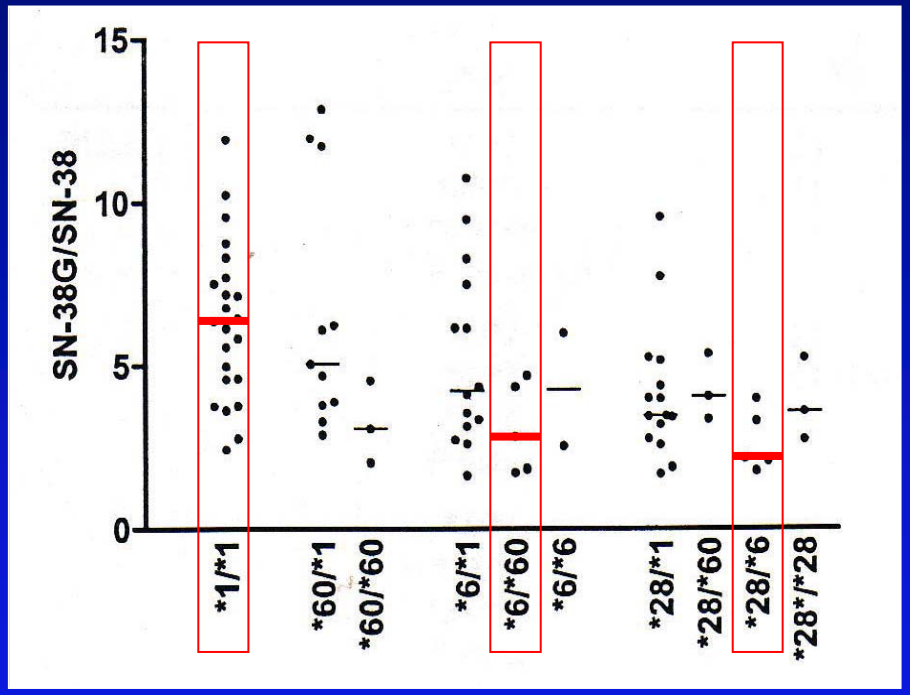
Common UGT1A1 Alleles

Allele	nt (aa) Change	Frequency (Japanese)
*1	wildtype	0.582
*6	211G>A (G71R)	0.151
*7	1456T>G (Y486D)	?
*27	686C>A (P229Q)	0.005
*28	$A(TA)_6TAA>A(TA)_7TAA$	0.131
*60	-3279T>G (n/a)	0.262

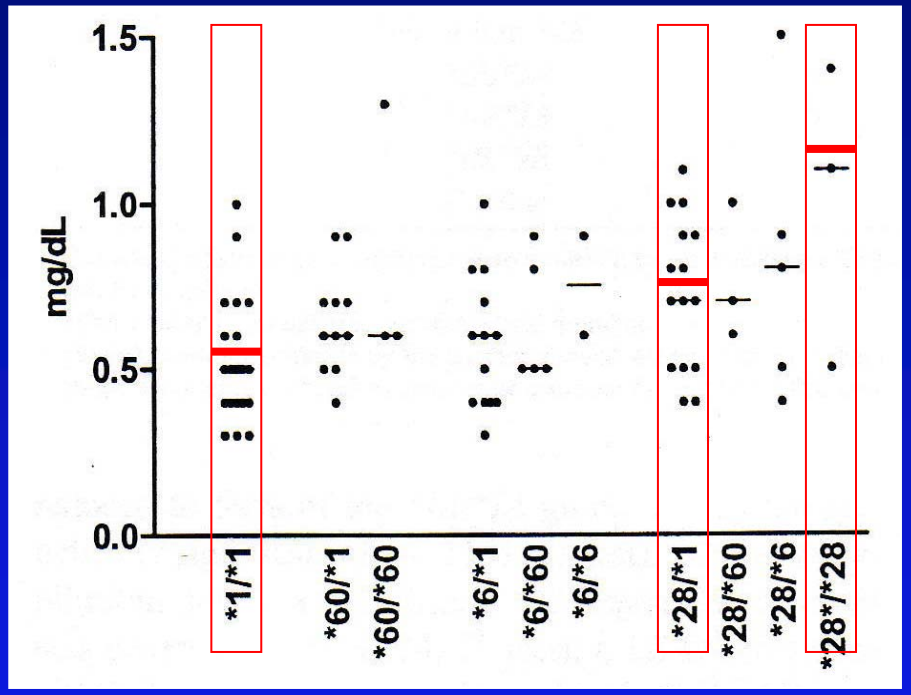


Effect of UGT1A1 *Diplotypes* on AUC of SN38G/SN-38 and Bilirubin Levels in Japanese Patients who Received Irinotecan

AUC Ratio



Total Bilirubin



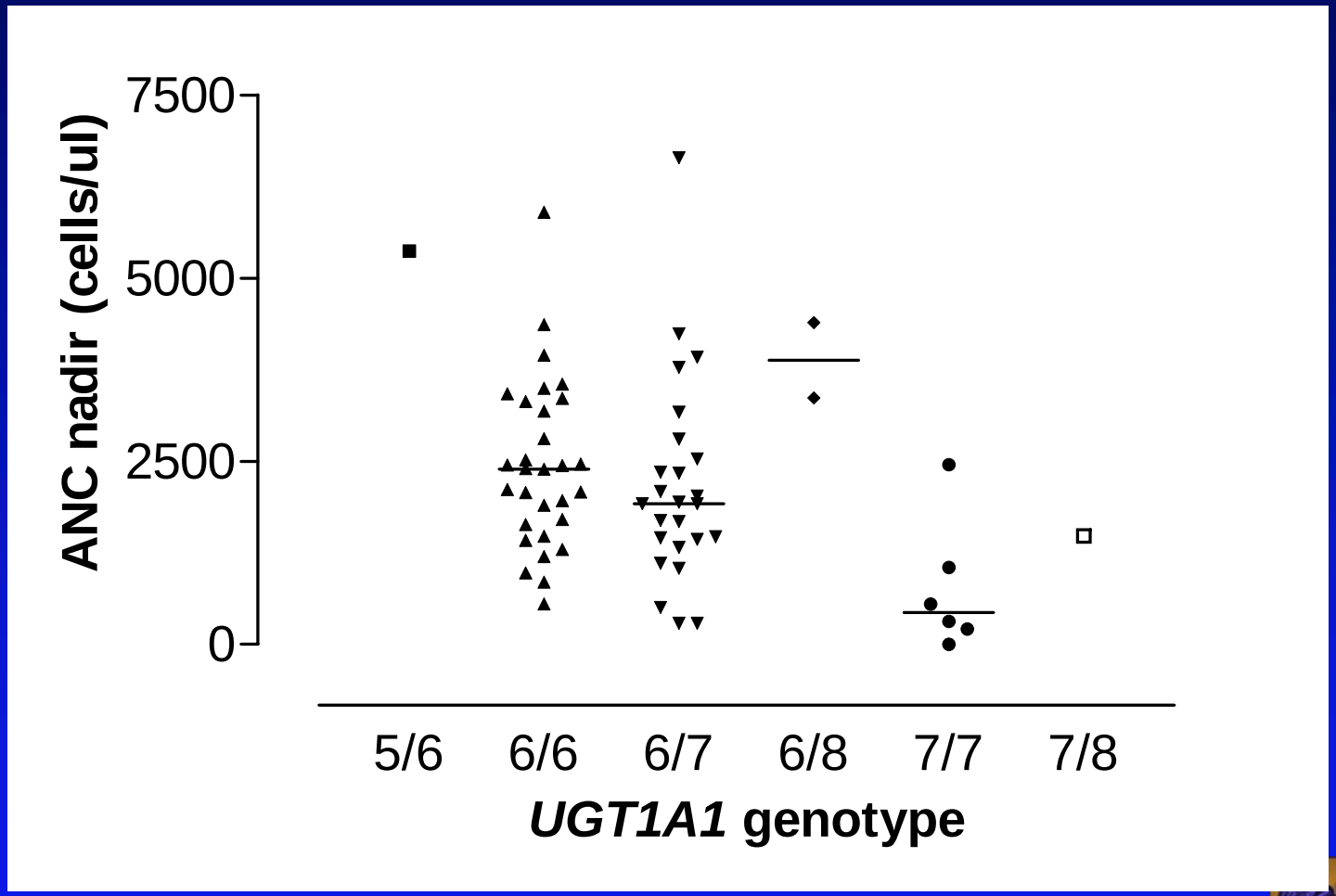
Reduced Glucuronidation and Increased Serum Bilirubin in Irinotecan-treated Japanese Patients with Cancer. Sai et al. *Clin. Pharmacol. Ther.* (2004) 75:501-15.

Prospective Study

- 66 patients received irinotecan every 3 weeks.
- Homozygous TA7 genotype patients had a relative risk of 9.3 (95% CI, 2.4 to 36.4) for grade 4 neutropenia.
- 50% (3 out of 6) of the homozygous TA7 patients had grade 4 neutropenia compared to 12.5% heterozygous TA6/7 patients (3 out of 24).
- No patients with the normal TA6 genotype (0 out of 29) had any grade 4 neutropenia.
- SN-38 exposure directly correlated with the UGT1A1 genotype.

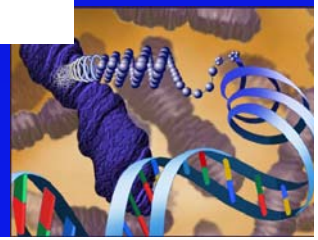
Neutropenia (q3 wk schedule) is Correlated with *UGT1A1* Genotype (*28)

(Innocenti et al, JCO, 2004)



Bar represents median values.

Nonparametric trend analysis among 6/6, 6/7, 7/7, p<0.01



UGT1A1 Testing for Grade 4 Neutropenia

- **Sensitivity**
  - **50% of pts who have Grade 4 neutropenia are 7/7**
- **Specificity**
  - **95% of pts who do not have Grade 4 neutropenia are not 7/7**
- **Positive predictive value**
  - **50% of pts who are 7/7 have Grade 4 neutropenia**
- **Negative predictive value**
  - **95% of pts who are not 7/7 do not have Grade 4 neutropenia**

UGT1A1 Testing for Grade 4 Neutropenia

- **Without testing, 100% of pts are treated and 10% have Gr 4 neutropenia**
- **With testing, 90% of pts are treated and 5% have Gr 4 neutropenia**
- **5% absolute reduction**
  - **Test 20 to protect 1**

UGT1A1 Testing for Grade 4 Neutropenia

- **Sufficient data exist to recommend that patients who are homozygous for *28 should not receive irinotecan at standard doses**

- **Alternative options**
  - **Accept greater toxicity**
  - **Reduce dose**
  - **Use alternative regimen (eg, oxaliplatin-based)**

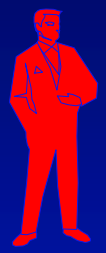
Current Understanding of PGx and Neutropenia

Group	Prevalence	Risk of Toxicity
All Patients	-----	10%
Patients That Are 7/7	10%	50%
Patients That Are 6/7	40%	12.5%
Patients That Are 6/6	50%	0%

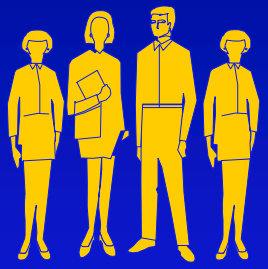
Based on data from Innocenti et al (2004)

Potential of UGT Testing to Guide Treatment

All Patients with Same Diagnosis (10% risk)



PGx profile for *high risk (50%):* treat with alternative drug or dose



PGx Profile for *moderate risk (12.5%):* treat with alternative drug or dose

PGx Profile for *low risk (0%):* treat with conventional dose

What would you do?

The Epidermal Growth Factor Receptor (EGFR) Story

1 2 3 4 5

EGFR

- **What is the EGFR role in cancer?**
  - **ErbB1 first sequenced in a four-member family of structurally related type or subclass 1 receptors known as tyrosine kinases.**
  - **Critical for mediating the proliferation and differentiation of normal cell growth**
  - **Widely expressed in epithelial, mesenchymal, and neuronal tissues**
  - **Aberrant activation of the kinase activity of these receptors appears to play a primary role in solid tumor development and/or progression**
  - **Breast, brain, lung, cervical, bladder, gastrointestinal, renal, and head and neck squamous cell carcinomas, have demonstrated an over expression of EGFR relative to normal tissue, which is associated with a poor clinical prognosis**

Iressa

FDA News

FOR IMMEDIATE RELEASE
P03-36
May 5, 2003

Media Inquiries: 301-827-6242
Consumer Inquiries: 888-INFO-FDA

FDA Approves New Type of Drug for Lung Cancer

The Food and Drug Administration (FDA) today announced the approval of Iressa (gefitinib) tablets as a single agent treatment for patients with advanced non-small cell lung cancer (NSCLC), the most common form of lung cancer in the US. Iressa is being approved as a treatment for patients whose cancer has continued to progress despite treatment with platinum-based and docetaxel chemotherapy, two drugs that are currently the standard of care in this disease.

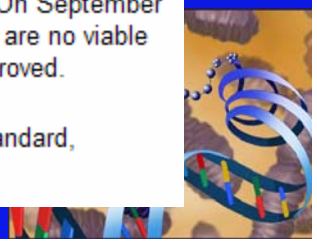
Iressa was reviewed and approved under FDA's accelerated approval program, which is intended to allow patients suffering from serious or life-threatening diseases earlier access to promising new drugs. As required by the accelerated approval regulations, Iressa's developer will perform additional studies to verify the drug's clinical benefit.

"FDA believes it is crucial for cancer patients to have many safe and effective treatment options available to them in their battle against this disease" said FDA Commissioner Mark B. McClellan, M.D., Ph.D. "With the approval of Iressa, thousands of patients with lung cancer will now have access to an additional treatment after others haven't worked to stop the progression of their disease."

The mechanism by which Iressa exerts its clinical benefit is not fully understood. However, Iressa was developed to block growth stimulatory signals in cancer cells. These signals are mediated in part by enzymes called tyrosine kinases. Iressa blocks several of these tyrosine kinases, including the one associated with Epidermal Growth Factor Receptor (EGFR).

FDA based the approval on the results of a study of 216 patients with NSCLC, including 142 patients with refractory disease, i.e., tumors resistant or unresponsive to two prior treatments. The response rate (defined as at least 50% tumor shrinkage lasting at least one month) was about 10%. There were more dramatic responses in some patients and the median duration of response was 7 months. On September 24, 2002, the Oncologic Drugs Advisory Committee (ODAC) recommended that in third-line treatment of NSCLC, where there are no viable treatment options, a 10% response rate was reasonably likely to predict clinical benefit and recommended that Iressa be approved.

Results from two large, controlled, randomized trials in initial treatment of NSCLC showed no benefit from adding Iressa to standard, platinum-based chemotherapy. Therefore, Iressa is not indicated for use in this setting.



Iressa Q&A

- **What is Iressa and how does it work?**
  - **anticancer drug**
  - **inhibits tyrosine kinase present in cancer cells**
- **What indication is Iressa used for?**
  - **single agent for the treatment of non-small cell lung cancer (NSCLC) that has progressed after, or failed to respond to two other types of chemotherapy (drugs used to kill cancer cells)**
  - **not indicated as the first chemotherapy drug given (first-line therapy) for the treatment of NSCLC because it has shown no benefit in two large, well-controlled studies when used in that context**
- **What is NSCLC?**
  - **lung cancer is divided into two major classes: small cell lung cancer and Non-Small Cell Lung Cancer**
  - **most common type of lung cancer (80% of lung cancers)**
  - **five types of NSCLC, each of which has different kinds of cancer cells**

Iressa Q&A

- **Is Iressa taken alone or is it taken in combination with other chemotherapy drugs?**
  - **Iressa is taken alone, not with other chemotherapy.**
- **Is Iressa a cure for NSCLC?**
  - **In the third line setting, i.e., after failure of two other agents, Iressa reduced tumor volume substantially in about 10% of people. There are no cures for NSCLC.**
- **How many clinical trials were performed with Iressa and what did they show?**
  - **The study on which FDA based its approval included 216 patients 139 of whom had failed treatment with two other chemotherapy treatments. In this trial, approximately 10% of patients responded to Iressa with a decrease in tumor size.**

Iressa Q&A

- **The sponsor also presented to FDA the results of two large (about 1000 patients each) clinical studies with Iressa as initial therapy for lung cancer.**
  - **In these studies all patients received, standard combination chemotherapy and were randomly given, in addition, either Iressa or a placebo. In these studies there was no effect of Iressa on survival, time to further growth of cancer, or on tumor size.**

- **Europe: not approved because no survival benefit.**

This is a revised version of an FDA statement originally issued December 17, 2004. Information on Alimta was added to the fourth paragraph.

FDA Statement

FOR IMMEDIATE RELEASE
Statement
December 17, 2004

Media Inquiries: 301-827-6242
Consumer Inquiries: 888-INFO-FDA

FDA Statement on Iressa

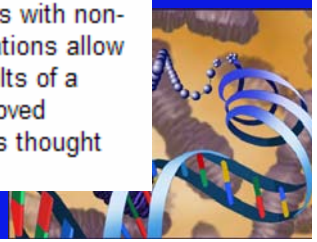
The FDA today released the following statement regarding the failure of a clinical trial of Iressa (gefitinib) to show an overall survival advantage in treating patients with lung cancer:

The Food and Drug Administration (FDA) learned yesterday from AstraZeneca that a large clinical trial comparing Iressa (gefitinib) with placebo in patients with non-small cell lung cancer who had failed other courses of cancer therapy showed no survival benefit from taking Iressa.

Patients currently taking Iressa should consult with their physicians as soon as possible; patients should not change their therapy without first consulting with their physicians.

Alternative therapies are available. FDA has approved Taxotere (docetaxel) and Tarceva (erlotinib), both of which have been shown in studies to improve survival in patients with non-small cell lung cancer whose cancer has progressed while on previous therapies. Alimta (pemetrexed) has received an accelerated approval based on the surrogate endpoint for this use but has not yet demonstrated any survival benefit.

FDA approved Iressa on May 2, 2003, under the Agency's accelerated approval (Subpart H) program, for the treatment of patients with non-small cell lung cancer who had failed two or more courses of chemotherapy. The accelerated approval provisions in FDA's regulations allow the agency to approve a drug for marketing based on an effect on a surrogate endpoint -- such as a sign of a disease or the results of a laboratory test -- that is considered reasonably likely to predict clinical benefit (improved symptoms or survival). Iressa was approved because the data from clinical trials showed that it caused significant shrinkage in tumors in about 10% of patients, and this was thought likely to increase patients' overall survival time.



What would you do?

Tarceva

National Cancer Institute
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Summaries of Newsworthy Clinical Trial Results

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Posted: 06/05/2004

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Erlotinib (Tarceva®) Extends Survival in Advanced Lung Cancer

Key Words

Lung cancer, non-small cell lung cancer, erlotinib (Tarceva®).
(Definitions of many terms related to cancer can be found in the Cancer.gov Dictionary.)

Summary

Erlotinib (Tarceva®) prolonged survival in patients with advanced non-small cell lung cancer who had progressed after standard chemotherapy.

Source

American Society of Clinical Oncology (ASCO) annual meeting, New Orleans, June 5, 2004.

Background

Up to now, patients with advanced non-small cell lung cancer who have relapsed after standard therapy have had few treatment options. Erlotinib is a targeted drug taken by mouth that works by interfering with cell signals controlled by a protein called the epidermal growth factor receptor (EGFR). This protein, also called HER1, is found on the surface of many tumor cells and affects tumor growth. Erlotinib is not yet approved by the U.S. Food and Drug Administration.

Related Pages

Search for Clinical Trials
NCI's PDQ® database of cancer clinical trials.

Lung Cancer Home Page
NCI's gateway for information about lung cancer.

Highlights from ASCO 2004
A collection of links to material summarizing some of the important clinical trial results announced at the 2004 annual meeting of the American Society of Clinical Oncology (ASCO).

FDA News

FOR IMMEDIATE RELEASE
P04-105
November 19, 2004

Media Inquiries: 301-827-6242
Consumer Inquiries: 888-INFO-FDA

FDA Approves New Drug for the Most Common Type of Lung Cancer

Drug Shows Survival Benefit

The Food and Drug Administration (FDA) announced the approval of Tarceva (erlotinib) tablets as a single agent treatment for patients with locally advanced or metastatic non-small cell lung cancer (NSCLC), the most common form of lung cancer in the U.S. Tarceva is being approved as a treatment for patients whose cancer has continued to progress despite other treatments, including at least one prior chemotherapy regimen.

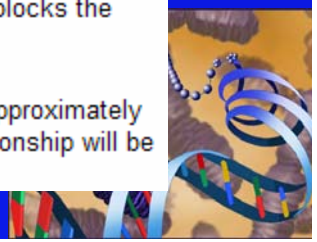
Tarceva is a drug that inhibits an enzyme, tyrosine kinase, associated with a Human Epidermal Growth Factor Receptor. The drug has shown improved survival in patients with locally advanced or metastatic NSCLC. Tarceva received "Fast Track" status from FDA during its development.

"FDA believes it is crucial for cancer patients to have many safe and effective treatment options available to them in their battle against this disease" said Dr. Lester M. Crawford, Acting FDA Commissioner. "With the approval of Tarceva thousands of patients with lung cancer will not only have access to another treatment option, but one that extends life."

Safety and efficacy were demonstrated in one randomized trial in 731 patients comparing Tarceva to placebo. The primary endpoint in this trial was survival. The median overall survival was 6.7 months in the Tarceva group compared with 4.7 months in the placebo group.

The mechanism of action by which Tarceva exerts its clinical benefit is not fully understood. However, Tarceva was developed to block growth stimulatory signals in cancer cells. These signals are mediated in part by enzymes called tyrosine kin sases. Tarceva blocks the tyrosine kinase associated with Epidermal Growth Factor Receptor (EGFR).

In about one third of the patients tumor cells were examined to see whether they had high or low levels of EGFR. Among the approximately 55% who had high EGFR the effect on survival was much greater than it was in people whose EGFR levels were low. The relationship will be explored further in the future.



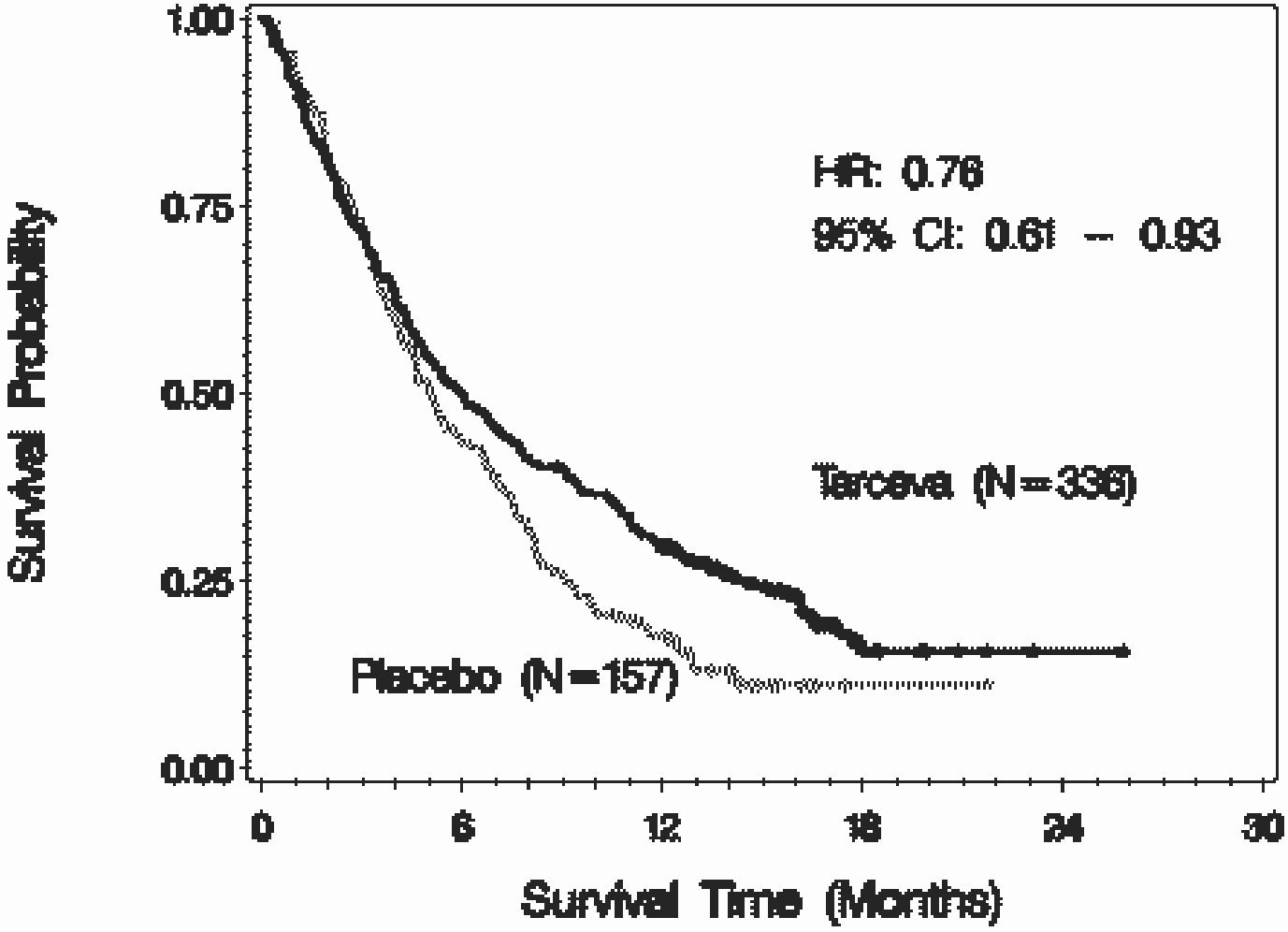
Tarceva Q&A

- **What is Tarceva™?**
  - **Tarceva™ is a selective inhibitor of EGFR tyrosine kinase.**
- **How does Tarceva™ work?**
  - **Tarceva™ competitively binds to the ATP-binding site in the intracellular tyrosine kinase domain, inhibiting ligand-induced EGFR tyrosine phosphorylation, thereby blocking the EGFR signal transduction pathway and cellular proliferation.**
- **What Phase III clinical trials have been conducted with Tarceva™?**
  - **Non-small-cell lung cancer trials:**
    - » **1st-line in combination with gemcitabine and cisplatin vs placebo**
    - » **1st-line in combination with carboplatin and paclitaxel vs placebo**
    - » **2nd-3rd-line monotherapy vs placebo**
  - **Pancreatic cancer trial:**
    - » **1st-line in combination with gemcitabine vs placebo**

Tarceva Q&A

- **What is the difference between Tarceva™ and Iressa™?**
  - **chemically similar quinazoline compounds**
  - **competitively inhibit EGFR tyrosine kinase activity**
  - **IC50 is different for each compound with a value of 0.020 mM for Iressa and 0.002 mM for Tarceva™**
  - **no comparative clinical study with these two compounds to evaluate any differences in safety or efficacy.**

Figure 5: Survival in EGFR Unmeasured Patients

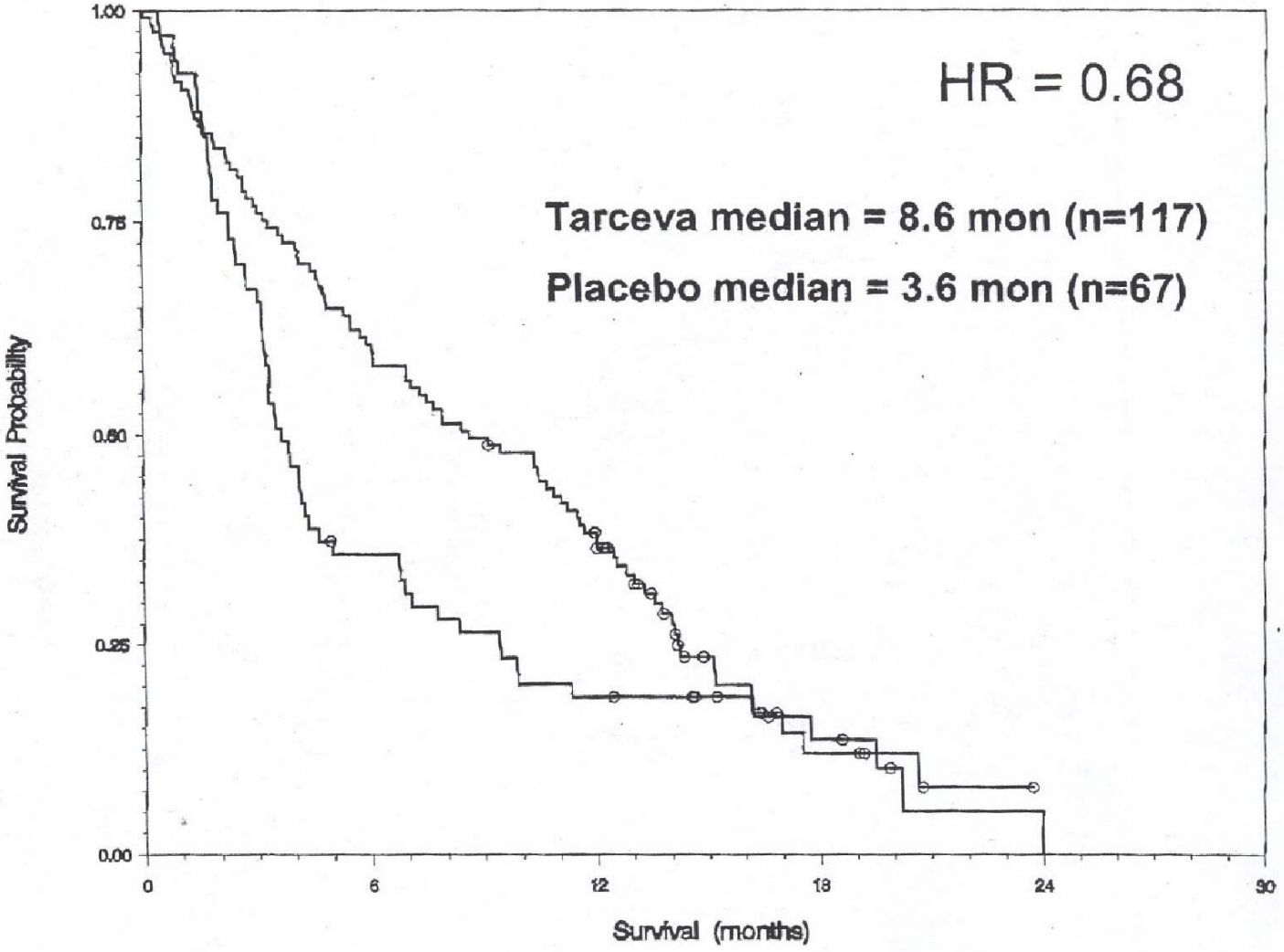


Comparison Between Label Statement and Current Results

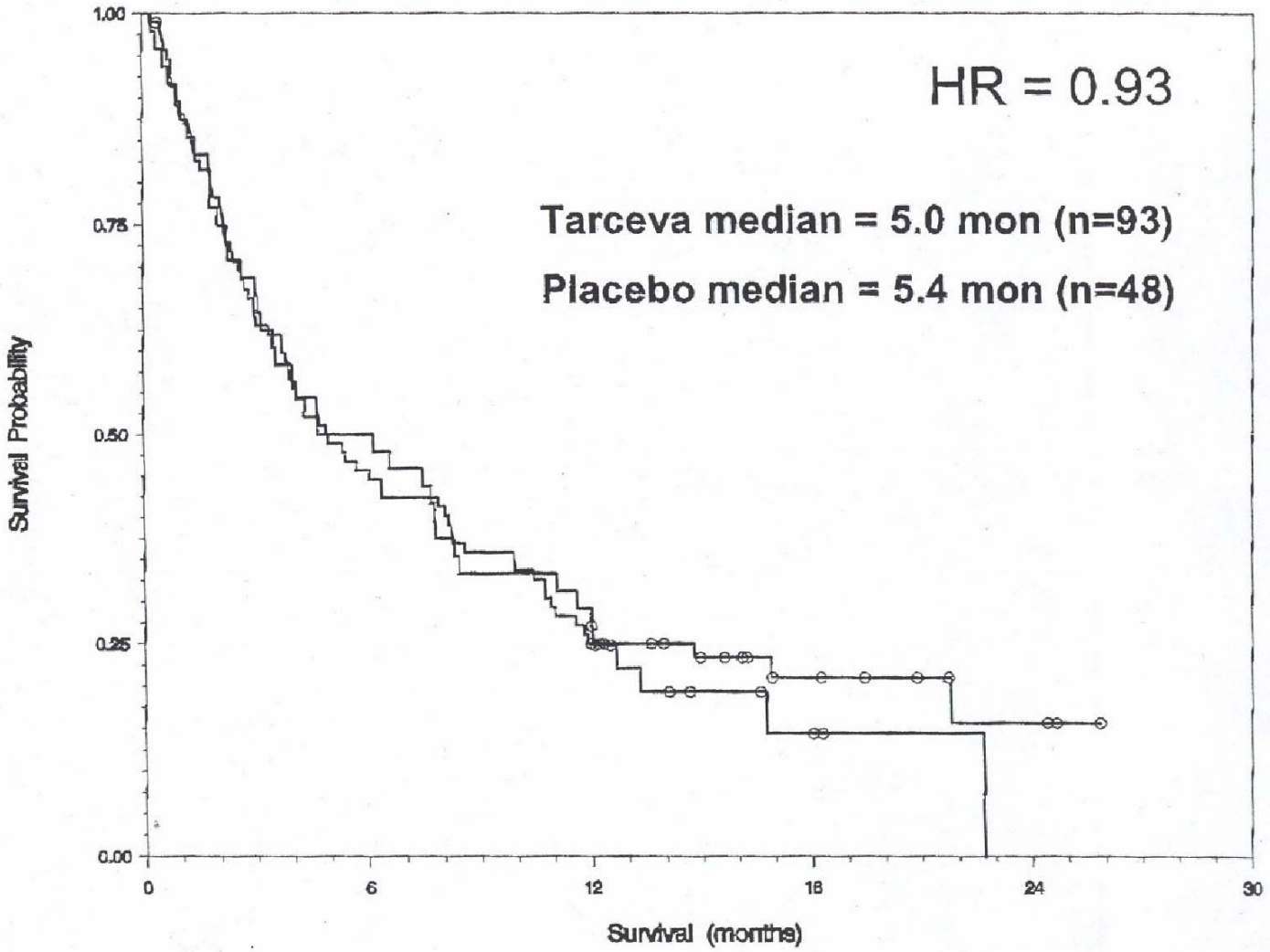
	Tarceva		*Placebo*			
	N	Median	N	Median	HR	HR (Label)
All Patients	488	6.7	243	4.7	0.76	0.73
IHC +	117/78	8.6	67/49	3.6	0.68	0.65
IHC -	93/74	5.0	48/37	5.4	0.93	1.01

Different survival benefits for the drug between the patient population as a whole and the population of IHC+ patients.

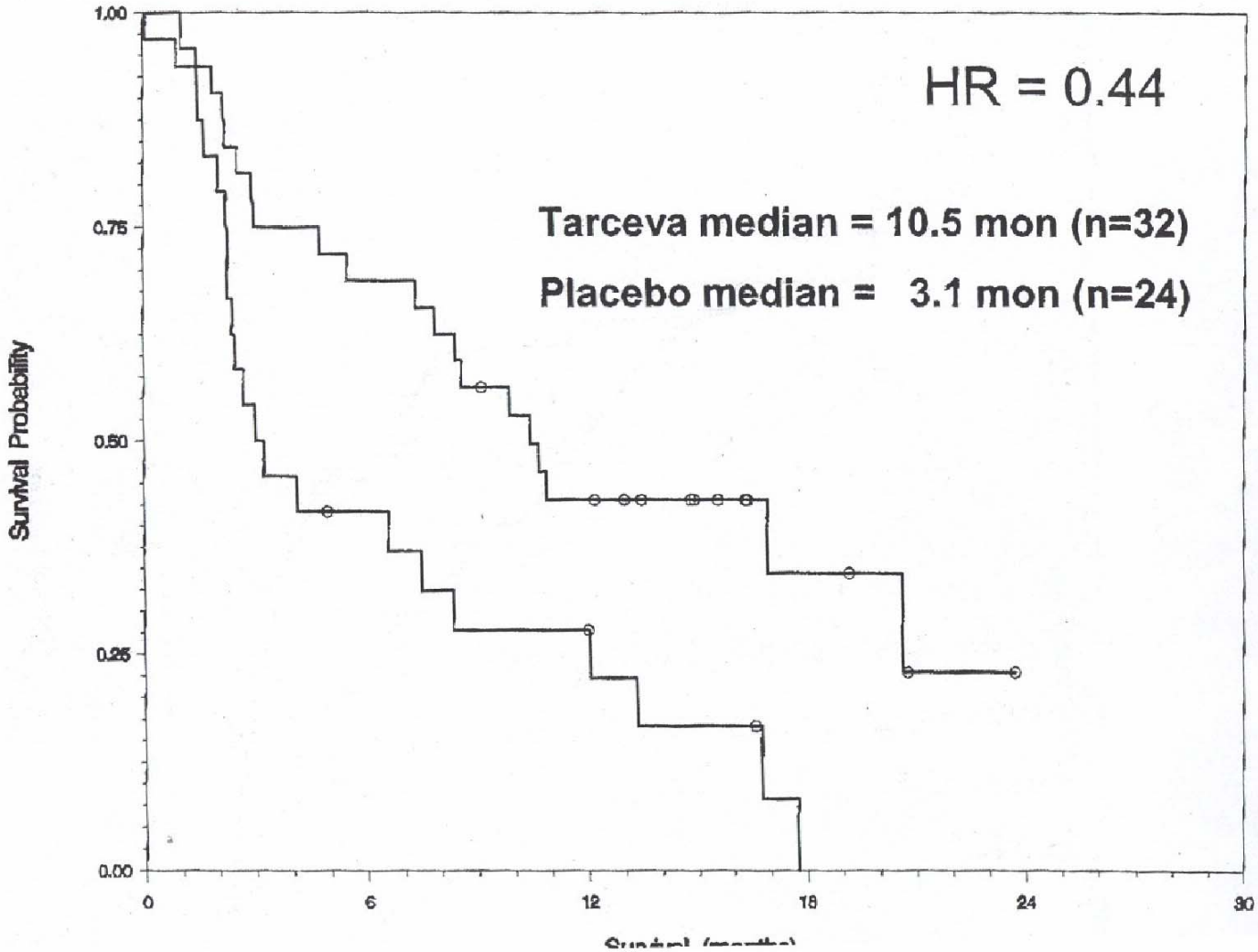
Survival: IHC+



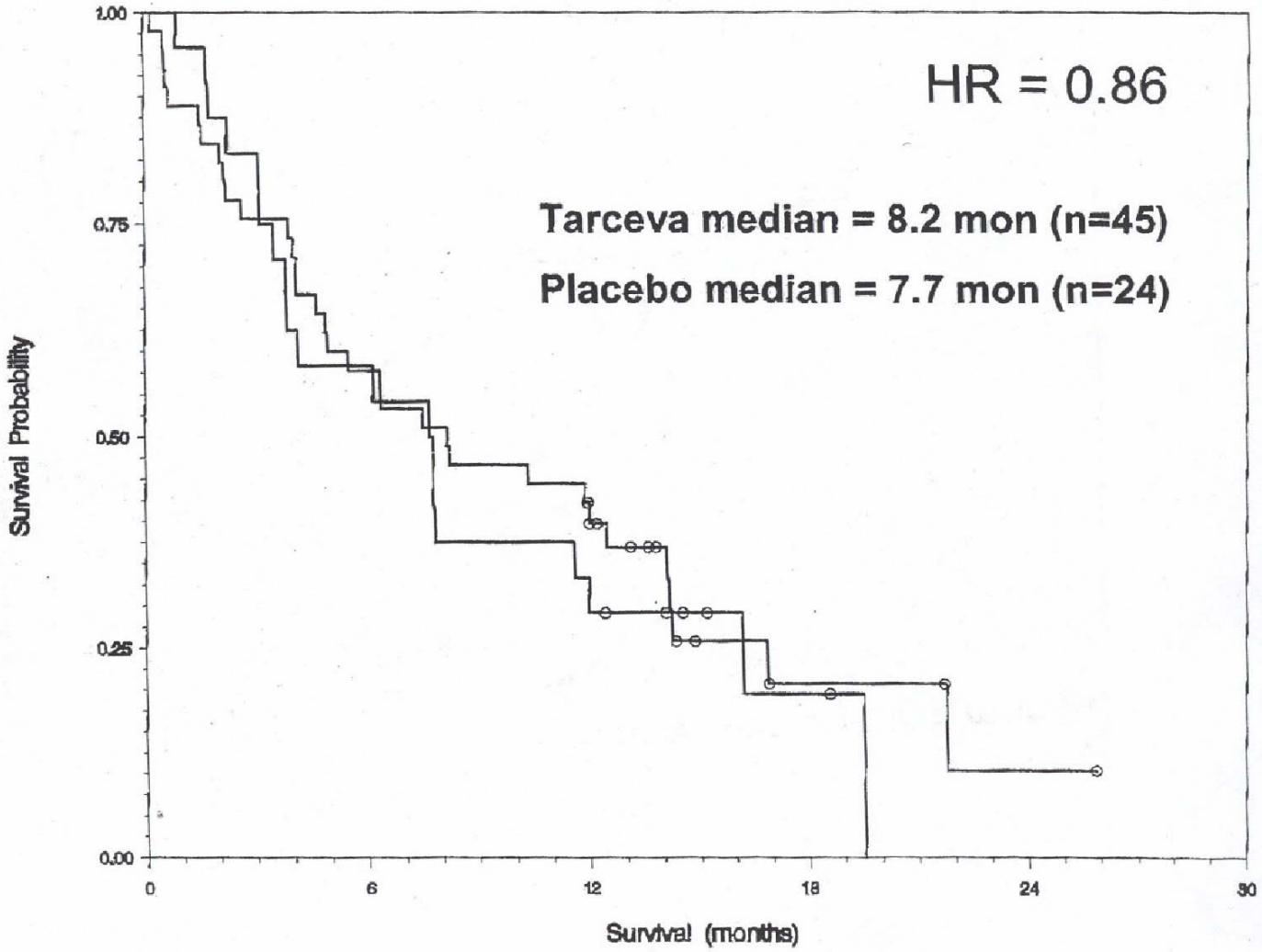
Survival: IHC-



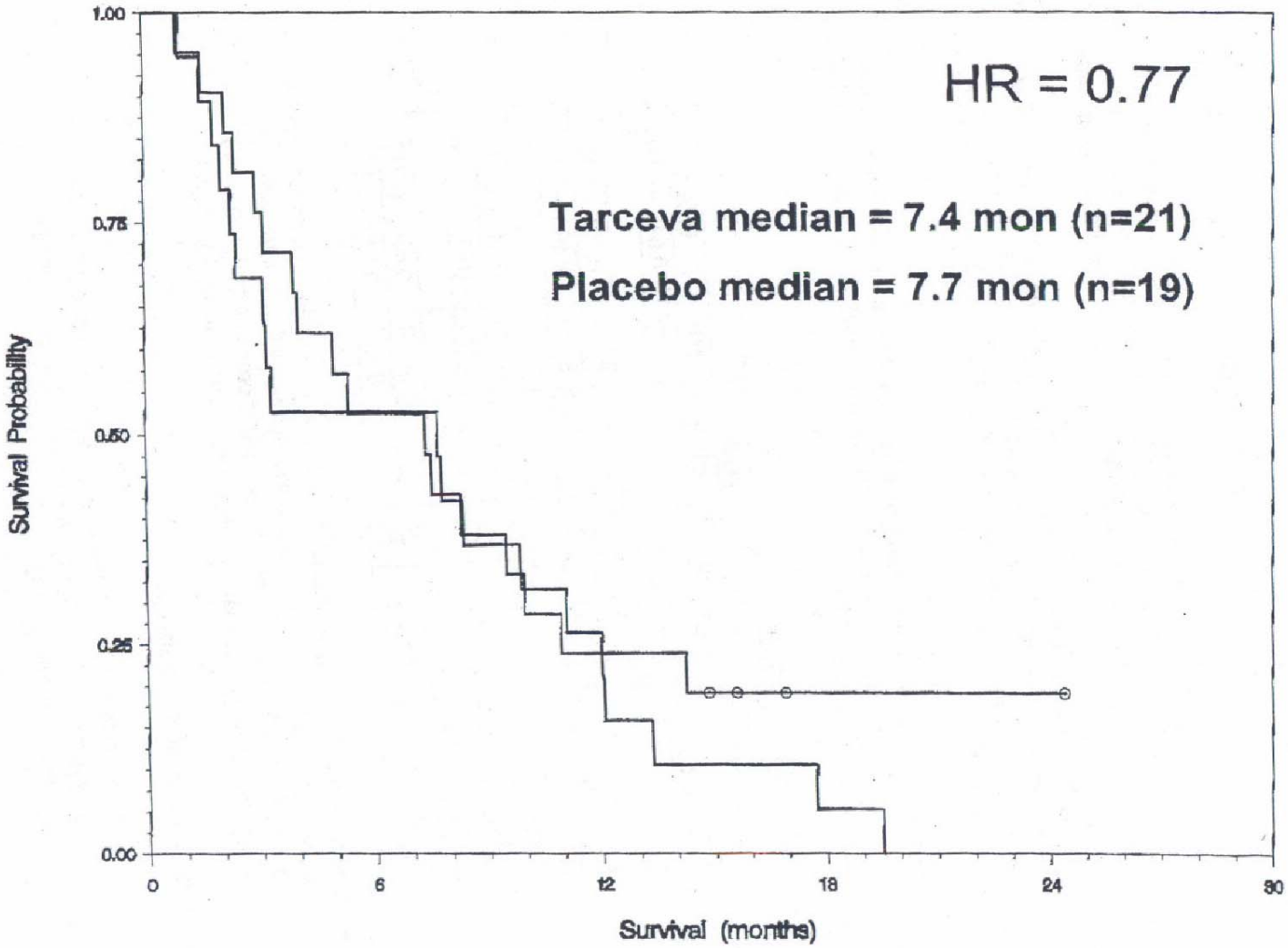
Survival: FISH+



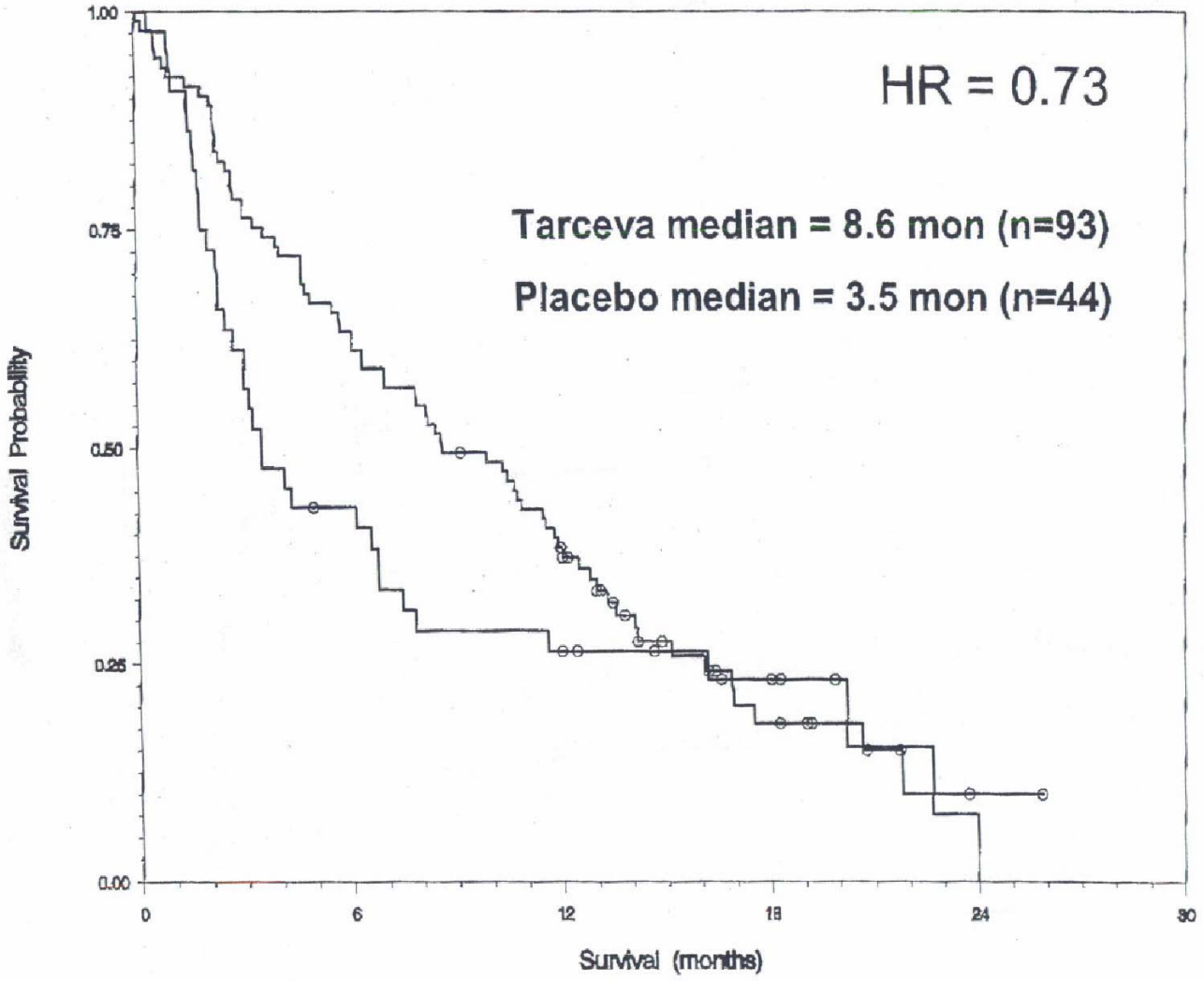
Survival: FISH-



Survival: Mutation+



Survival: Mutation-



Tarceva Conclusions

- **EGFR mutations, gene amplification, and gene expression are associated with increased tumor response in Tarceva arm.**
- **EGFR gene amplification and gene expression predict longer survival with Tarceva treatment.**
- **EGFR mutation does not predict for longer survival with Tarceva treatment.**
- **EGFR mutation may be associated with longer survival irrespective of treatment.**

What would you do?

Erbitux

FDA News

FOR IMMEDIATE RELEASE
P04-20
February 12, 2004

Media Inquiries: 301-827-6242
Consumer Inquiries: 888-INFO-FDA

FDA Approves Erbitux for Colorectal Cancer

FDA today approved Erbitux (cetuximab) to treat patients with advanced colorectal cancer that has spread to other parts of the body. Erbitux is the first monoclonal antibody approved to treat this type of cancer and is indicated as a combination treatment to be given intravenously with irinotecan, another drug approved to fight colorectal cancer, or alone if patients cannot tolerate irinotecan.

Erbitux was approved under FDA's accelerated approval program, which allows FDA to approve products for cancer and other serious or life-threatening diseases based on early evidence of a product's effectiveness. Although treatment with Erbitux has not been shown to extend patients' lives, it was shown to shrink tumors in some patients and delay tumor growth, especially when used as a combination treatment.

Erbitux is a genetically engineered version of a mouse antibody that contains both human and mouse components. (Antibodies in the body are substances produced by the immune system to fight foreign substances.) It can be produced in large quantities in the laboratory. This new monoclonal antibody is believed to work by targeting a natural protein called "epidermal growth factor receptor" (EGFR) on the surface of cancer cells, interfering with their growth.

For patients with tumors that express EGFR and who no longer responded to treatment with irinotecan alone or in combination with other chemotherapy drugs, the combination treatment of Erbitux and irinotecan shrank tumors in 22.9% of patients and delayed tumor growth by approximately 4.1 months. For patients who received Erbitux alone, the tumor response rate was 10.8% and tumor growth was delayed by 1.5 months.

Colorectal cancer -- cancer of the colon or rectum -- is the third most common cancer affecting men and women in the U.S. and, according to the Centers for Disease Control and Prevention (CDC), and is the second leading cause of cancer-related death. Colorectal cancer is also one of the most commonly diagnosed cancers in the U.S.; approximately 147,500 new cases were diagnosed in 2003.

Erbitux Q&A

- **What is Erbitux (Cetuximab)?**
  - **monoclonal antibody that targets EGFR**
  - **interfere with the growth of cancer cells by binding to EGFR so that the normal (natural) epidermal growth factors cannot bind and stimulate the cells to grow**
  - **approved label requires test for EGFR positivity (immunohistochemistry test)**

Erbitux: *The Label*

ERBITUX (Cetuximab) was studied as a single agent in a multicenter, open-label, single-arm clinical trial in patients with EGFR-expressing, metastatic colorectal cancer who progressed following an irinotecan-containing regimen. Of 57 patients enrolled, 28 patients had documented progression to irinotecan. The overall response rate was 9% for the all-treated group and 14% for the irinotecan-failure group. The median times to progression were 1.4 and 1.3 months, respectively. The median duration of response was 4.2 months for both groups.

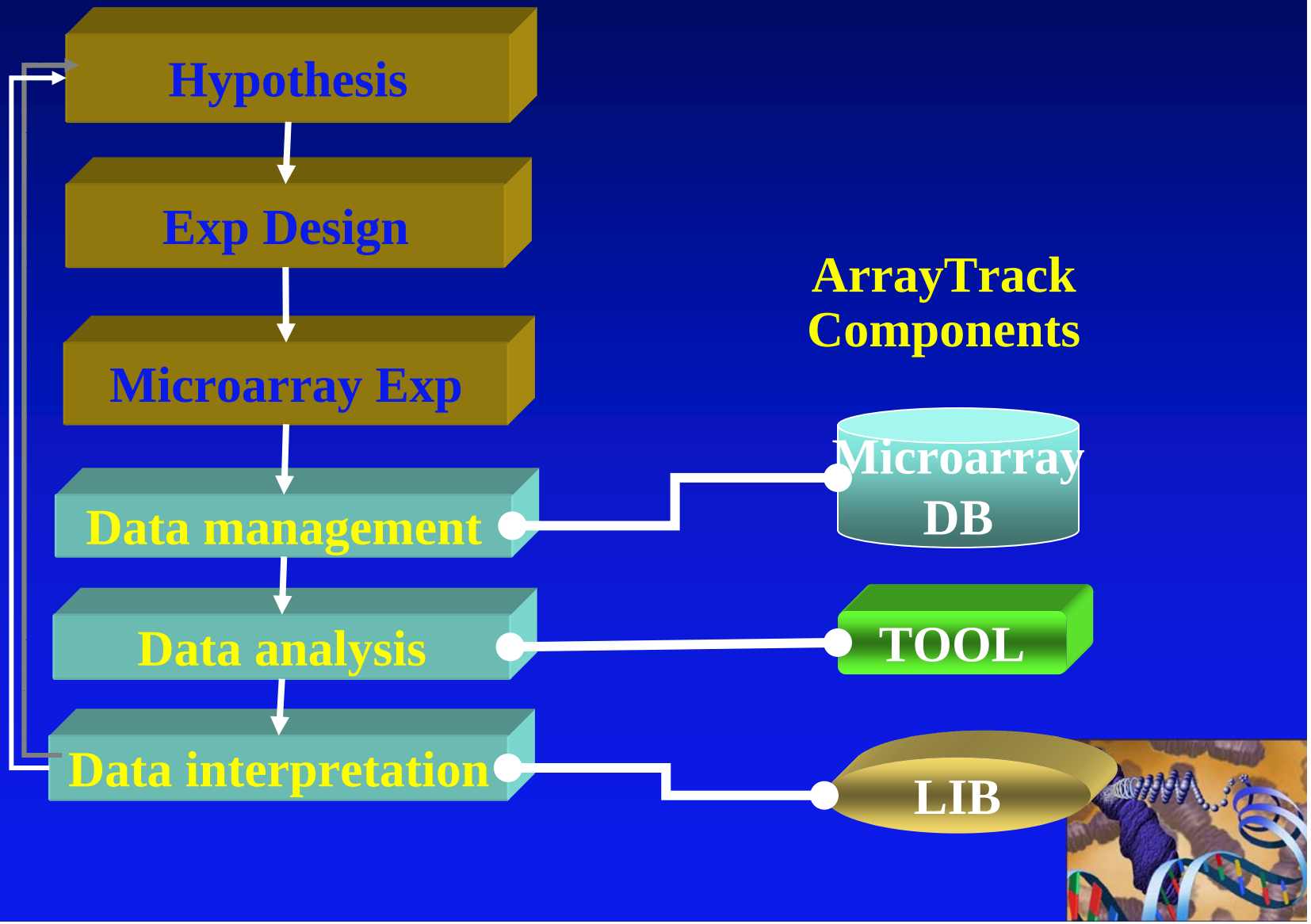
EGFR Expression and Response
Patients enrolled in the clinical studies were required to have immunohistochemical evidence of positive EGFR expression. Primary tumor or tumor from a metastatic site was tested with the DakoCytomation EGFR pharmDx™ test kit. Specimens were scored based on the percentage of cells expressing EGFR and intensity (barely/faint, weak to moderate, and strong). Response rate did not correlate with either the percentage of positive cells or the intensity of EGFR expression.

INDICATIONS AND USAGE
ERBITUX, used in combination with irinotecan, is indicated for the treatment of EGFR-expressing, metastatic colorectal carcinoma in patients who are refractory to irinotecan-based chemotherapy. ERBITUX administered as a single agent is indicated for the treatment of EGFR-expressing, metastatic colorectal carcinoma in patients who are intolerant to irinotecan-based chemotherapy.The effectiveness of ERBITUX is based on objective response rates (see **CLINICAL STUDIES). Currently, no data are** available that demonstrate an improvement in disease-related symptoms or increased survival with ERBITUX.

What could we predict about the pharmacogenomics of Erbitux on the basis of what we learned about Iressa and Tarceva?

ArrayTrack and Toxicogenomics

ArrayTrack Consists of Three Components: MicroarrayDB, TOOL and LIB



Microarray Database: Storing data associated with a microarray experiment

Microarray database:

- **Handling both one- and two-channel data, including affy data**
- **Only the CEL file is required for affy data**
- **Supporting toxicogenomics research by storing tox parameters, e.g., dose schedule and treatment, sacrifice time**
- **MIAME supportive to capture the key data of a microarray experiment**
- **Will be MAGE-ML compliant to ensure inter-exchangeability between ArrayTrack and other public databases**

TOOL: Microarray Data Analysis

Analysis tools:

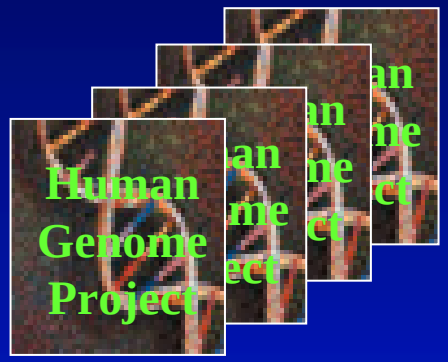
- **Four normalization methods**
  - **Mean/median scaling for affy data**
  - **LOWESS for 2-color array**
- **Gene selection method**
  - **T-test, permutation t-test, …**
  - **Filtering using fold changes, intensity, flag inf …**
  - **Volcano plot, p-value plot …**
- **Data exploring (e.g., HCA, PCA)**
- **Many visualization tools (e.g., flexible scatter plot, Bar chart viewer,…**

LIB: Functional Information for Microarray Data Interpretation

Functional data:

- Individual gene analysis
- Pathway-based analysis
- Gene Ontology – based analysis
- Linking expression data to the traditional toxicological data

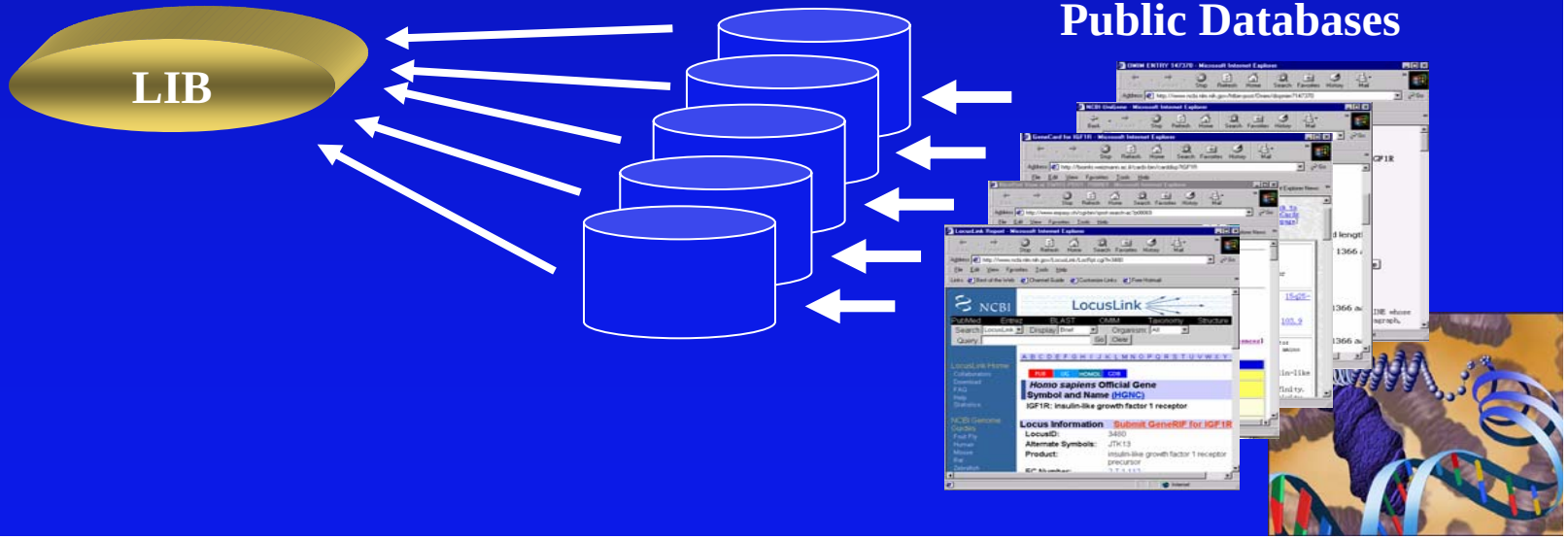
Microarray DB



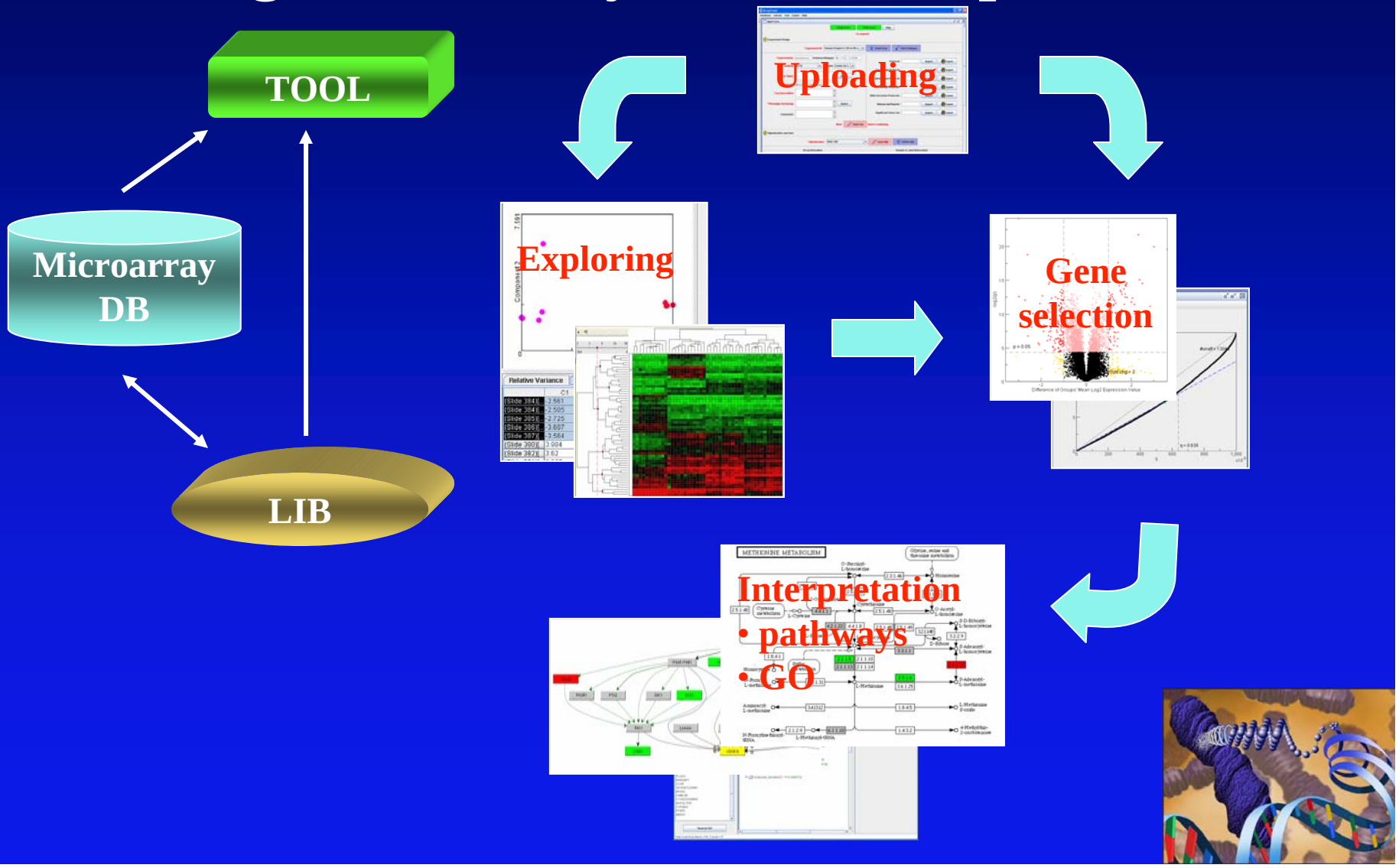
Mirrored Databases

Public Databases

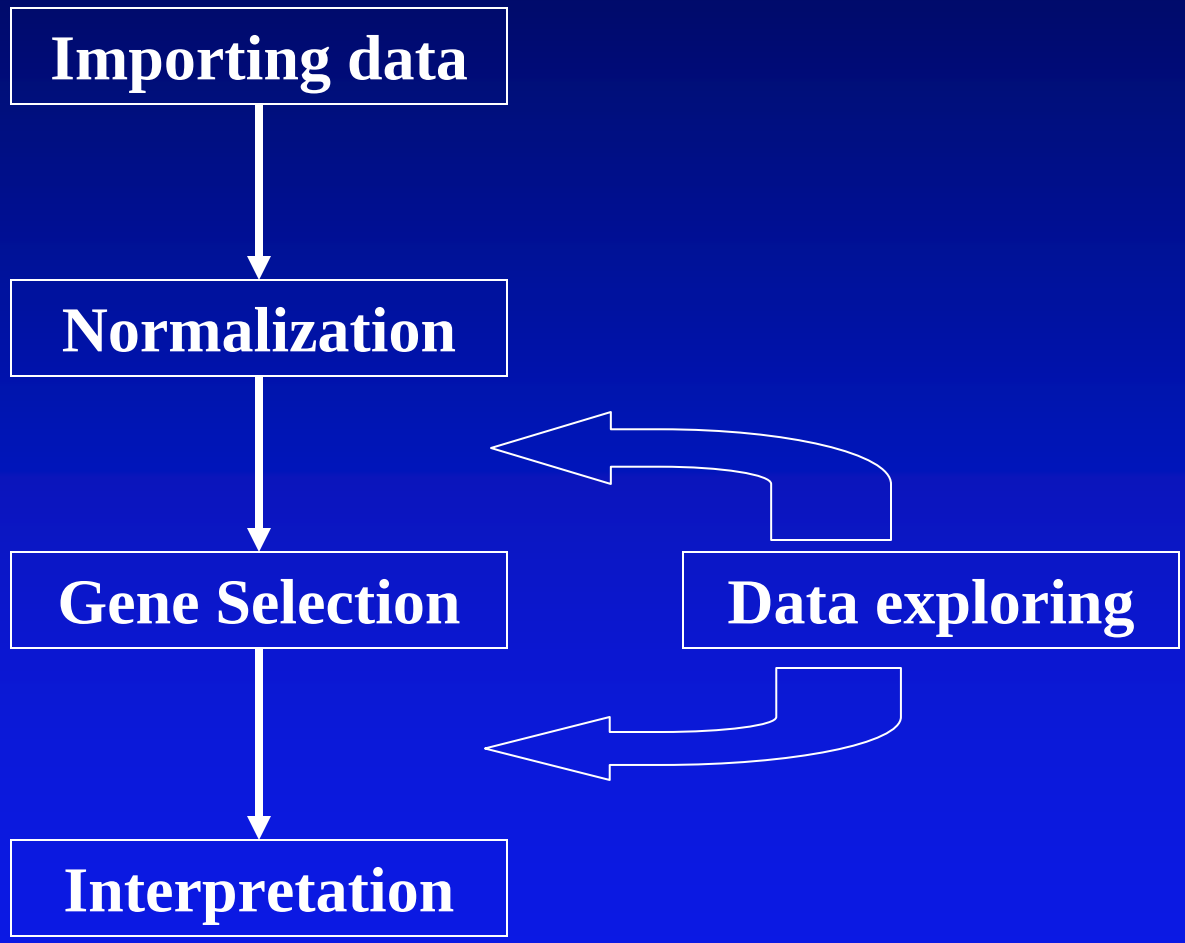
LIB



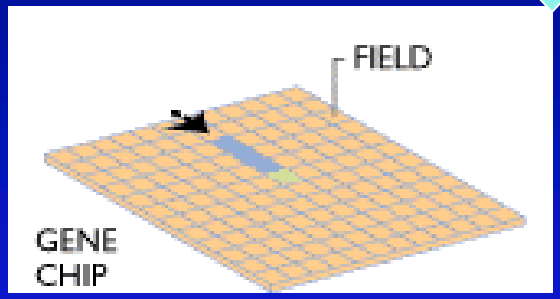
ArrayTrack: MicroarrayDB-LIB-TOOL: Integrated environment for microarray data management, analysis and interpretation.



Microarray Data Processing: From Start to Finish



Affymetrix Chip, Field, Probe Set and Gene

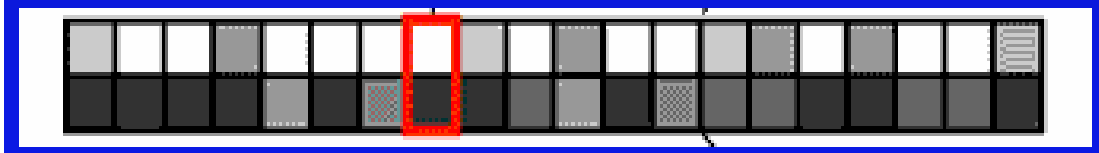


Several data formats:

.CEL - Probe level data

.CHP - Gene (probset) level data

.DAT - Image file



PM
MM

16-20 Probe pairs / Probe Set

1 gene is represented by a Probe Set

Microarray Data Processing: Four Steps for Hybridization Data Processing

Importing data ← **Load Affy data (.CEL) into ArrayTrack**

↓

Normalization ← **Ensure cross-chip comparison**

↓

Gene Selection ← **Identify a list of significant genes**

↓

Interpretation ← **Interpret data using pathways and GO**

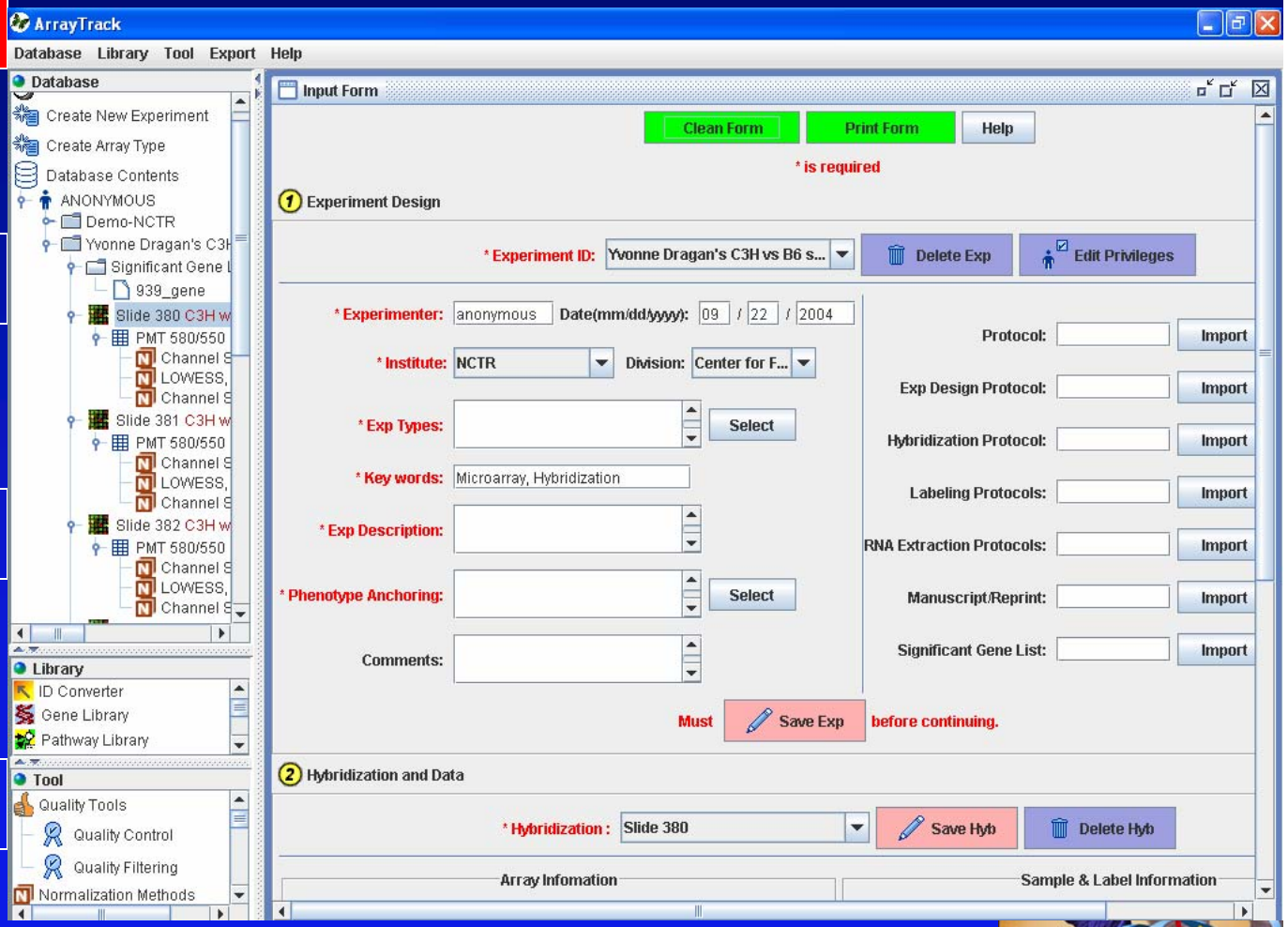
Step 1 – Import Data (MicroarrayDB): Data Is Uploaded with Data Input Form

Import Data

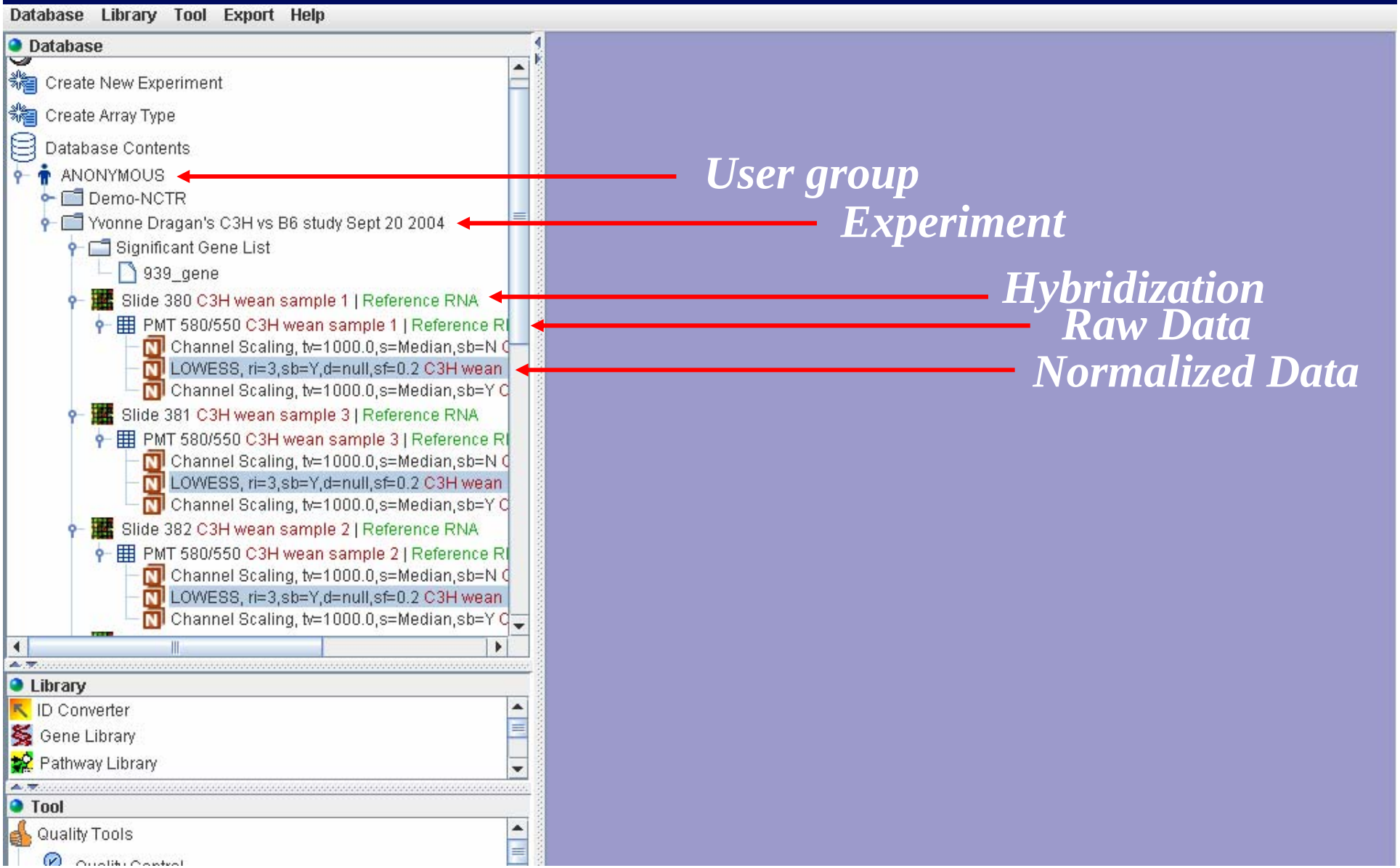
Normalization

Gene Selection

Interpretation



Step 1 – Importing Data (MicroarrayDB): Data Organized in a Hierarchical Tree Structure



Step 2 – Normalization: Remove Systematic Variation Across Chips and Ensure Valid Cross-Chip Comparisons

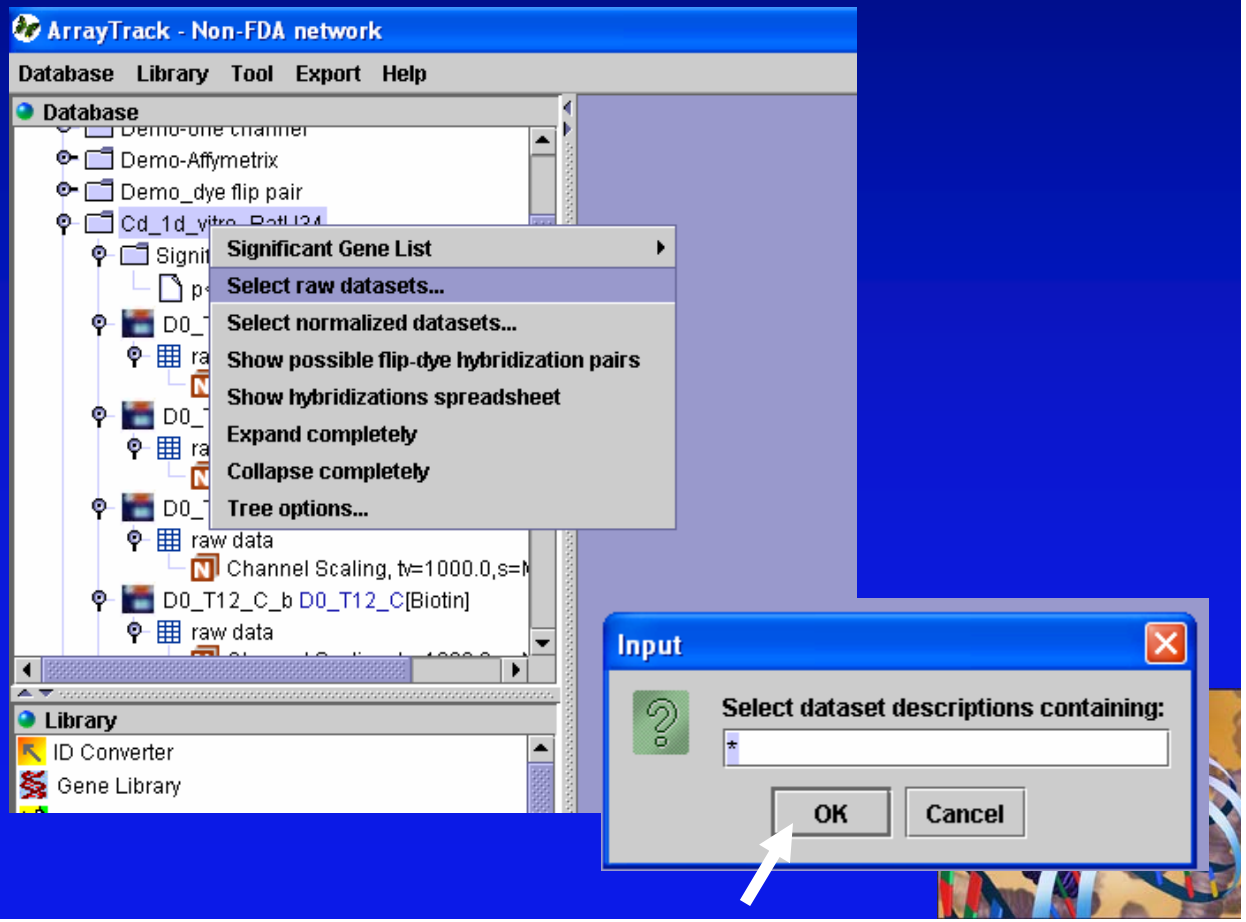
Import Data

Normalization

Gene Selection

Interpretation

1. *Highlight and right click the experiment (Cd_1d_vitro_RatU34)*
2. *Select "raw datasets…" and hit "OK"*



Step 2 – Normalization

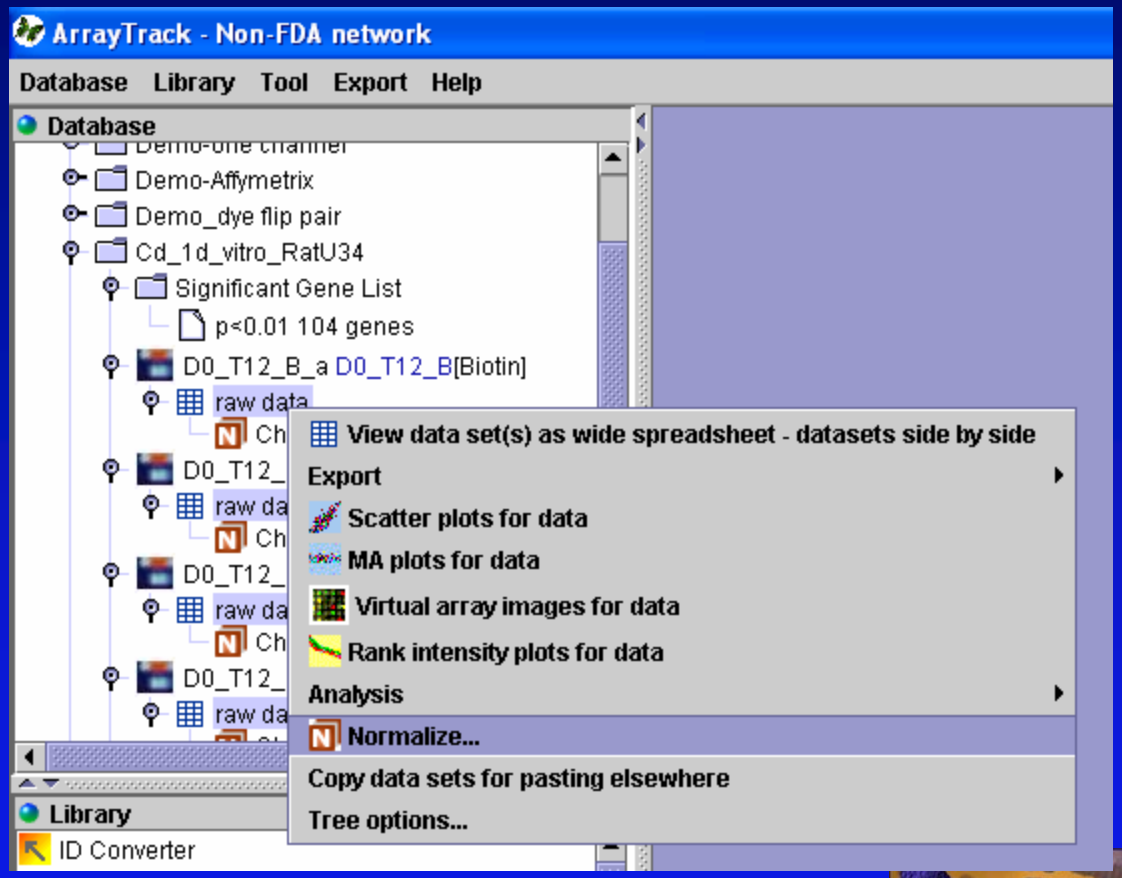
Import Data

Normalization

Gene Selection

Interpretation

1. *Right click any highlighted data (raw data)*
2. *Select "Normalization…"*



Step 2 – Normalization

Import Data

↓

Normalization

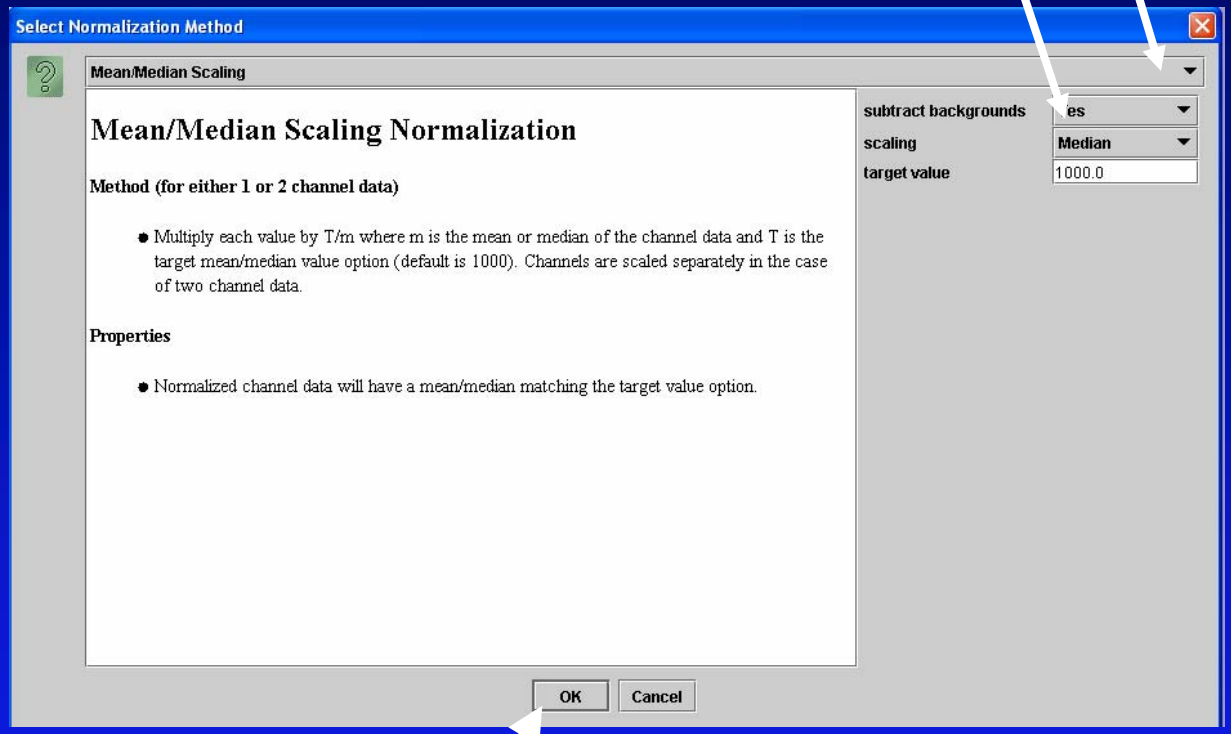
↓

Gene Selection

↓

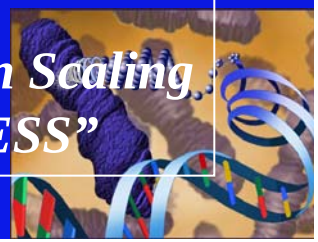
Interpretation

Select normalization method
Set normalization parameters



Tips:

- ***For Affy data, chose "Mean/Median Scaling"***
- ***For 2-channel data, choose "LOWESS"***



CDRH/CDER Nephrotoxicity Study Sample Definitions (Raw Data from Affymetrix Hybridizations from Karol Thompson from Study by Peter Goering)

- **Kidney RNA from Rats treated with Saline**
  - **59-7**
  - **60-1**
  - **60-2**
- **Kidney RNA from Rats treated with Hg**
  - **58-5**
  - **58-8**
  - **60-4**
- **Kidney RNA from Rats treated with Gentamicin**
  - **57-5**
  - **57-6**
  - **57-7**
  - **58-2**
- **Kidney RNA from Rats treated with Hg and Gentamicin**
  - **57-1**
  - **57-2**
  - **57-3**