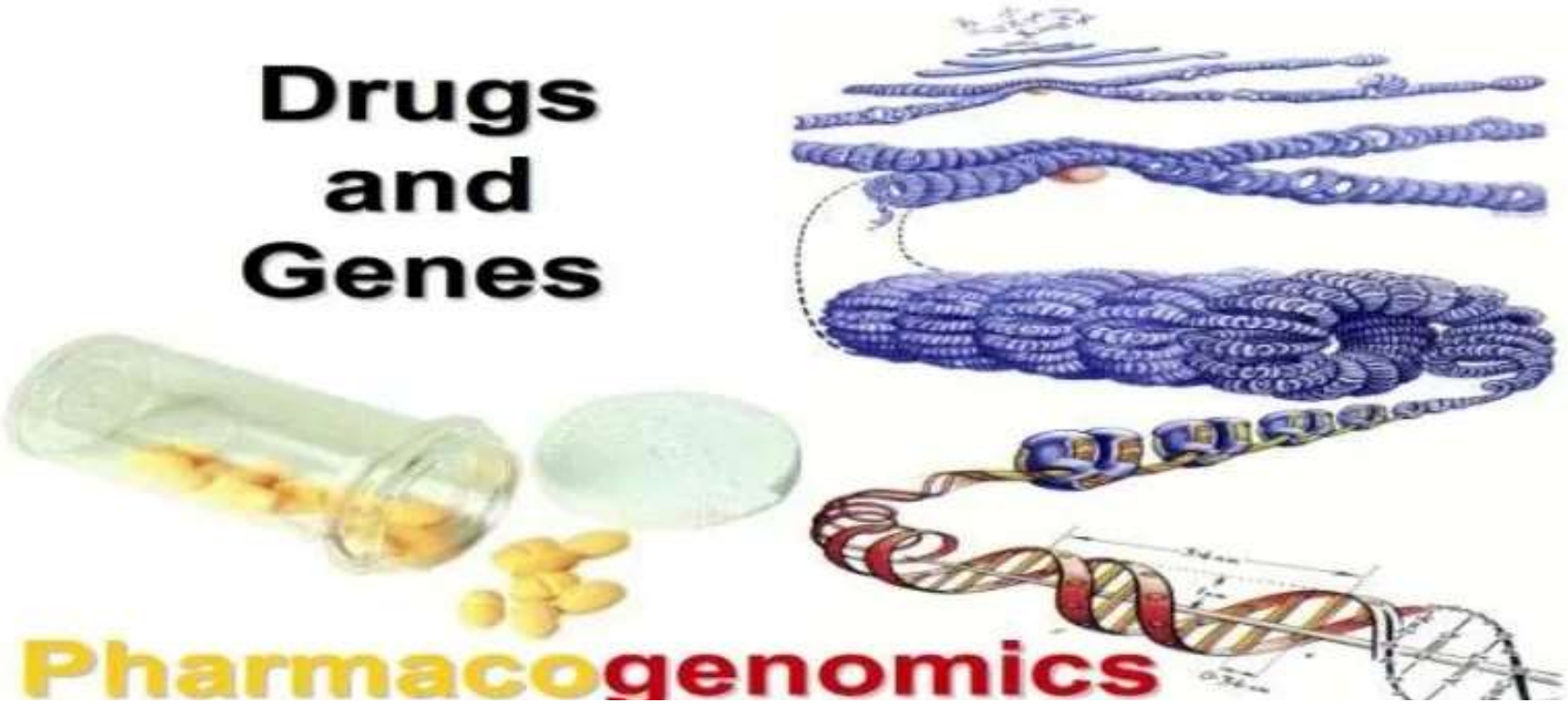
SCOPE OF PHARMACY AND SPECIAL ATTENTION TO PHARMACOGENOMICS



AIMS & OBJECTIVES

- to develop rational means to optimize drug therapy,
- to ensure maximum efficiency with minimal adverse effects.
- attempts to eliminate the trial-and-error method of prescribing, allowing physicians to take into consideration their patient's genes, the functionality of these genes,
- to achieve better treatment outcomes, greater efficacy, minimization of the occurrence of drug toxicities and adverse drug reactions (ADRs).
- two possible types of input can be used: genotyping or exome or whole genome sequencing. Sequencing provides many more data points, including

PHARMACOGENOMICS AND PHARMACOLOGY

- Pharmacogenomics is the study of the role of the genome in drug response. Its name (pharmaco- + genomics) reflects its combining of pharmacology and genomics. Although both terms relate to drug response based on genetic influences, pharmacogenetics focuses on single drug-gene interactions, while pharmacogenomics encompasses a more genome-wide association approach, incorporating genomics and epigenetics while dealing with the effects of multiple genes on drug response.

PERSONALIZED MEDICINE

- Medicine is personal:
  - We are all different.
  - Some of our differences translate into how we react to drugs as individuals.
  - This is why personalized medicine is important to everyone.
- Why does someone need twice the standard dose to be effective?
- Why does this drug work for you but not me?
- Why do I have side-effects and you don't?

IS MEDICINE A SCIENCE OR AN ART?

If it were not for the great variability among individuals, medicine might well be a science, not an art.

- Sir William Osler, Physician 1892
- Johns Hopkins School of Medicine
- Johns Hopkins Hospital
- Father of modern medicine

THE GOAL OF PERSONALIZED MEDICINE

- The Right Dose of
- The Right Drug for
- The Right Indication for
- The Right Patient at
- The Right Time.

Or

Ioatrogenic diseases & Adv.Drug. Reaction

- 10% hospital patients

PHARMACOGENETICS & PHARMACOGENOMICS

- Pharmacogenetics: The role of genetics in drug responses due to differences in metabolism according to age, sex, colour or

  The branch of pharmacology concerned with the effect of genetic factors on reactions to drugs.

- Pharmacogenomics : The science that allows us to predict a response to drugs based on an individuals genetic make up or

  How genetic make up in the body response to

PHARMACOGENETICS & PHARMACOGENOMICS

- Pharmacogenetics: study of individual gene-drug interactions, usually one or two genes that have dominant effect on a drug response (SIMPLE relationship)

- Pharmacogenomics: study of genomic influence o drug response, often using high-throughput data.
  - *Asian appears to process the drug differently and half of the standard dr has same effect as in full dose of USA or Europeans. Full dose can incre*

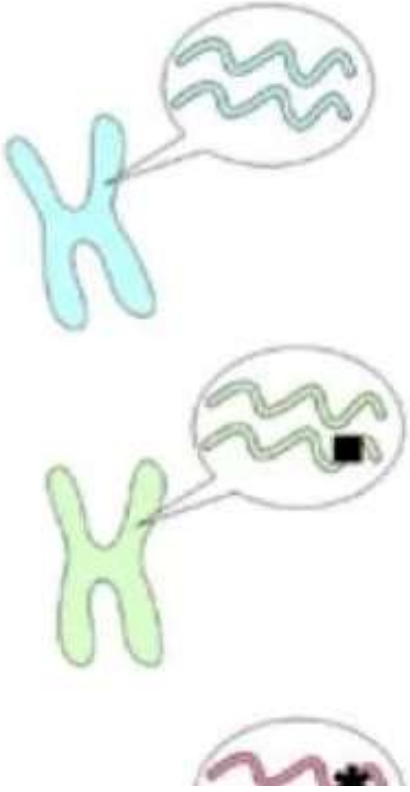
Pharmacogenetics: A Case Study

Individuals respond differently to the anti-leukemia drug 6-mercaptopurine.

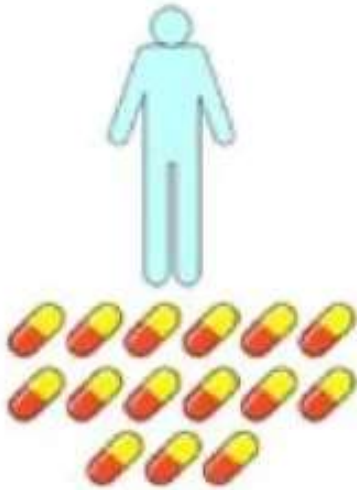
Most people metabolize the drug quickly. Doses need to be high enough to treat leukemia and prevent relapses.

Others metabolize the drug slowly and need lower doses to avoid toxic side effects of the drug.

The diversity in responses is due to variations in the gene for an enzyme called TPMT, or thiopurine methyltransferase.



After a simple blood test, individuals can be given d of medication that are tail to their genetic profile.



Normal dose

EXAMPLE: CODEINE AND CYTOCHROME P450 CYP2D6

- Codeine is a commonly used opioid
  - Codeine is a prodrug
  - It must be metabolized into morphine for activity
- Cytochrome P450 allele CYP2D6 is the metabolizing enzyme in the liver
  - codeine does not work effectively in these individuals

EFFECT OF METABOLIC RATE ON DRUG DOSAGE

Drug	Poor Metabolizer Phenotype
Prodrug, needs metabolism to work (eg. codeine is metabolized by CYP 2D6 to morphine)	Poor efficacy Possible accumulation of prodrug
Active drug, inactivated by metabolism (example is omeprazole)	Good efficacy Accumulation of active drug can produce adverse reactions May need lower dose

Drug	Ultra-rapid Metabolizer Phenotype
Prodrug, needs metabolism to work (eg. codeine is metabolized by CYP 2D6 to	Good efficacy, rapid effect

WARFARIN: SIGNIFICANT PROBLEMS FOR HUMANS!

- Ranks #1 in total mentions of deaths for drugs causing adverse events
- Ranks among the top drugs associated hospital emergency room visits for bleeding
- Overall frequency of major bleeding range from 2% to 16% (versus 0.1% for most drugs)

WHY MAINTAINING WARFARIN THERAPEUTIC RANGE IS CRITICA

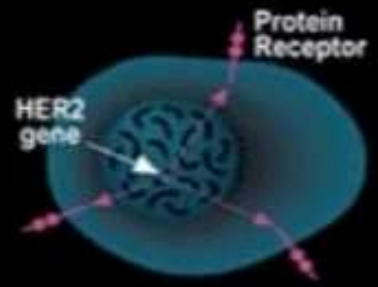
GENETIC ANALYSIS PERMITS

- More rapid determination of stable therapeutic dose.
- Better prediction of dose than clinical methods alone.
- Applicable to the 70-75% of patients not in controlled anticoagulation centers.

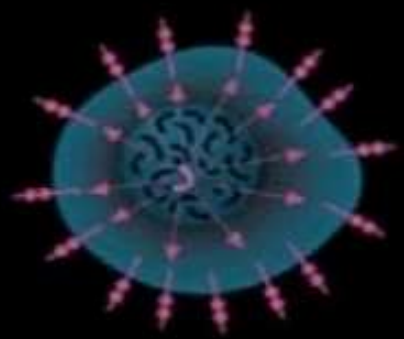
WHAT ARE TARGETED DRUGS?

- Often, drugs are only effective in specific "sub-populations" (responders).
- Early identification of responders can have a dramatic effect of treatment success.
- Treatment of non-responders puts these individuals at unnecessary risk of adverse events, while providing no benefit.

Trastuzumab (Herceptin®



In a normal breast tissue cell, the Her-2 ge
is expressing cell surface receptor required
for normal cell growth.



In certain types of breast cancers, the
Her-2 gene is over-expressing this cell
surface receptor, contributing to cancerou
cell growth.
This is the case in ~30% of breast cancers.

PERSONALIZED DRUGS

- Herceptin (breast cancer, target: Her2/neu)
- Erbitux (colorectal cancer, target: EGFR)
- Tarceva (lung cancer, target: EGFR)
- Strattera (attention-deficit/ hyperactivity disorder, Metabolism: P4502D6)
- 6-MP (leukemia, Metabolism: TPMT)
- Antivirals (i.e. resistance based on form of