Drug Resistance in Cancer

• May affect multiple drugs used simultaneously: known as multidrug resistance (MDR)
• Affects all classes of drugs, including newly designed targeted drugs
• Just as oncogene targets have been catalogued, we need to enumerate all mechanisms of drug resistance in cancer to solve this problem and circumvent resistance

Ultimate Goals

1. Molecular analysis of human cancers to predict response to therapy
2. Use this information to develop novel drugs to treat cancer and new imaging modalities for cancer
3. To learn more about cellular pharmacology and pharmacokinetics of drugs
Drug Resistance in Cancer

- May reflect resistance to single agents generally by altering targets; resistance may arise from mutations in targets or by mutations that bypass targets
- Multidrug resistance affects all classes of drugs, including newly designed targeted drugs, and frequently results from alterations in mechanisms that detoxify drugs (e.g., uptake, metabolism, sequestration, efflux, etc.)
- Both single agent and multidrug resistance may also result from alterations in growth-promoting pathways or altered differentiation pathways (e.g., EMT); cancer heterogeneity and different cells of origin provide a fertile starting point for multidrug resistance

Mechanisms of resistance to anti-cancer drugs

- Reduced apoptosis
- Altered cell cycle checkpoints and/or growth pathways
- Increased metabolism of drugs
- Increased or altered targets
- Increased repair of damage
- Compartmentalization

Why study multidrug transporters?

- Important role in multidrug resistance in cancer and in pathogens
- Important role in drug pharmacokinetics (uptake, distribution, and excretion)
- Important role in drug toxicity
- Key role in development (stem cells, morphogenesis)
- To learn about the biology of all transport systems
ATP-Binding Cassette (ABC) Transporter Superfamily

- One of the largest family of transport proteins known. Currently, more than 2000 members have been identified.

- Transport substrates include ions, sugars, glycans, phospholipids, cholesterol, peptides, proteins, toxins, antibiotics, and hydrophobic natural product anticancer drugs.

- Structurally, consist of various combinations of ATP-binding cassettes and segments with 6 trans-membrane domains.

The Eukaryotic ABCome
57 ABC-family genes

From M. Dean

48 Human ABC Genes

The Clustal W program was used to make the alignment of the NBDs and the tree was built by using the MEGA program – By Mike Dean, NCI
ABC transporters determine oral bioavailability, excretion, penetration and protect the organism against airborne xenobiotics

Human diseases associated with an ABC Transporter

- Cancer: ABCB1, ABC1, ABCG2
- Cystic fibrosis: ABCC7 (CFTR)
- Stargardt disease & AMD: ABCC6 (MRP6)
- Tangier Disease (HDL deficiency): ABCA1 (ABC1)
- Progressive familial intrahepatic cholestasis: ABCB4 (MDR2)
- Demyelinating syndromes: ABCC2 (MRP2)
- Pulmonary fibrosis: ABCC3 (MRP3)
- Persistent hypoglycemia of infancy, neonatal diabetes: ABCB6 (TAP1), ABCB12 (TAP2)
- Sideroblastic anemia and ataxia: ABCB1 (ALD)
- Sclerdermata: ABCG5, ABCG8
- Immune deficiency: ABCB2 (TAP1), ABCB1 (TAP2)

ABC transporters that confer MDR: Domain organization

ABC transporters determine oral bioavailability, excretion, penetration and protect the organism against airborne xenobiotics.
Overlapping substrate specificity of ABCB1, ABCG2 and ABCC1

- Prazosin
- Topotecan
- Mitoxantrone
- Doxorubicin
- Daunorubicin
- Paclitaxel
- Colchicine
- Verapamil
- Calcein-AM
- Etoposide
- Calcein
- LTC4
- NEM-GS
- Etoposide-AM
- Methotrexate
- Pheophorbide A
- Sulfasalazine
- Prolidase
- Flavopiridol
- Nilotinib
- Bisantrene
- Estrone-3-sulfate

Multiple ABC Transporters Confer Resistance to Anti-Cancer Drugs

Confers resistance
Selected

Hypothetical Model of Human P-glycoprotein
P-glycoprotein removes hydrophobic substrates directly from the plasma membrane

**Physiologic Role of P-glycoprotein**

Mouse P-gp at 3.8Å (Aller and Chang)  
Human P-gp model based on Sav1866 (Xia)
Role of P-glycoprotein in cancer

- Approximately 50% of human cancers express P-glycoprotein at levels sufficient to confer MDR
- Cancers which acquire expression of P-gp following treatment of the patient include leukemias, myeloma, lymphomas, breast, ovarian cancer; preliminary results with P-gp inhibitors suggest improved response to chemotherapy in some of these patients
- Cancers which express P-gp at time of diagnosis include colon, kidney, pancreas, liver; these do not respond to P-gp inhibitors alone and have other mechanisms of resistance
- Animal models with human cancer xenografts and BRCA1-driven mouse mammary cancers show role for P-gp in MDR (Pajic et al., Cancer Res. 69, 6396-6404, 2009)