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
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, glycos, 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

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 xenobiots.
Human diseases associated with an ABC Transporter

- Cancer: ABCB1, ABCG2, ABCG1
- Cystic fibrosis: ABCC7 (CFTR)
- Stargardt disease & AMD: ABCC6 (MRP6)
- Tangier Disease: ABCA1 (ABC1)
- Progressive familial intrahepatic cholestasis: ABCB11 (SPGP), ABCB4 (MDR2)
- Duarte syndrome: ABCG2 (MRP5)
- Pseudoxanthoma elasticum: ABCA4 (ABCR)
- Persistent hyperglycemia of infancy: ABCB1 (MRP7)
- Sideroblastic anemia and ataxia: ABCB7 (ABC7)
- Adrenoleukodystrophy: ABCD1 (ALD)
- Sitosterolemia: ABCG5, ABCG8
- Immune deficiency: ABCB2 (Tap1), ABCB3 (Tap2)

ABC transporters that confer MDR: Domain organization

Overlapping substrate specificity of ABCB1, ABCG2 and ABCC1
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
Atomic models of the structures of P-gp

Mouse P-gp at 3.8Å (Aller and Chang)  Human P-gp model based on Sav1866 (Xia)

Physiologic Role of P-glycoprotein

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)