Overall Goals

- Define molecular mechanisms of drug resistance in cancer (natural products, platinum compounds)
- Determine the clinical relevance of mechanisms derived from *in vitro* studies
- Develop new approaches to exploit or circumvent clinically significant resistance mechanisms
- To learn more about the cellular pharmacology and pharmacokinetics of drugs
Cell-based mechanisms of resistance to anti-cancer drugs

- Decreased Uptake-- 100’s of Solute carriers
- Increased Efflux—48 ABC transporters

- 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, glycan, 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 play excretory and/or protective physiological roles

3 main multidrug transporters:

- ABCB1 (P-gp, P-glycoprotein)
- ABCC1 (MRP1)
- ABCG2 (BCRP, MXR)

Kanann et al., Clin Pharmacol. Ther., 2009
Human diseases associated with an ABC Transporter

- Cancer: ABCB1, ABCG1, ABCG2
- Cystic fibrosis: ABCC7 (CFTR)
- Stargardt disease & AMD: ABCA4 (ABCR)
- Tangier Disease: ABCA1 (ABCG1)
- Progressive familial intrahepatic cholestasis: ABCB4 (MDR2), ABCB11 (SPGP)
- Dilation heart disease: ABCG2 (ABCB2)
- Persistent hypoglycemia of infancy: ABCB3 (ABCG2)
- Staphylococcal foods in infants: ABCG2 (ABCB2)
- Sideroblastic anemia and ataxia: ABCB7 (ABCG1)
- Scleroderma: ABCA1 (ABCG1)
- Leukodystrophy: ABCD1 (ALD)
- 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

**Hypothetical Model of Human P-glycoprotein**

- P-glycoprotein removes hydrophobic substrates directly from the plasma membrane.
**Physiologic Role of P-glycoprotein**

- Oral Intake → Intestine → Fecal Excretion
- IV → Vascular space → Urinary Excretion → Interstitial space

**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)