Drug Repurposing: An Academic Perspective

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NIH U54MH074425/084690

- **Academic Motivation/Drivers**
- **Repurposing Experiences at UNMCMD**
- **Personalized Medicine/Compassionate Use/Genomics**
- **Lessons Learned**

UNM HEALTH SCIENCES CENTER | *Center for Molecular Discovery*

Discovery Comes to Academia

- **NIH Programs:**
  - **Biomedical Engineering Consortia 1999 (Technology Development)**
  - **Molecular Libraries Pilot /Production Phases 2005/2008**
    - **Mol Lib Small Molecule Repository updates include approved drugs**
    - **X01/R03 funding mechanisms to target providers and screening centers**
    - **Funding evolves to R01 and R21 mechanisms**
  - **NCI Experimental Therapeutics Program (NExT) consolidates therapeutics programs**
  - **NCI designated cancer centers mandate investigator initiated trials**
  - **Clinical and Translation Science Award (CTSA) Consortium mandates translation of experimental findings; pilot project funding mechanisms for repurposing screens**
- **New and Emerging Opportunities**
  - **Proliferation of discovery meetings, funding initiatives, compound collections, screening technologies**
  - **Pharma/biotech business models evolve (late stage value proposition)**
  - **Academic Drug Discovery Consortium ~75 members**
  - **International Chemical Biology Society**

Academic Landscape Seen From Within

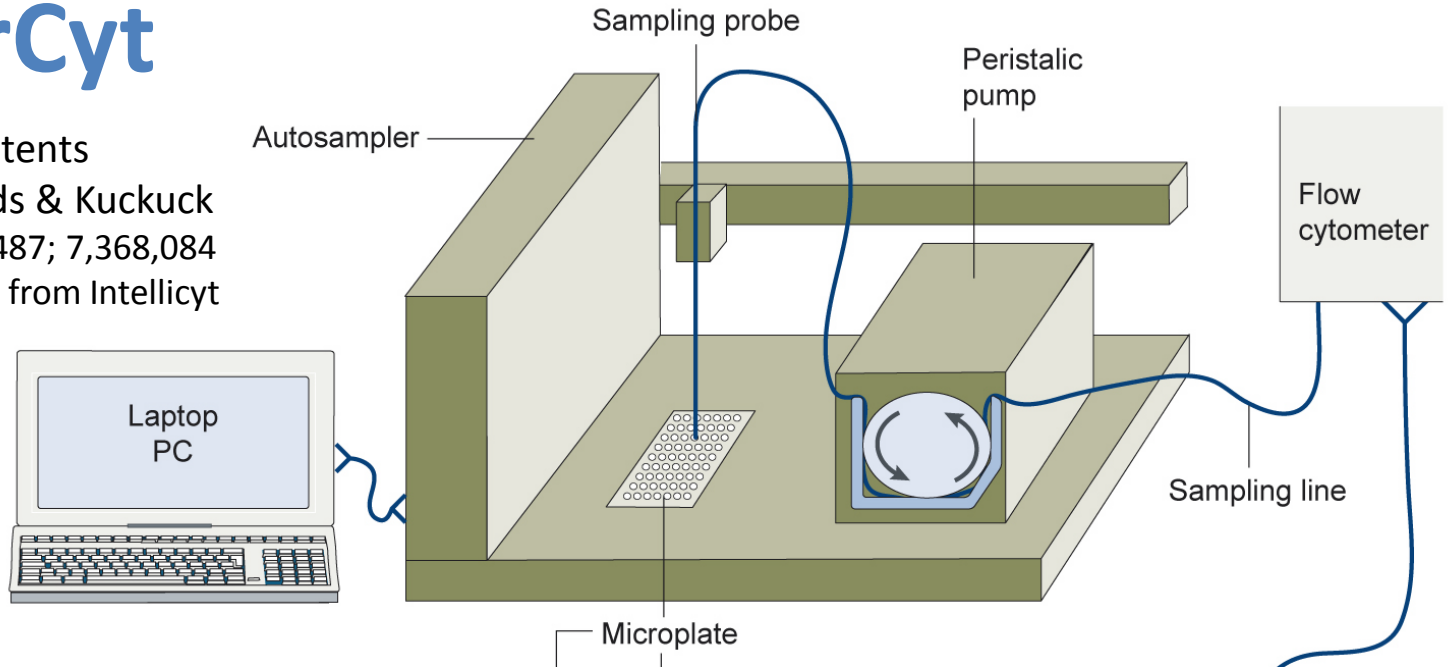
- Faculty Business Model:
  - Research, Service, Education
- Individual Success Measures:
  - Publications, Tenure, Intellectual Property
- Translation becomes priority
  - Commercialization/Technology Transfer/Economic Development
  - Clinical Trials
  - Centers programs (NCI/CTSA) mandate investigated initiated trials on short time lines
- Collaborators, agencies, patients are clients

The View from UNMCMD

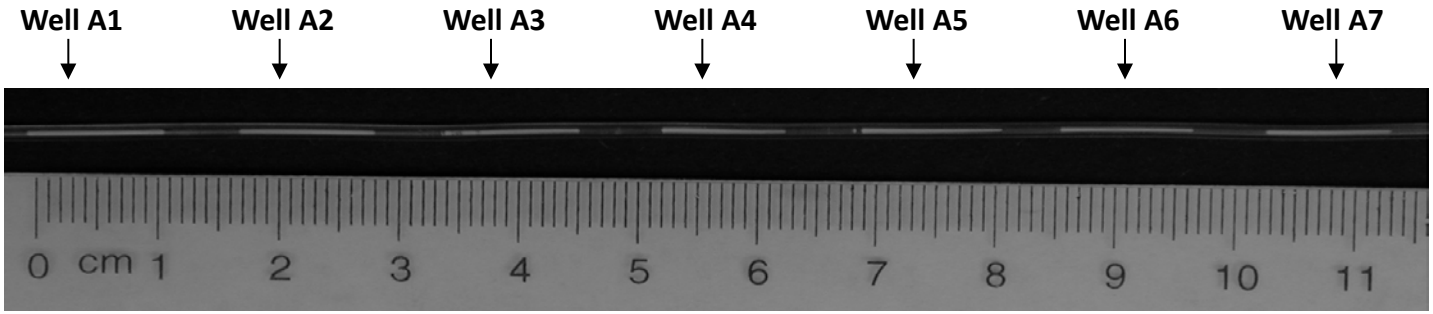
- 1999: 1st round BECON/BRP to develop HT flow cytometry
- 2000: Cancer Center Planning Grant
- 2005: Molecular Libraries Pilot Phase (10 comprehensive centers)
- 2005: Cancer Center at UNM
- 2008: Molecular Libraries Production Phase
  - 4 comprehensive, 2 chemistry, 3 specialty centers
- 2008: NExT Program (MLP/non MLP centers compete)
- 2009: CTSA program at UNM includes repurposing
- 2010: Molecular Libraries R01 funds update from 384 to 1536 wells (B. Edwards)
- 2010: Cancer Center Renewal includes repurposing
- 2010: ARRA funding allow enhancement of UNMCMD
- 2010: Molecular Libraries adds translational “extended probe characterization”
- 2013: UNMCMD moves into new space

HyperCyt

US Patents
Sklar, Edwards & Kuckuck
6,878,556; 6,890,487; 7,368,084
HyperVu software from Intellicyt



Samples: 40/min, 2 μl Each, Separated by Air Bubbles



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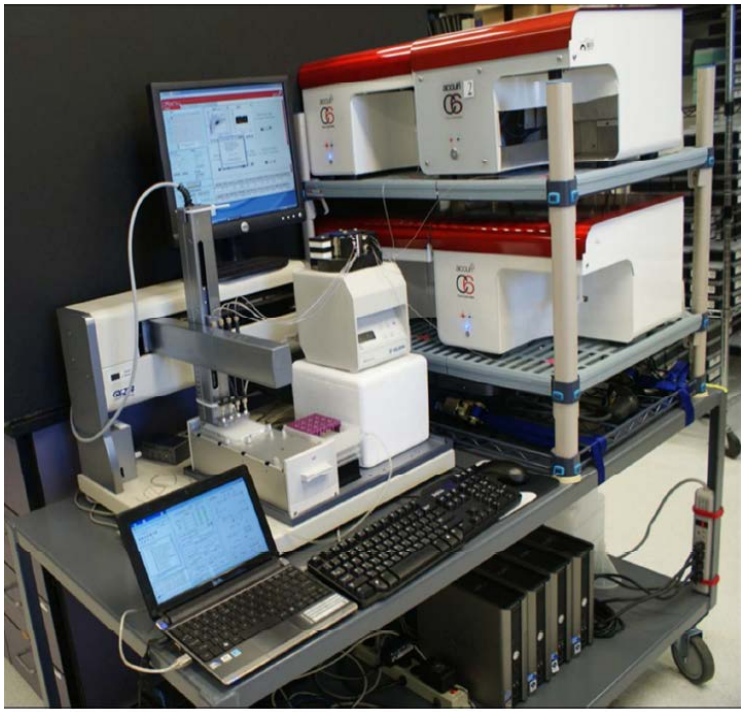
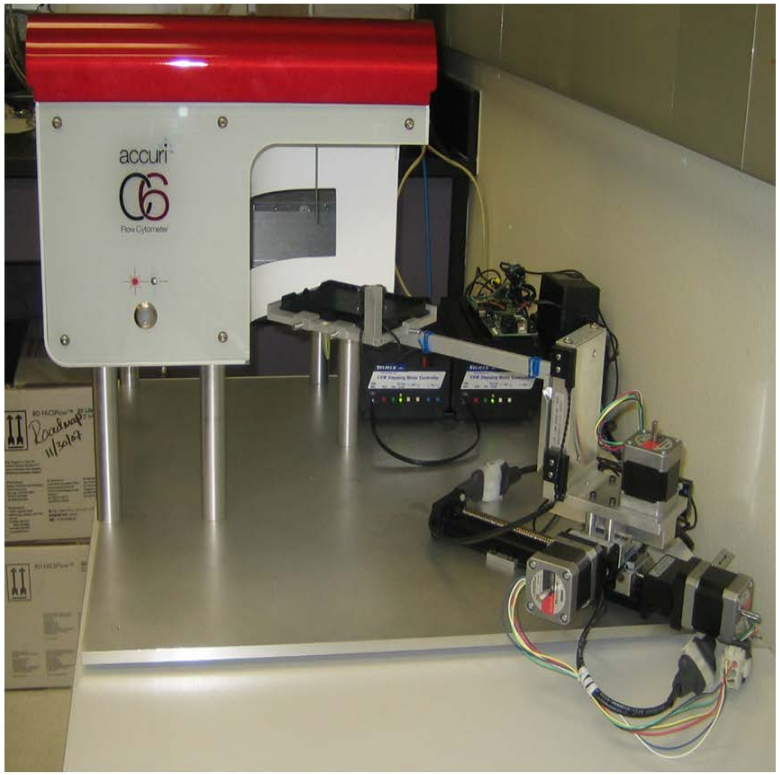
UNM CANCER RESEARCH & TREATMENT CENTER
A NATIONAL CANCER INSTITUTE DESIGNATED CANCER CENTER
UNM CYTOMETRY
MolecularLibraries
Pathways to Discovery
intellicyt
accelerating discovery
Los Alamos
NATIONAL LABORATORY
EST. 1943
NFCR
National Flow Cytometry Resource

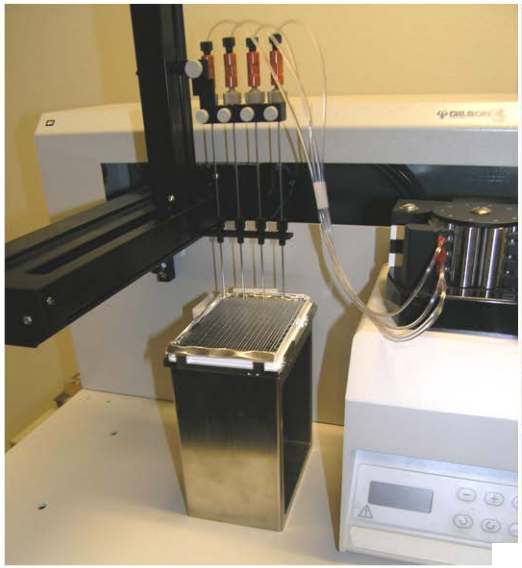
NEXT GEN HTS
Edwards

1536



DIRECT FEED





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A National Cancer Institute Designated Cancer Center

UNM CYTOMETRY

MolecularLibraries
Pathways to Discovery

intellicyt
accelerating discovery

Los Alamos
NATIONAL LABORATORY
EST.1943

NFCR
National Flow Cytometry Resource

Repurposing Input

- **Experimental**
  - **Integrin, Transporters, GPCR, GTPase, GRK2**
- **Modeling and Docking**
  - **Metnase**
- **Chem Informatics**
  - **Cyclobenzaprine: similarity between mono-amine transporter and serotonin receptor ligands**
- **Off label indications from clinicians**
- **Hybrid, experiments followed by computation**
  - **GTPase**

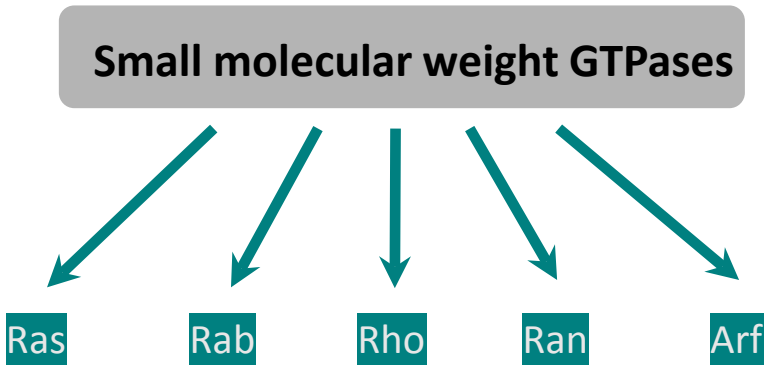
Informatics Workflow

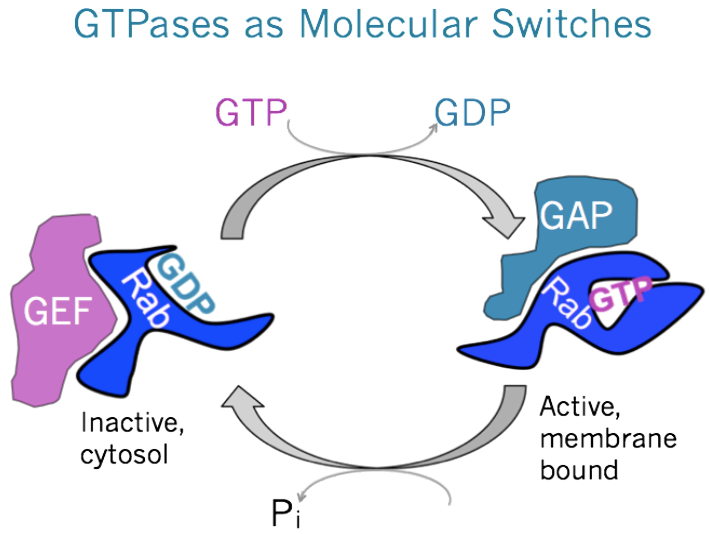
- **DRUGSDB: Annotating Medicines**
  - **40,000 drugs mapped onto 1700 active pharmaceutical ingredients**
  - **1200 APIs account for 13000 numerical bioactivities alone; proceed to pathways**
  - **Maps drugs, indications, targets, off-label usage from electronic health records**
  - **Decision Making;**
    - **On label/Off label**
    - **Contraindications**
    - **Public Domain/Prior Art**
    - **Implications for Target/Clinical Outcomes**
- **WOMBAT (Sunset Molecular Product/Oprea)**
  - **Effective concentration via PK data, Serum trough, MRTD, Bioavailability, Volume of Distribution, "Medi Index"**

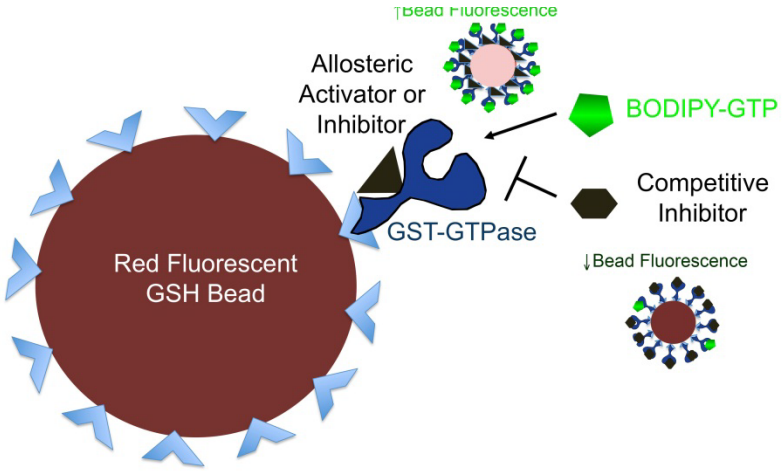
Screening Based on Novel Technology

- HTS Flow Cytometry
  - Suspension targets, no wash binding, multiplex
- Multiplex targets:
  - GTPase, Bcl family regulators, etc.
- Integrin LIBS:
  - thioridazine is allosteric integrin regulator
- Transporters: chemoresistance in cancer and infectious disease
- Tagged GPCR:
  - anisomycin downregulates B2AR

HTS for Small Molecule GTPase Activators & Inhibitors: Wandinger-Ness, UNMCMD, KUSCCC

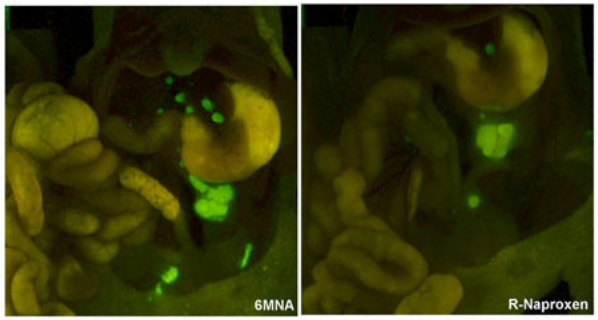


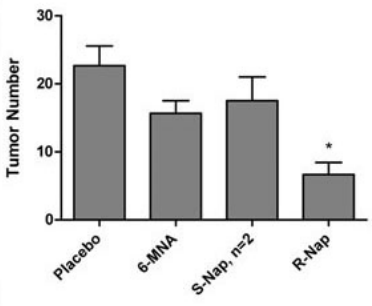




Outcome: Pan-activator probes, Rho family inhibitor, Cdc42 inhibitor probe, Pan-inhibitor probe. Ketoralac regulates Rab7/EGFR in ovarian cancer

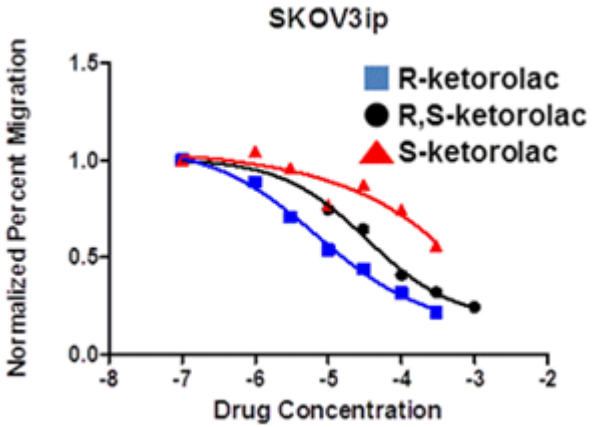
Ketorolac as GTPase Inhibitor



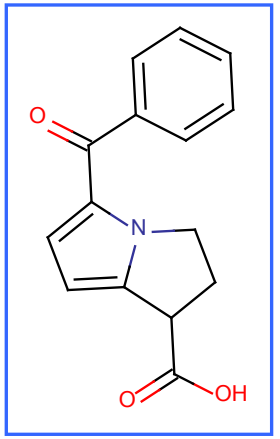


R-Naproxen reduces tumor number in xenograft model. Athymic nude mice after oral doses (10mg/kg) of each compound. Tumor: GFP-tagged SKOV3ip cells (h. ovarian). *Work by Angela Wandinger Ness and colleagues*

Based on R-Naproxen (early hit), nabumetone and ketorolac were evaluated. The lack of activity by >20 other NSAIDs against GTPase targets strongly suggests enantiomer-selective targeting of Rac1 and Cdc42 by R-naproxen and R-ketorolac.



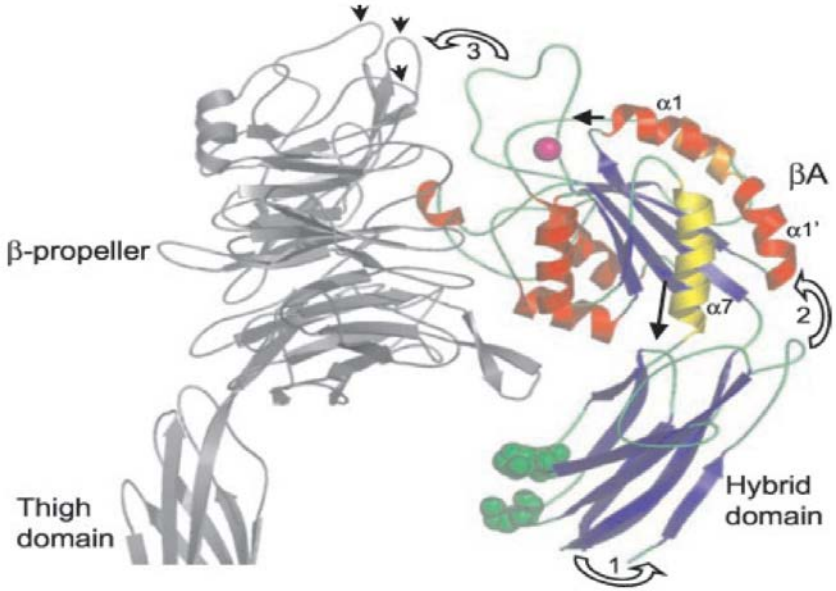
Once the "α-methyl-carboxylate" moiety was identified as critical, a number of NSAIDs and other α-Me-COOH drugs were evaluated. Ketorolac was rapidly identified as matching both the moiety and indication requirements.

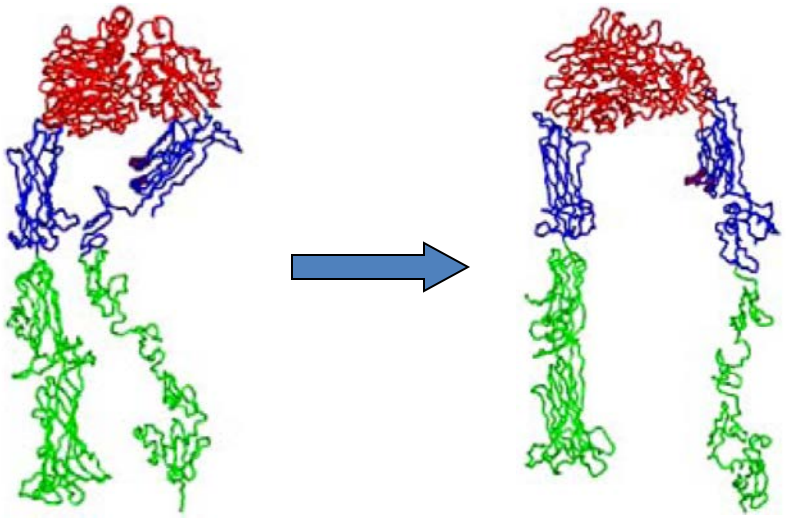


Ketorolac (Toradol™, Acular™) is approved as racemate.

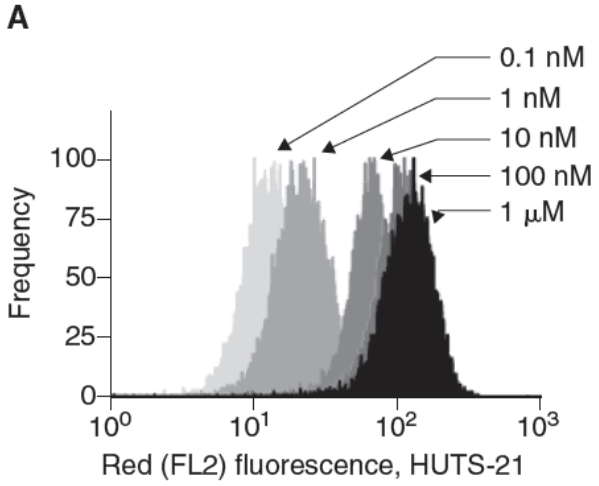
Currently, ketorolac is under clinical evaluation (concept testing) at the UNM Cancer Center as adjuvant therapy in ovarian cancer (PI: Carolyn Muller, MD).

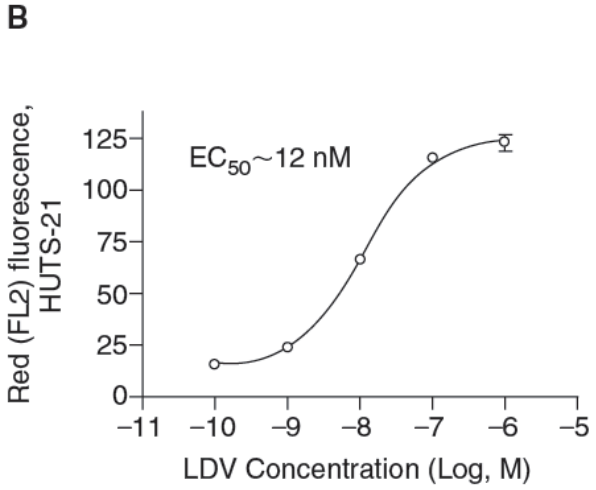
Detection of Ligand Induced Binding Sites (LIBS) for Allosteric Regulators (Chigaev, Sklar, Wu)





LIBS antibody epitopes exposed by conformational change on ligand binding





Thioridazine regulates VLA-4 LIBS. Starting trial for stem cell mobilization; potential for environmental mediated drug resistance.
Chiagev, Sklar JBC 2011

UNM CYTOMETRY

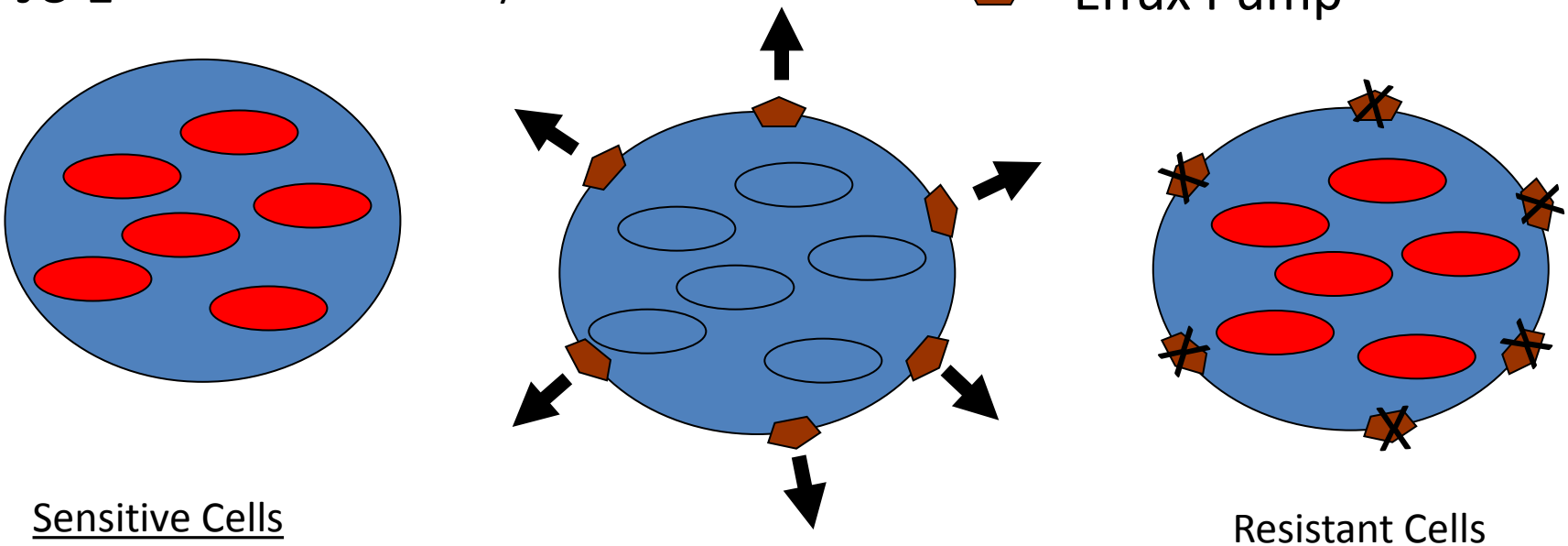
Drug Resistance Efflux Pumps

Larson, Winter, Ivnitski, Edwards, Young, Strouse, Perez, et al

Protect cancer cells from therapeutic drugs by pumping the drugs out of the cells before damage can be incurred

JC-1 Mitochondrial dye

Effux Pump



Sensitive Cells
No efflux pumps
Red fluorescent

Resistant Cells
Pump JC-1 out

Resistant Cells
+ Pump Inhibitor

Mometasone furoate for allergic rhinitis, regulates pumps; off-target/side effect liabilities.

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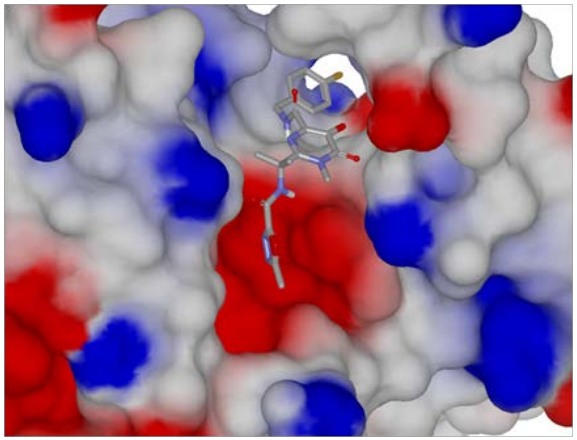
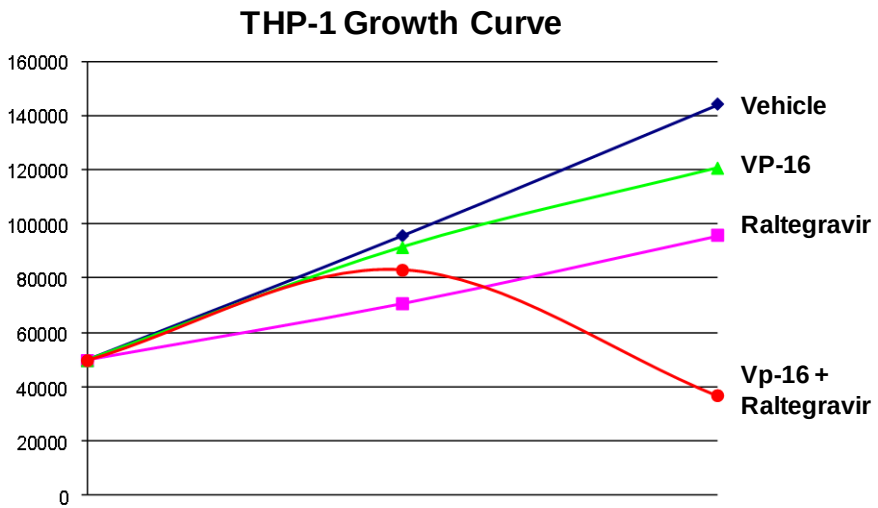
Metnase as Drug Target for Raltegravir



Raltegravir docked into Metnase



Rob Hromas and colleagues isolated and characterized metnase, a DNA repair enzyme with a transposase domain
Williamson et al Cancer Research 2012

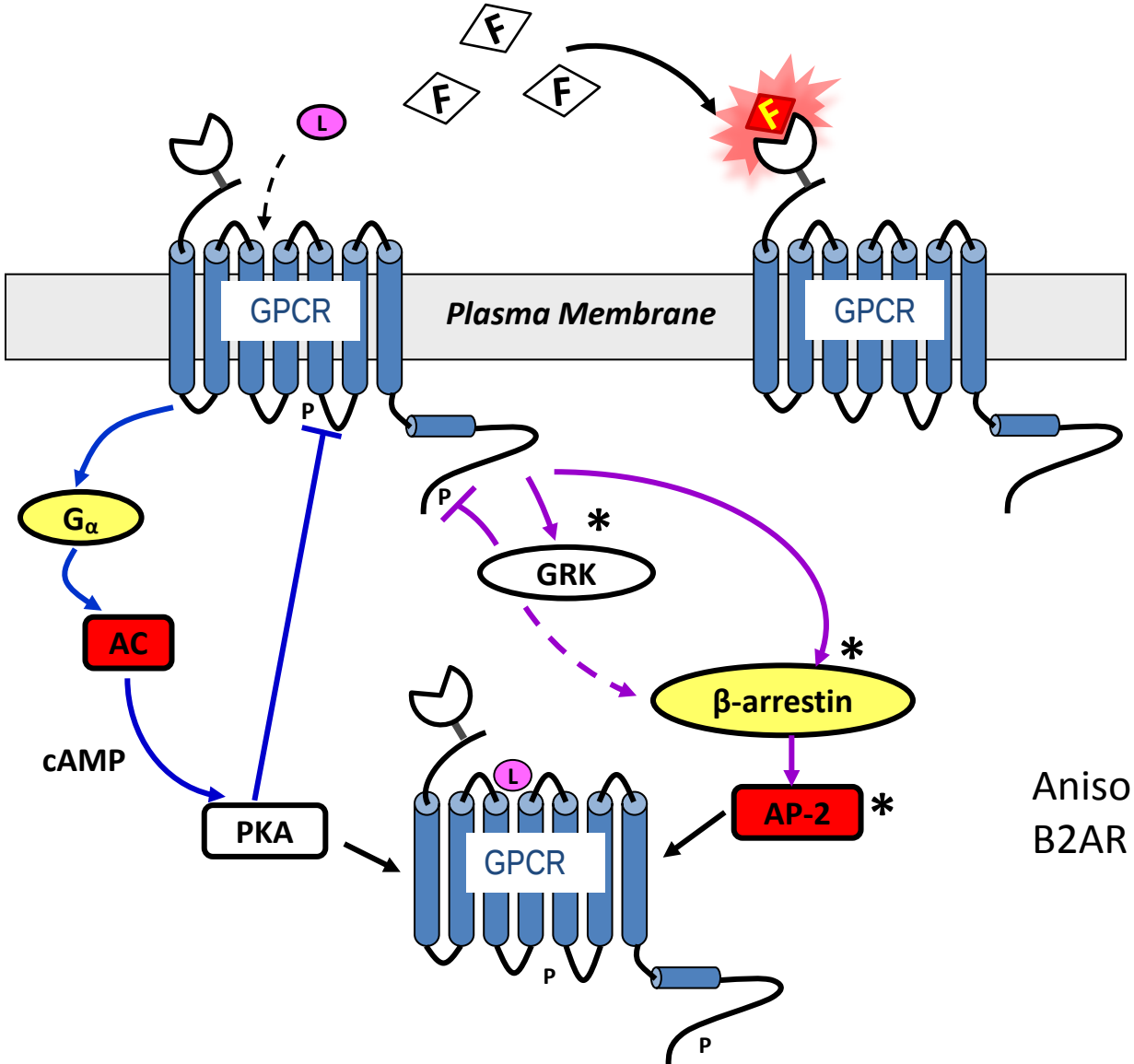
Virtual screening using the 3D structure model for Metnase suggested that the FDA-approved HIV integrase inhibitor Raltegravir (Isentress™) can bind into its nuclease active site. Raltegravir blocks Metnase's flap endonuclease activity. Adding raltegravir to VP-16 restores chemosensitivity in leukemia cells. We also have some medchem leads in the area…

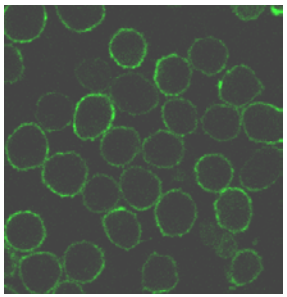
Raltegravir is under evaluation for head & neck squamous cell carcinoma at UNM CC

GPCR Signaling & FAP-Detection

Wu, Tapia, Fisher, Bruchez, Waggoner, Jarvik (Mol Pharm, 2012)

mbic
Molecular Biosensor and Imaging Center





Anisomycin regulates
B2AR Internatilzation

Two Models of Precision Leukemia Medicine

Prognostic (Nodality)

- Patient diagnosis
- Small collection of drugs (6-10) representing therapeutic options
- Drug sensitivity markers in patient sample (few samples)
  - "Deep" pathway analysis or phenotypic responses
- Drugs recommendations are prioritized based on pathway responses

Compassionate Use (FIMM)

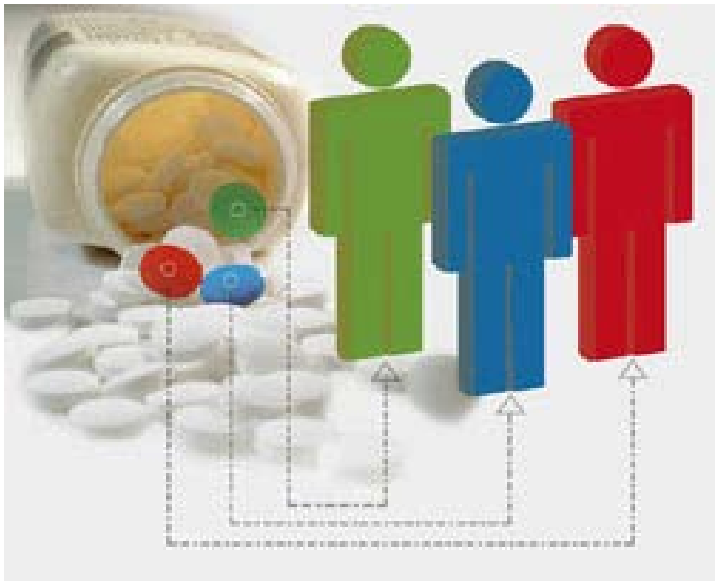
- Patients fails chemotherapy (refractory or relapsed)
- Molecular profiling and clinical information
- Collection of drug represents oncology drugs (approved >100, trials >200); expanded by safe or approved drugs
- Phenotypic drug sensitivity (e.g., viability, many samples)
- Systematic testing of drug combinations guided by sensitivity, pathway analysis, profiling
- Compassionate use guided by all available information

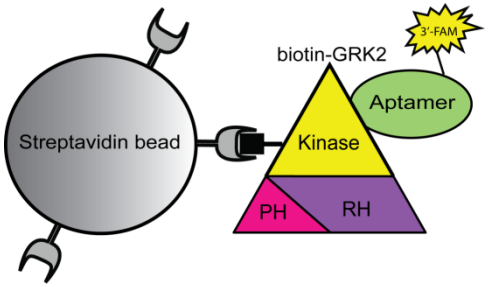
Lessons Learned

- Typical to find activities in repurposing screens
- Mechanism of action of off-target effects suggests new indications
- Academics bring new screens for old targets
- Often pair screens for NCE and repurposing depending on resources
- Align resources for followup, pre-clinical work, formulation, clinician engagement early

Summary Highlights

- **GTPases (ML97-99, ML142, ML231 and Repurposed NSAIDs)**
  - **FDA approved NSAIDs in ovarian cancer models**
- **Multidrug Resistance/Cancer Chemoresistance (Larson) (ML 230 and Repurposed)**
  - **Reverse chemoresistance in blood cancers, solid tumors**
- **Cell adhesion regulators (Chigaev/Sklar) (Repurposed)**
  - **IND Phenothiazines releases cells from bone marrow**
- **Non-canonical GRK2 inhibitor Paxil strengthens myocardial contractions (Tesmer, ACS Chem Biol 2012)**
- **Opportunities for non-canonical GPCR regulators**
- **Personalized medicine in blood cancers**





http://www.policymed.com/2010/12/tufts-study-shows-drug-development-for-personalize-medicine-on-the-rise.html