Rationale: Drugs targeting the androgen receptor (AR) signaling pathway are foundational therapies for the treatment of metastatic prostate cancer. Insights into mechanisms of acquired resistance to AR pathway therapy point to multiple different combination therapy regimens that could prevent resistance in molecularly defined subgroups of patients.

**Aim 1:** Conduct preclinical combination studies based on mechanistic insights from resistance to AR pathway therapy.

**Aim 2:** Evaluate these combinations across a range of organoid and PDX models with clinical grade inhibitors

**Aim 3:** Identify biomarkers of patient response in our preclinical models, with input from clinical datasets
Time

Disease Burden

Castration

Castration-Sensitive Castration-Resistant

2nd Generation Antiandrogen

Enzalutamide (Enz)

1. AR mutation/amp
2. AR bypass (GR, etc)
3. Lineage plasticity

1st generation AR therapy

Enzalutamide (Enz)

Tran et al Science 2009
Scher et al, Lancet 2010
Scher et al, NEJM, 2012
Balbas et al eLife 2013
Arora et al, Cell 2013
A few take homes:

1) no tumor that harbors genetic alterations of AR lose AR activity during progression
2) RB1 loss tumors are highly enriched for TP53 loss and loss of AR gene expression, with aberrant expression of SOX2
3) a subset of AR negative tumors aberrantly express FGF8/FGF9
4) HNF4G and HNF1A, two master regulators of the gastrointestinal lineage, are aberrantly expressed in ~30% of CRPC
Metastatic Prostate Cancer

ADT/ARA = response

Mechanism 1

Resistance via AR: AR Program Active
- AR-AMP
- PTEN-/

Resistance via GR: AR Program Active
- AR-OFF
- AR Program ON

Resistance AR Independent: AR Program Inactive
- TP53-/
- RB1-/

KEY
- T = Testosterone
- DHT = Dihydrotestosterone
- ADT = androgen deprivation therapy
- ARA = AR pathway antagonist
- NHR = nuclear hormone receptor
- GR = glucocorticoid receptor
- AR+ = mutated AR
- AR++ = AR splice variant

Drug Resistance and Sensitivity Center

Context Dependent Combination Therapy

Project 1
- AR Resistance Caused by AR Pathway Reactivation

Project 3
- Combination Trials with Kinase Inhibitors to Prolong Response to AR Therapy

Project 2
- Reversing Resistance Caused by Lineage Plasticity Through Epigenetic Therapy

Organoids

Clinical
- omics
- specimens
- trials

Informatics

Drug Resistance and Sensitivity Network
- Resistance to targeted therapeutics
  - NHRs
  - Kinase Pathways
  - Epigenetic Modifiers

PDX

National Cancer Institute
Project 1: Targeting resistance caused by restored AR pathway function by targeting the glucocorticoid receptor (GR) and/or androgen receptor (AR).

Project 2: Targeting resistant CRPC without AR activity caused by lineage plasticity.

Project 3: Kinase inhibitors in PI3K/AKT activation with PTEN loss and in FGFR activation with autocrine FGF8/FGF9 production.

Team members

Charles Sawyers, overall PI
Pete Nelson, co-PI
Yu Chen, HNF4G/HNF1A
Brett Carver, PI3K pathway
Eva Corey, PDX models
Christina Leslie, computational biology
Irina Ostrovnaya, biostats
• **Project 1:** Targeting resistance caused by restored AR pathway function by targeting the glucocorticoid receptor (GR) and/or androgen receptor (AR).

  Aim 1: Evaluation of two pharmacologic strategies to inhibit GR activity in AR+/GR+ CRPC (BETi, direct GR inhibitor)

  Aim 2: Strategies to enhance the activity of Enz in AR+ CRPC (CBP/p300 inhibitor; G9A/EHMT2 inhibitor)

• **Project 2:** Targeting resistant CRPC without AR activity caused by lineage plasticity.

  Aim 1: EZH2 inhibition to restore AR dependence in tumors with TP53/RB1 loss mediated lineage plasticity

  Aim 2: BET inhibition to reverse AR pathway independence though HNF1A/HNF4G mediated expression of GI lineage

  Aim 3. Determine in vivo response profile and identify response biomarkers to EZH2, BET and P300/CBP inhibitors

• **Project 3:** Kinase inhibitors in PI3K/AKT activation with PTEN loss and in FGFR activation with autocrine FGF8/FGF9 production.

  Aim 1. Biomarkers of sensitivity and resistance to ipatasertib (AKT inhibitor) and combined androgen blockade

  Aim 2. Optimizing AR pathway inhibition in intrinsic resistance models of PI3K-AR reciprocal feedback

  Aim 3. Co-targeting the FGF/FGFR pathway to inhibit resistance to AR targeted therapy