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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

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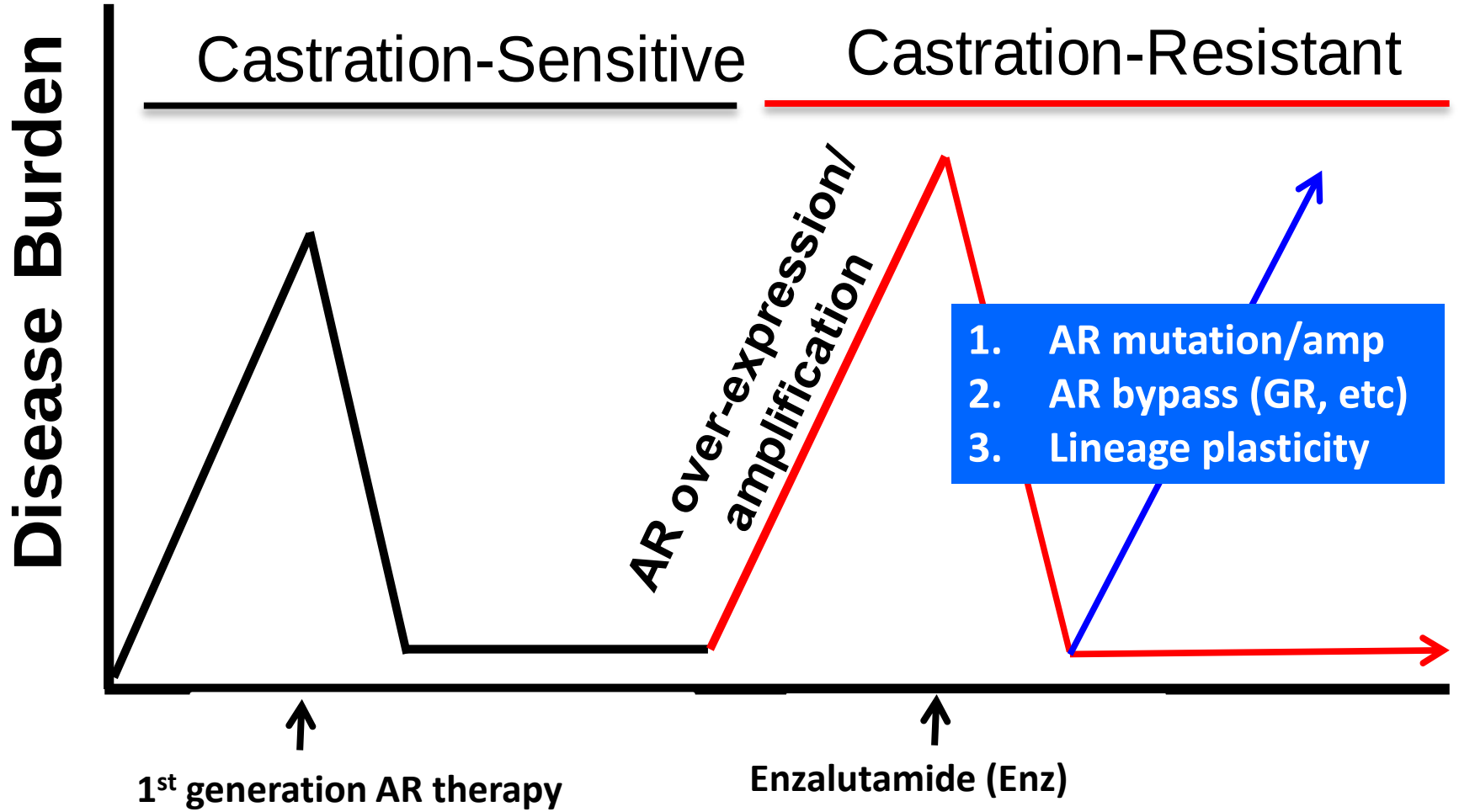

Tran et al Science 2009
Scher et al, Lancet 2010
Scher et al, NEJM, 2012

Balbas et al eLife 2013
Arora et al, Cell 2013

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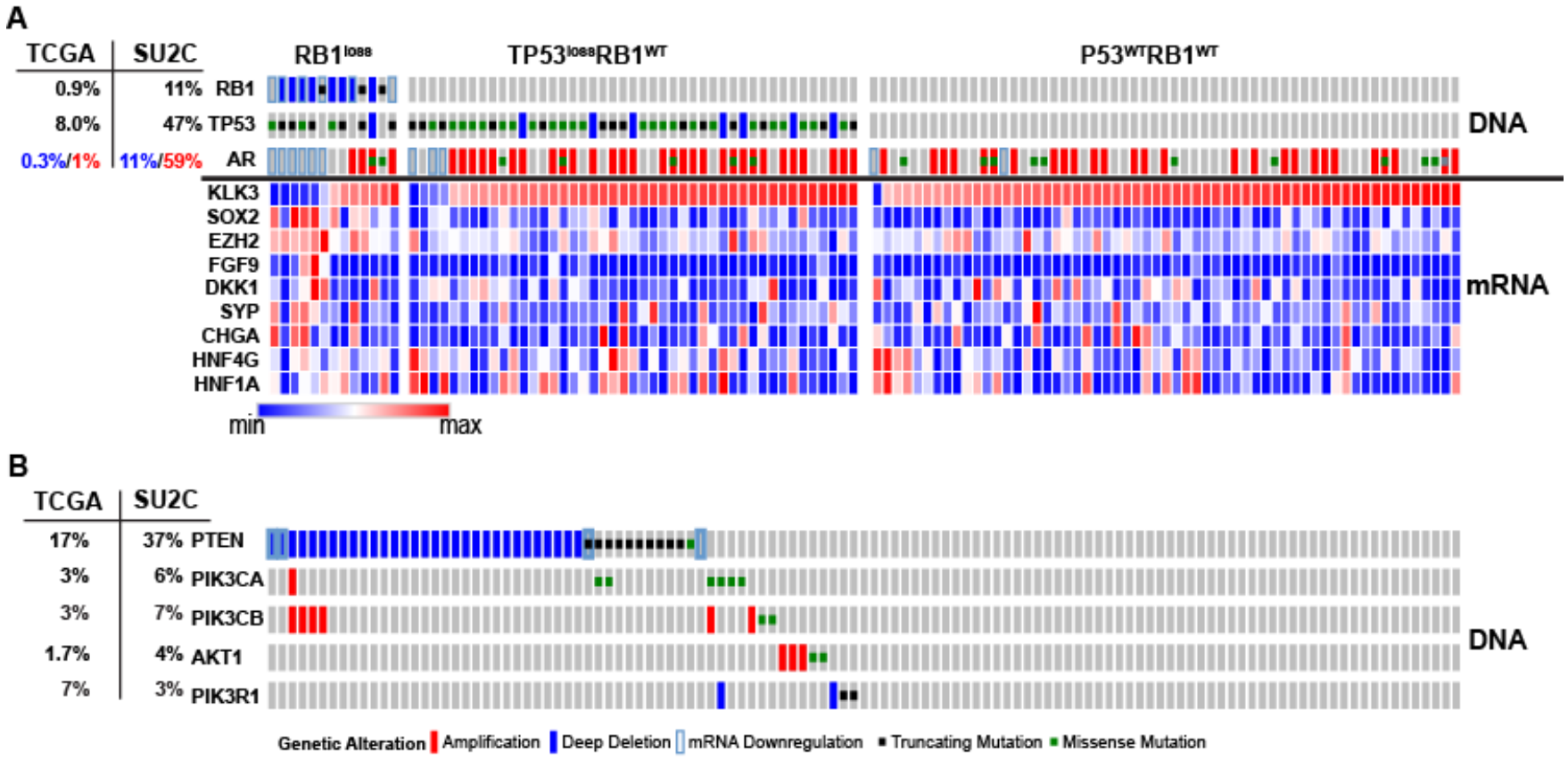
GENOMIC LANDSCAPE OF CRPC



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

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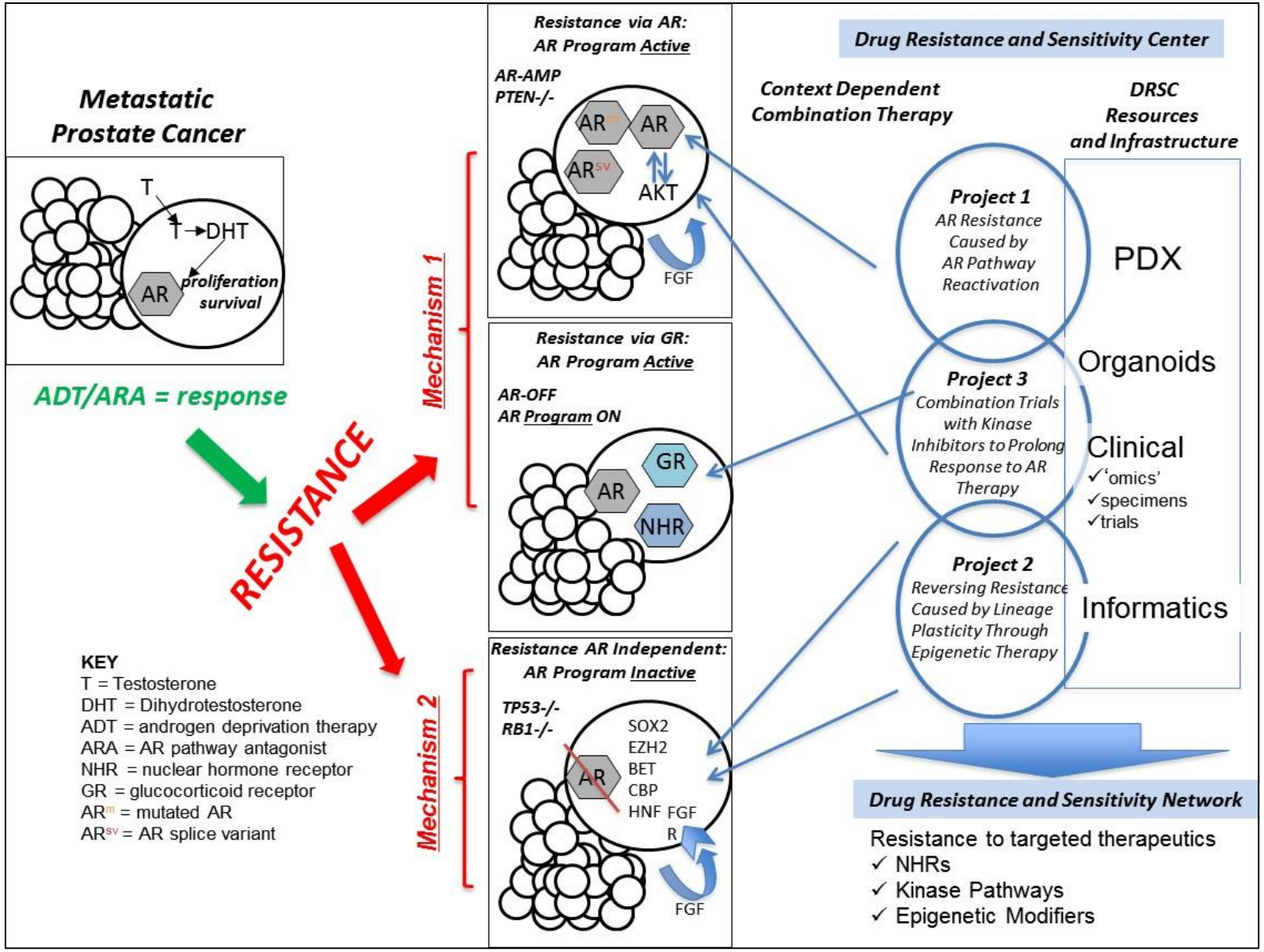

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- **Project 1:** Targeting resistance caused by restored AR pathway function by targeting the glucocorticoid receptor (GR) and/or androgen receptor (AR).
- **Project 2:** Targeting resistant CRPC without AR activity caused by lineage plasticity
- **Project 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

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- **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