Current Topics in Prostate Cancer Research

RPN532 (Tang, Dean G.; Pharmacol & Therap)/04/06/2017

Paper for students:

Ku SY et al., Rb1 and Trp53 cooperate to suppress prostate cancer lineage plasticity, metastasis, and antiandrogen resistance. Science 355: 78-83, 2017.

Points to discuss:

*Why do current treatments (ADT) fail – Cellular heterogeneity?
*Prostate cancer genetics: AR & beyond
*Normal cell lineage: stem cells & their progeny
*Cancer cell plasticity: Genetic, epigenetic, & treatment-induced

Prostate Cancer Treatments

Charles Huggins —1941→ Castration (Lupron [leuprolide acetate]/Casodex [bicalutamide])

2004 —Taxotere (docetaxel)→ Advanced metastatic patients who no longer respond to castration

2010 —Cabazitaxel (Jevtana)→ For tumors that have stopped responding to docetaxel

2010 —Sipuleucel-T (Provenge)→ Vaccine (for advanced/met patients who no longer respond to castr)

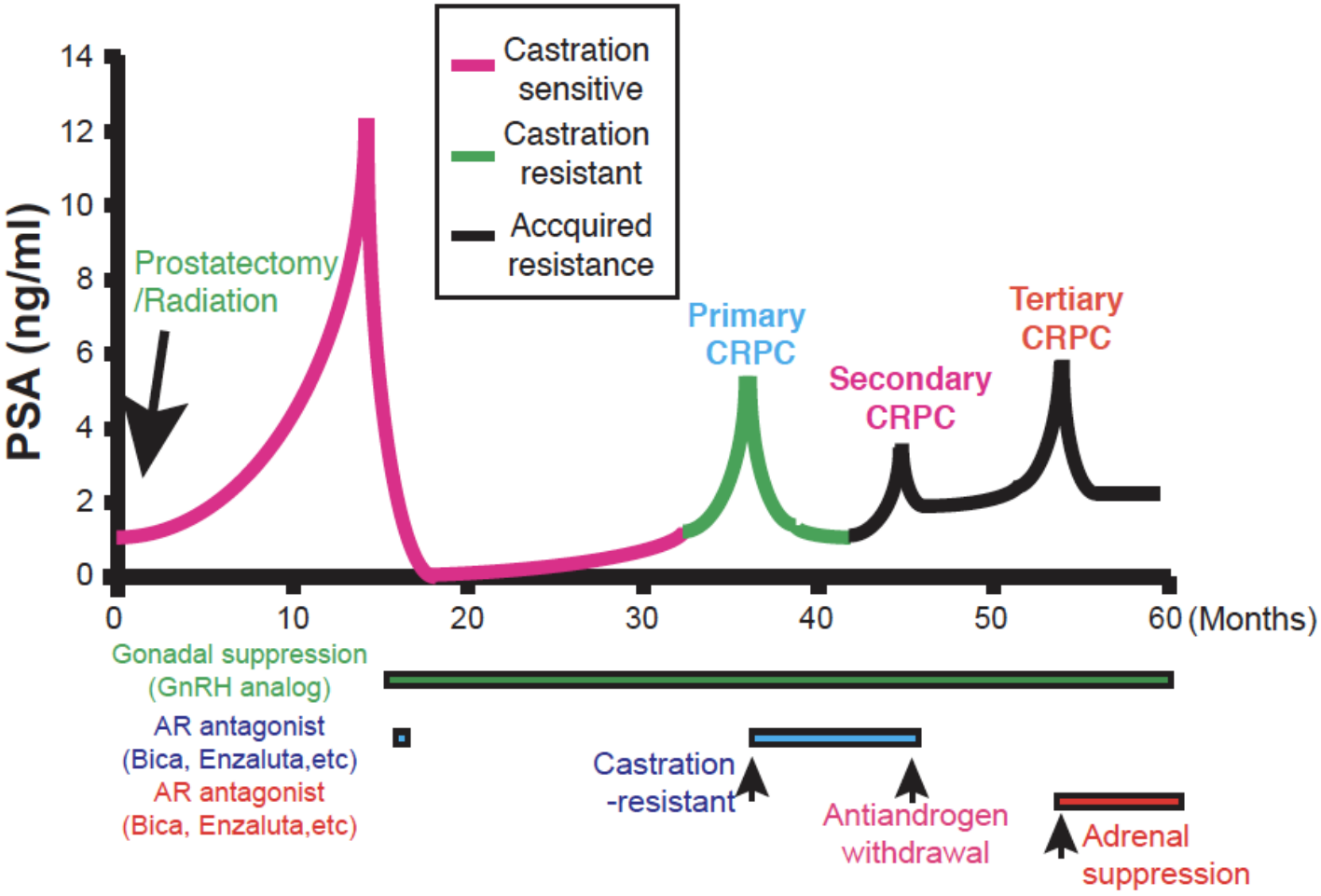
2012 → Zytiga (abiraterone acetate) + Xtandi (enzalutamide)

2013 —Radium 223 (Xofigo)→ Metastases that have spread to the bone

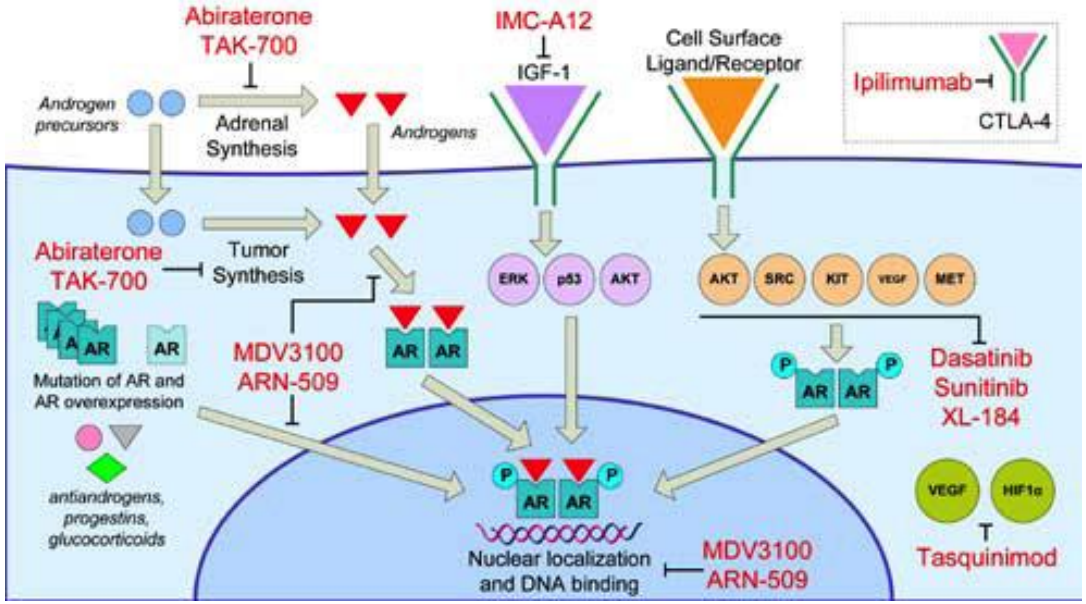
Patient survival:

Docetaxel	3.3 months (vs. mitoxantrone)
Cabazitaxel	2.4 months (vs. mitoxantrone)
Sipuleucel-T	4.1 months (vs. placebo)
Abiraterone	3.9 months (vs. placebo)
Enzalutamide	4.8 months (vs. placebo)
Radium-223	2.8 months (vs. placebo)
Ipilimumab	No (vs. placebo after radiotherapy; toxic – more patients died)
Prostvac	PROSPECT Phase III trial (PSA-targeted IT)/second half of 2017
ARN-509	SPARTAN & ATLAS trials??(2019)

Clinical treatment of PCa patients by chemical castration and anti-AR drugs (anti-androgens)



New anti-PCa drug development



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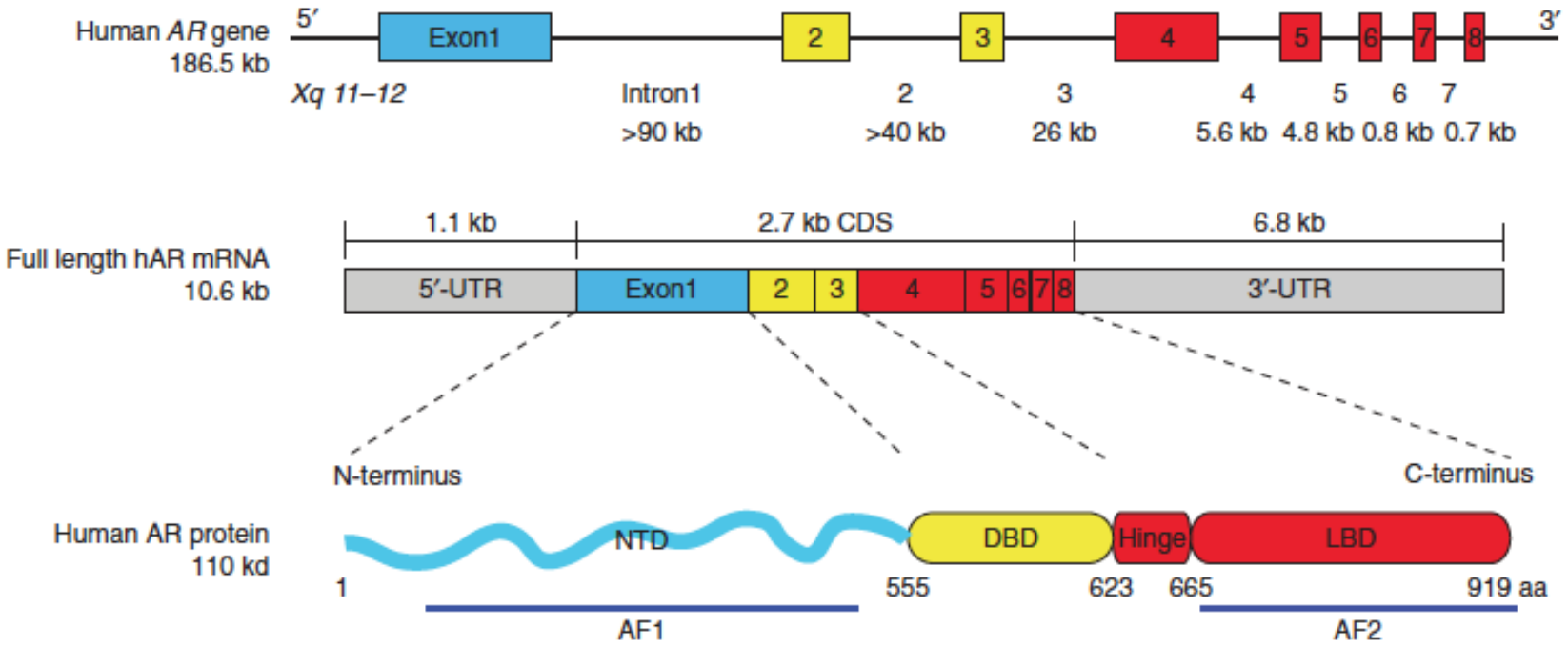
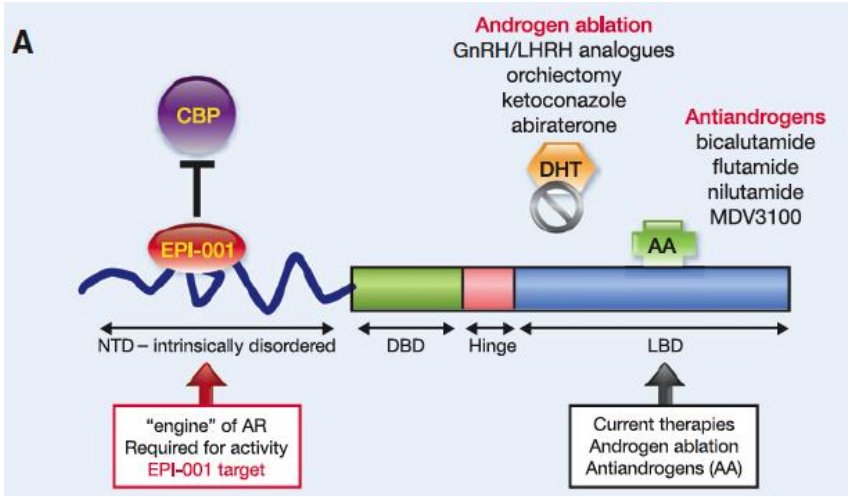
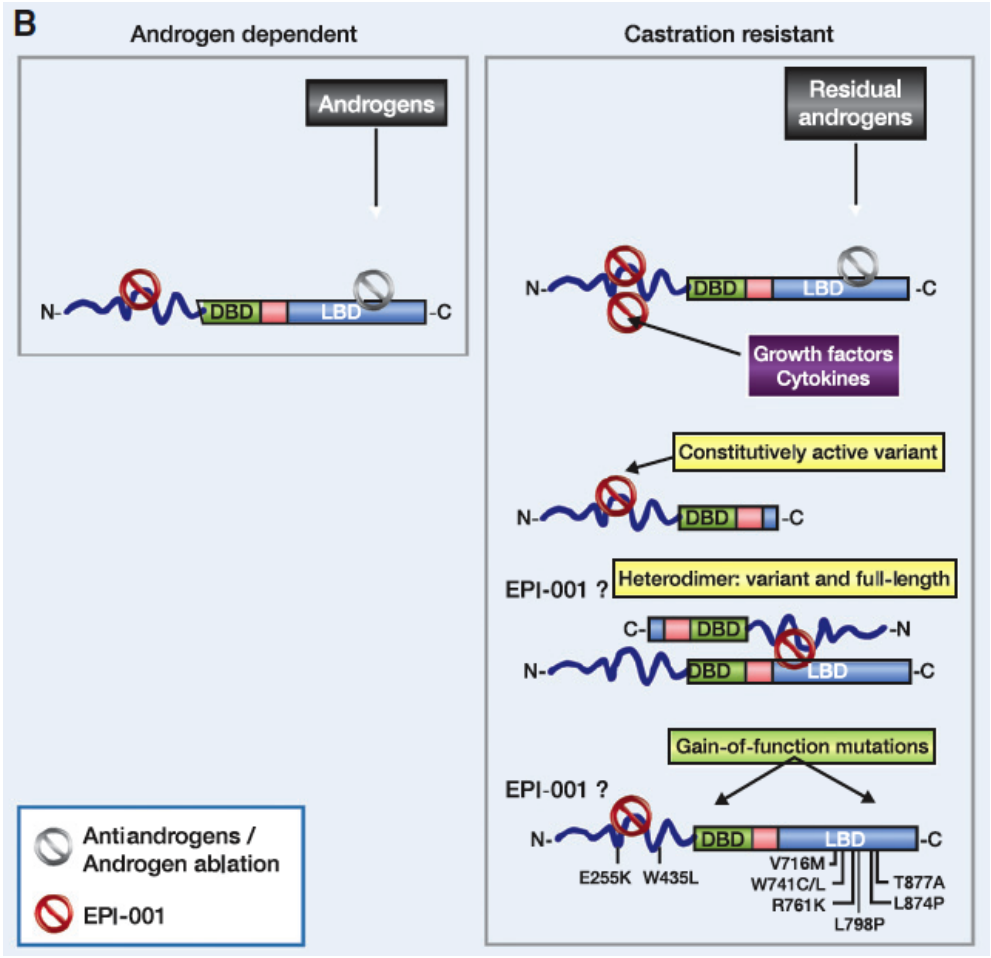
AR gene, mRNA, and protein



Deng & Tang, *Endocr Relat. Cancer*, 2015

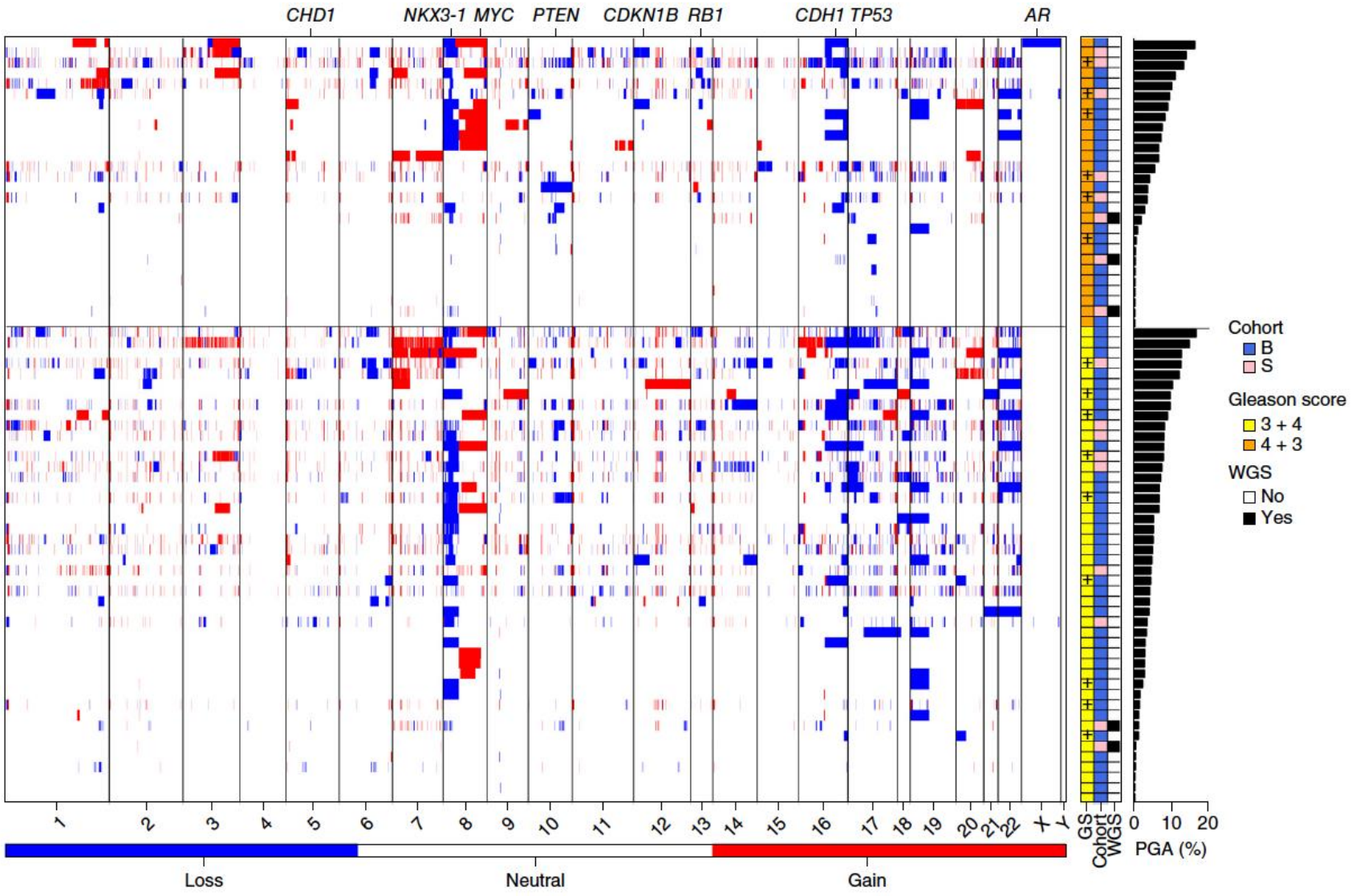
AR and drug targets





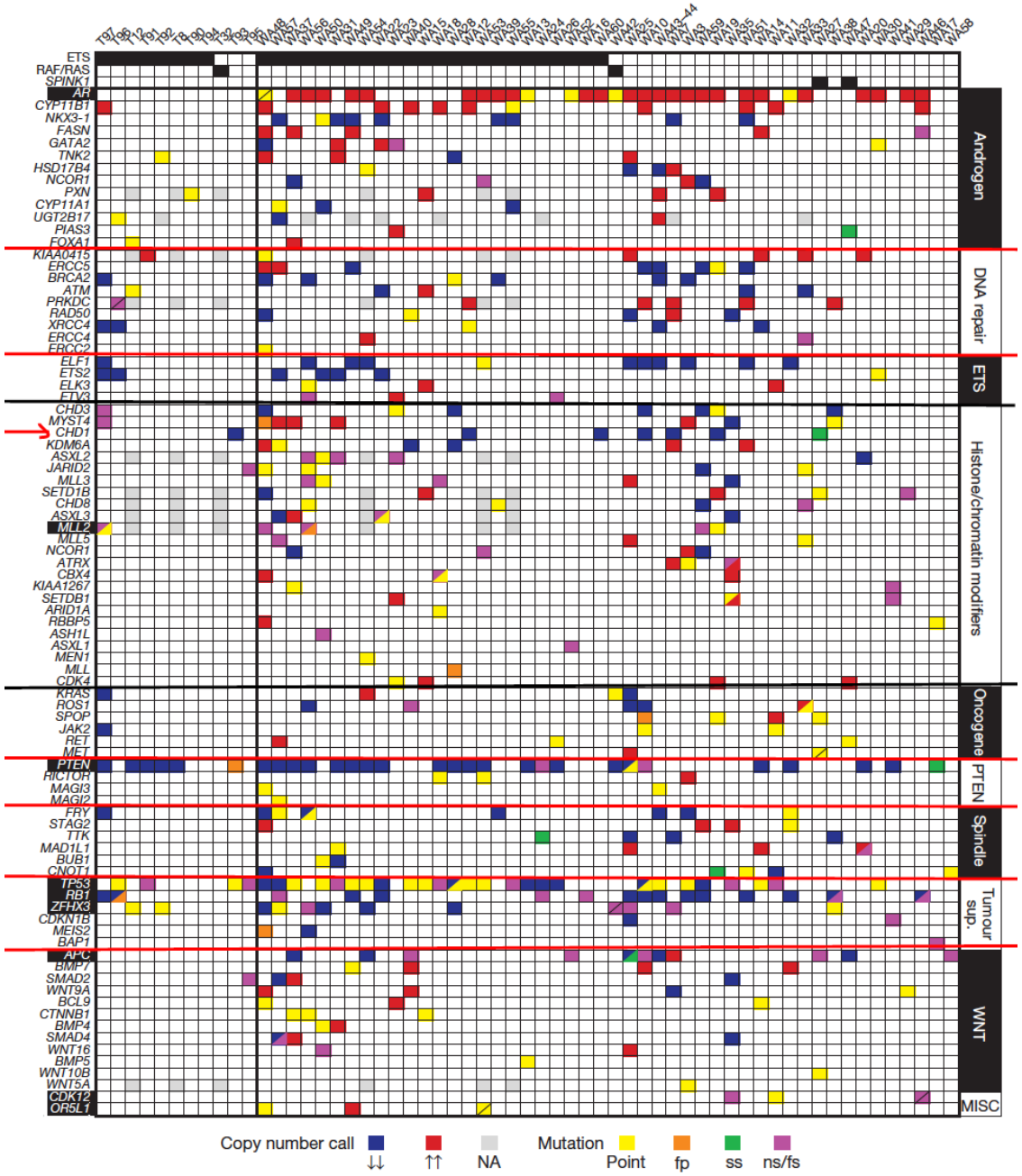
Sadar MD. Cancer Res. 71, 1208 2011

Genomic heterogeneity within localized, multifocal prostate cancer



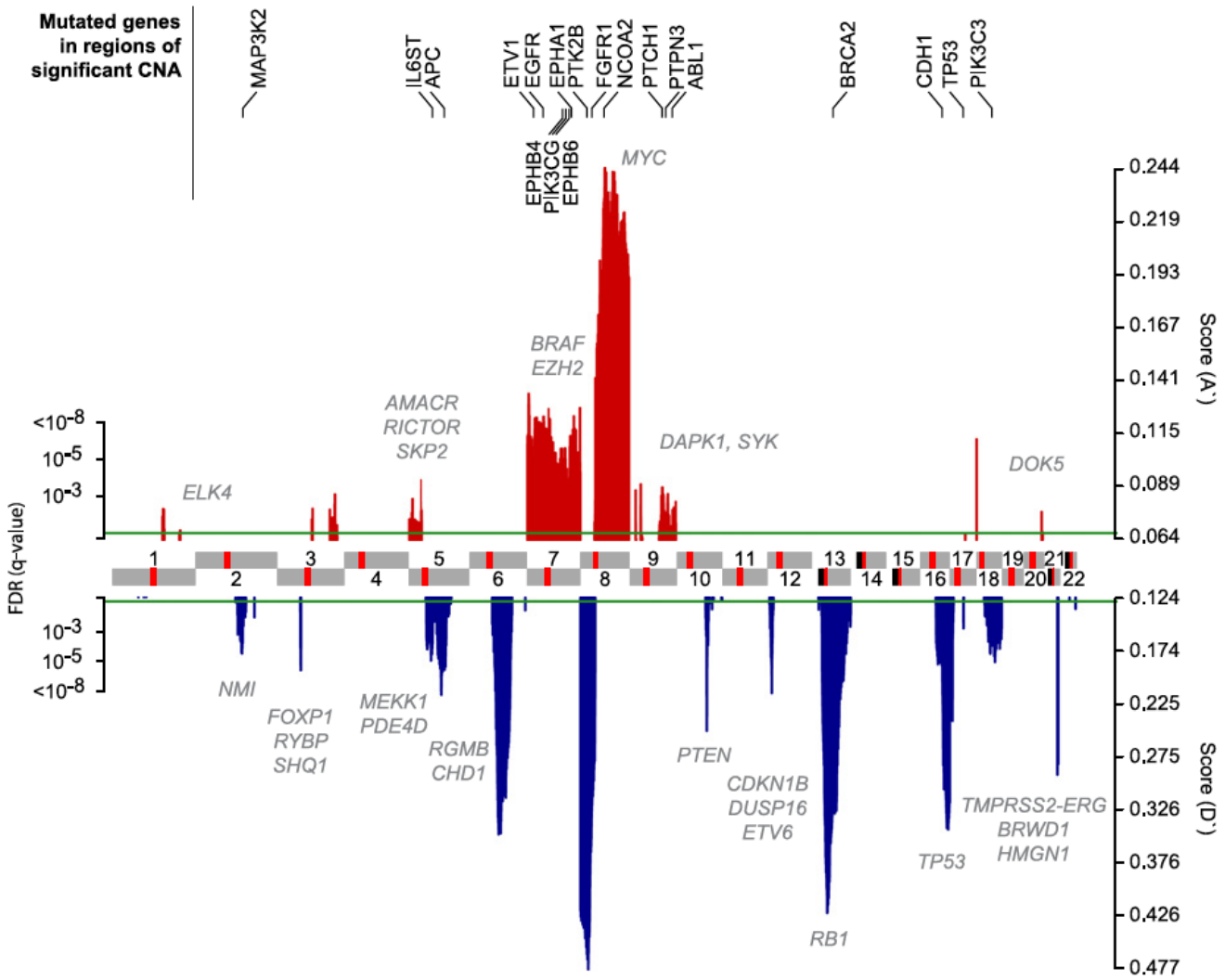
Boutrous PC et al., Nat Genet 2015, May 25

Mutational landscape of lethal metastatic CRPC



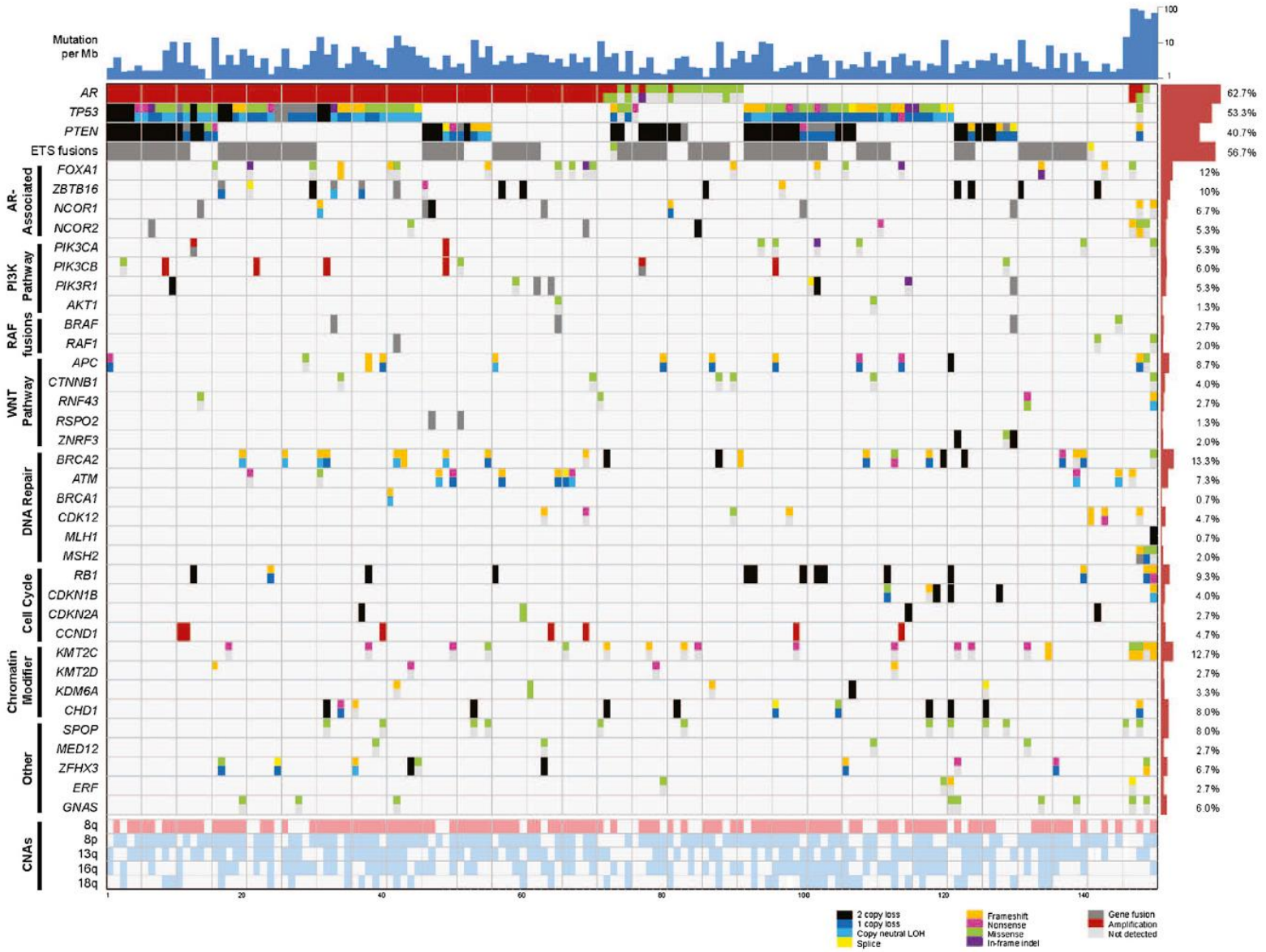
Grasso CS et al.,
Nature 2012

A global view of advanced PCa genome



Taylor et al., Cancer Cell 18, 11-22, 2010.

Integrative Clinical Genomics of mCRPC

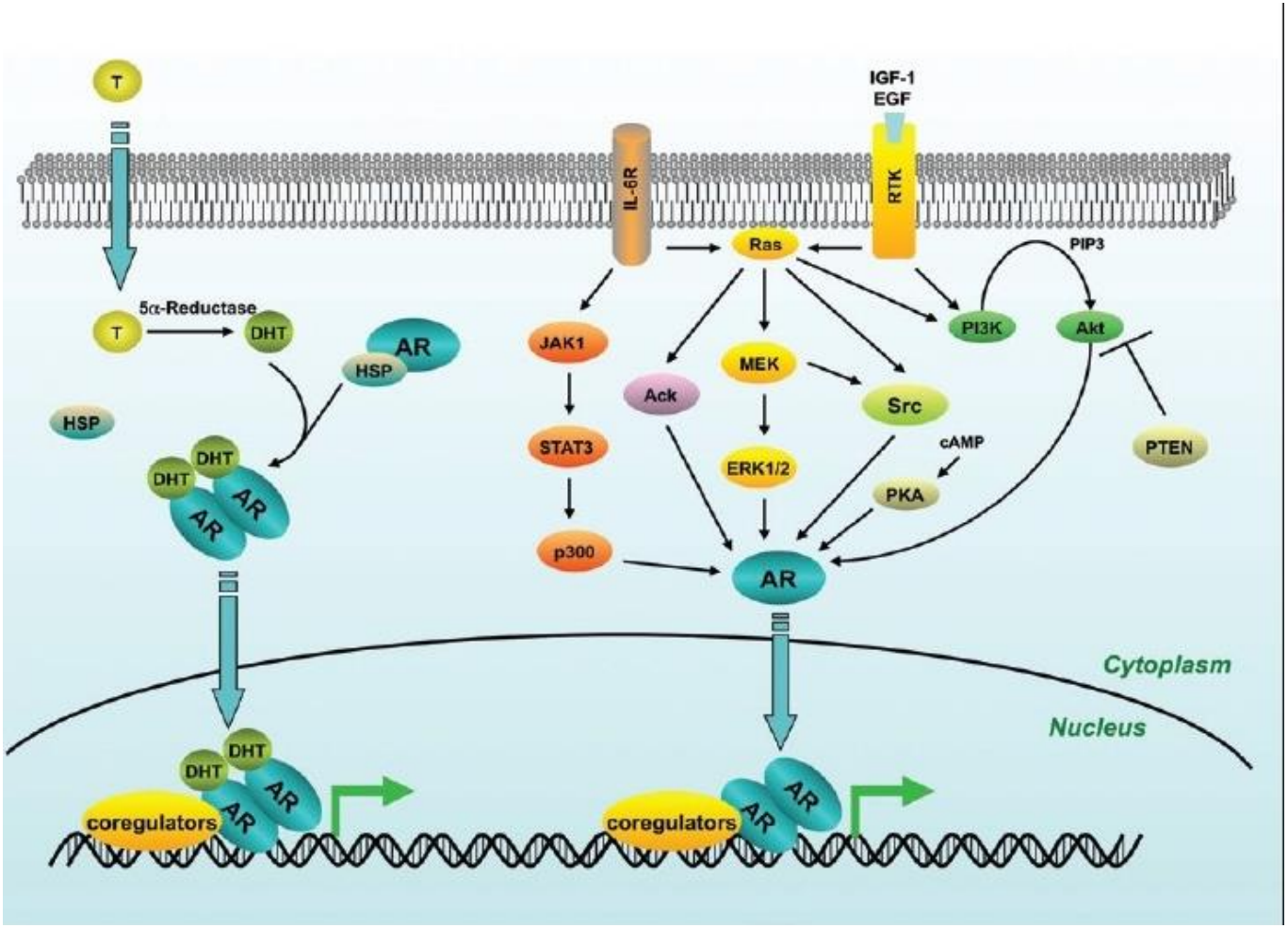


Robinson D et al., Cell, 161, 1215-28, 2015

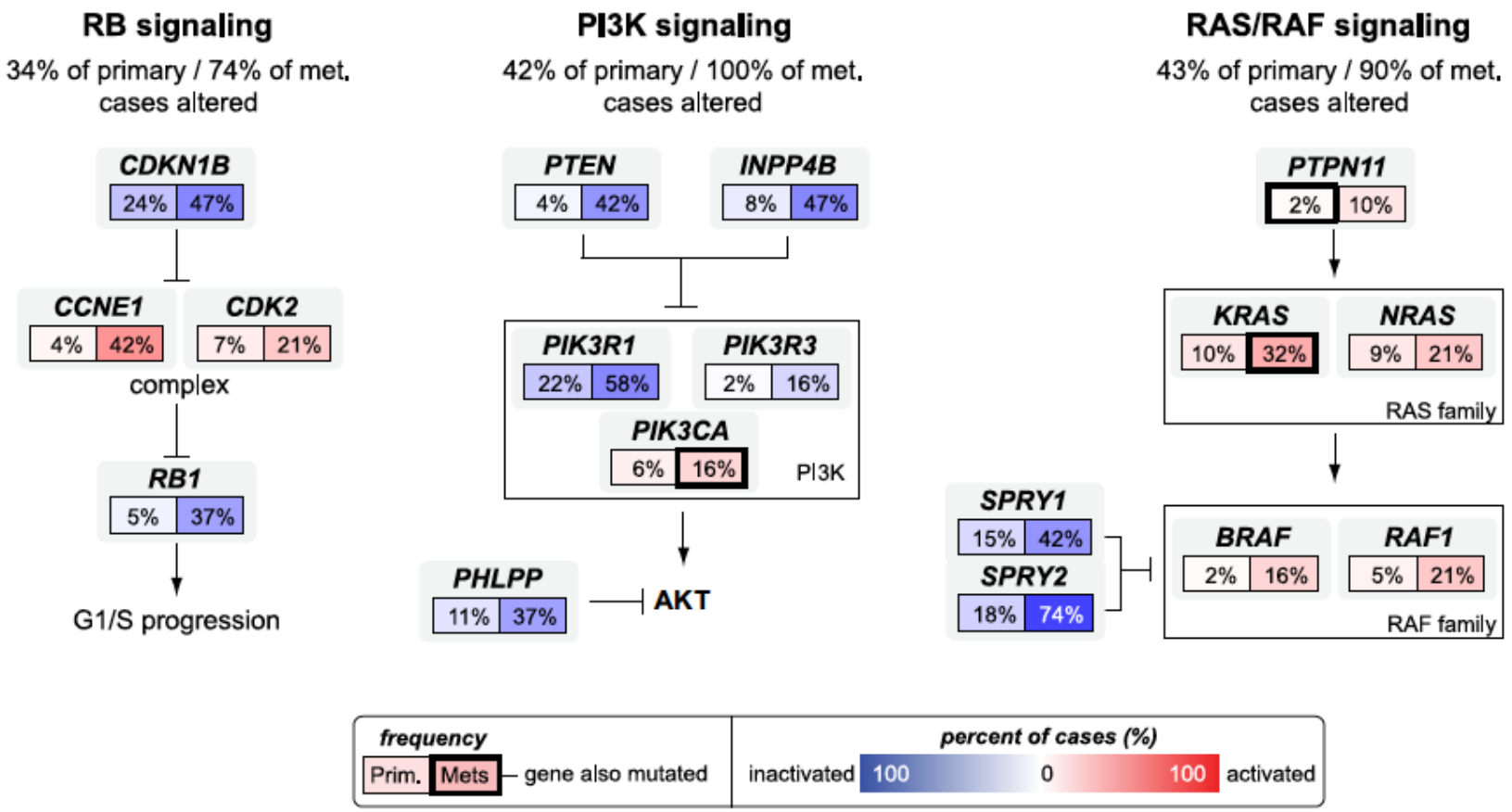
AR splice variants

AR Pre-mRNA 

Variants found in PCa	Domain excluded	Domain-disrupted	Protein MW
AR23 		DBD	106kDa
AR-V14 			85kDa
AR-V13 		LBD	85kDa
AR-V12 	LBD		84kDa
AR^{v567es} 	LBD	LBD	80kDa
AR-V7 	HD to LBD		80kDa
AR-V9 	HD to LBD		80kDa
AR-V5 	HD to LBD		80kDa
AR-V1 	HD to LBD		80kda
AR-V3 	ZF2 to LBD		75kDa
AR$^{Ex1/2b}$ 	ZF1 to LBD		75kDa


T
IGF-1
EGF
IL-6R
RTK
Ras
PIP3
5α-Reductase
T
DHT
AR
HSP
HSP
DHT
DHT
AR
AR
JAK1
Ack
MEK
Src
PI3K
Akt
STAT3
ERK1/2
cAMP
PKA
PTEN
p300
AR
Cytoplasm
Nucleus
DHT
DHT
AR
AR
coregulators
coregulators
AR
AR

A global view of advanced PCa genome



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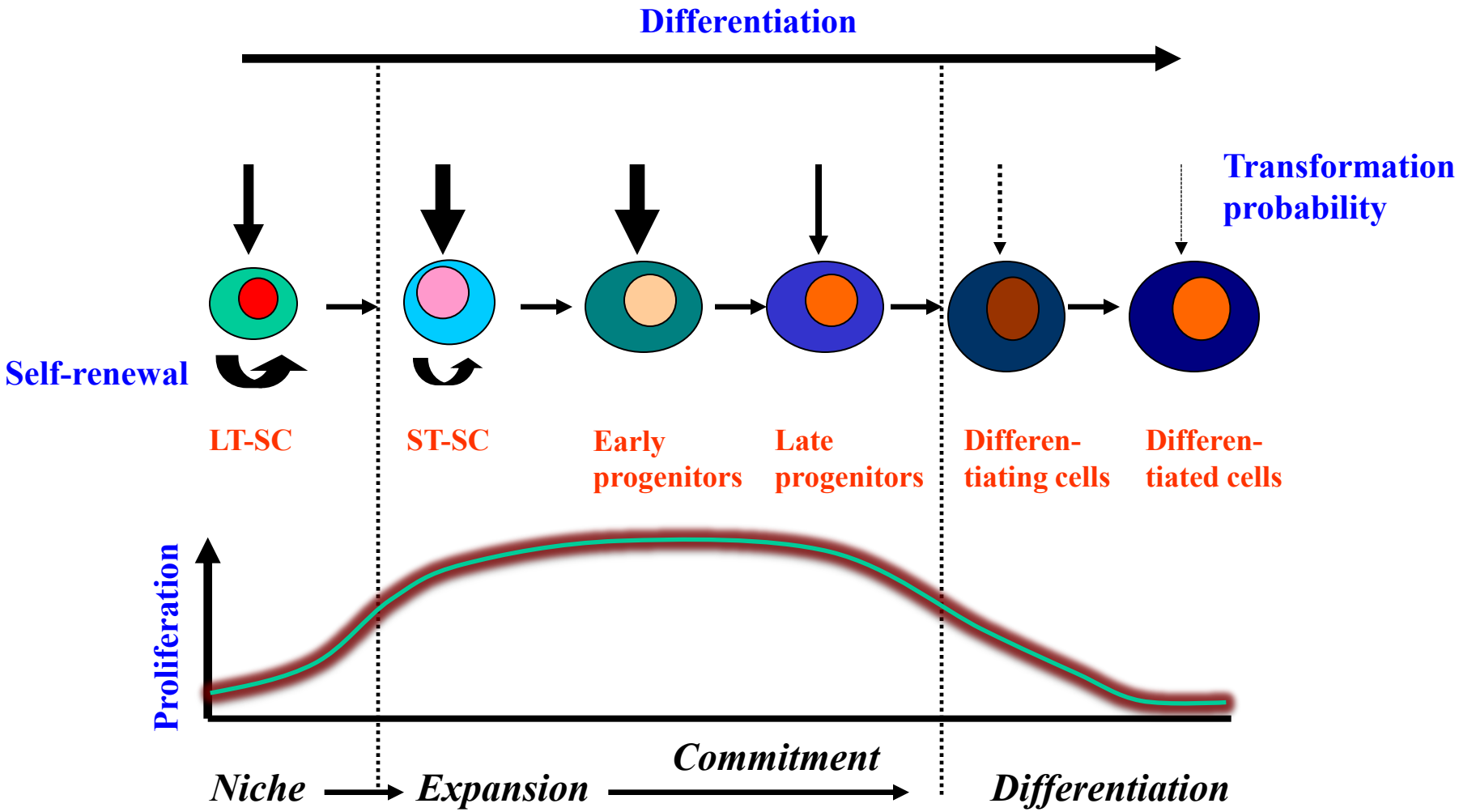
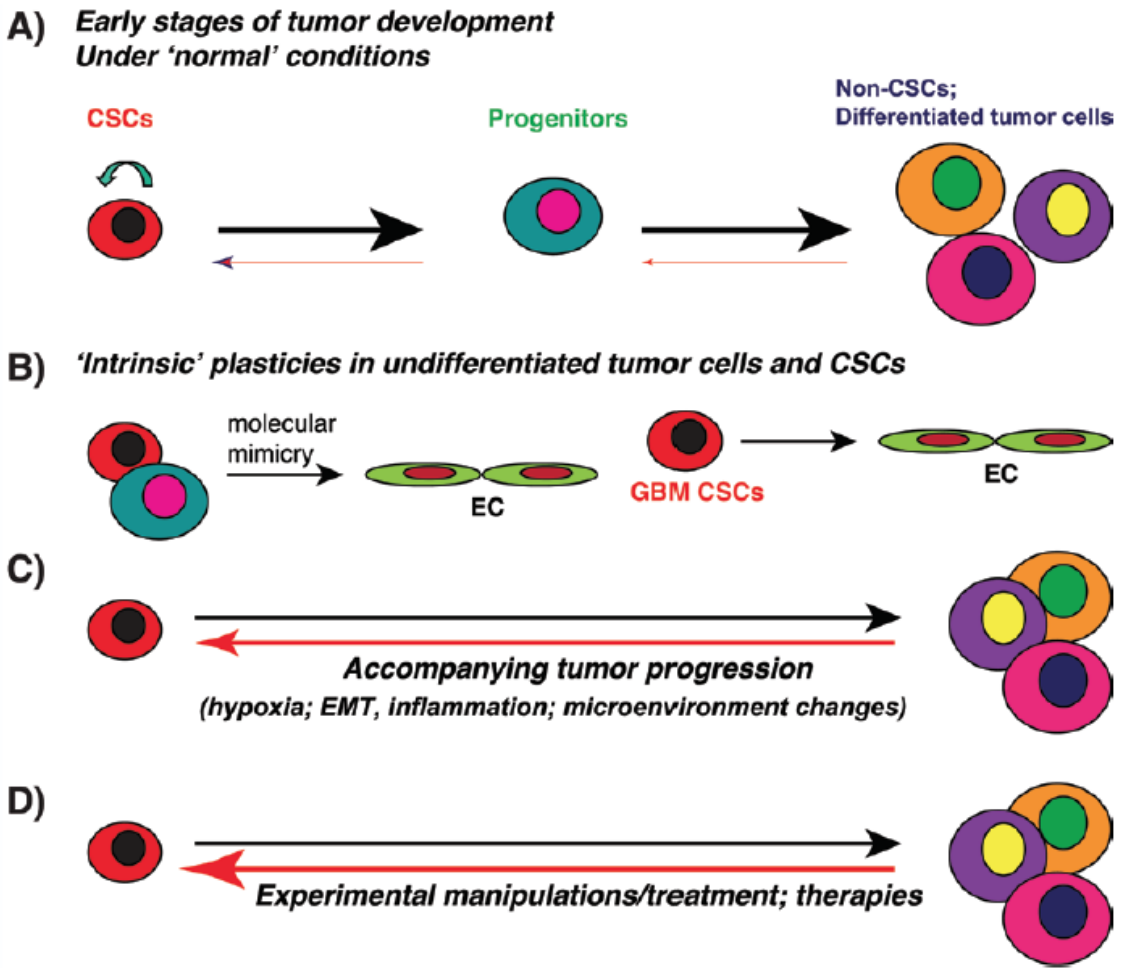
Cell lineage development: Self-renewal, proliferation, & differentiation



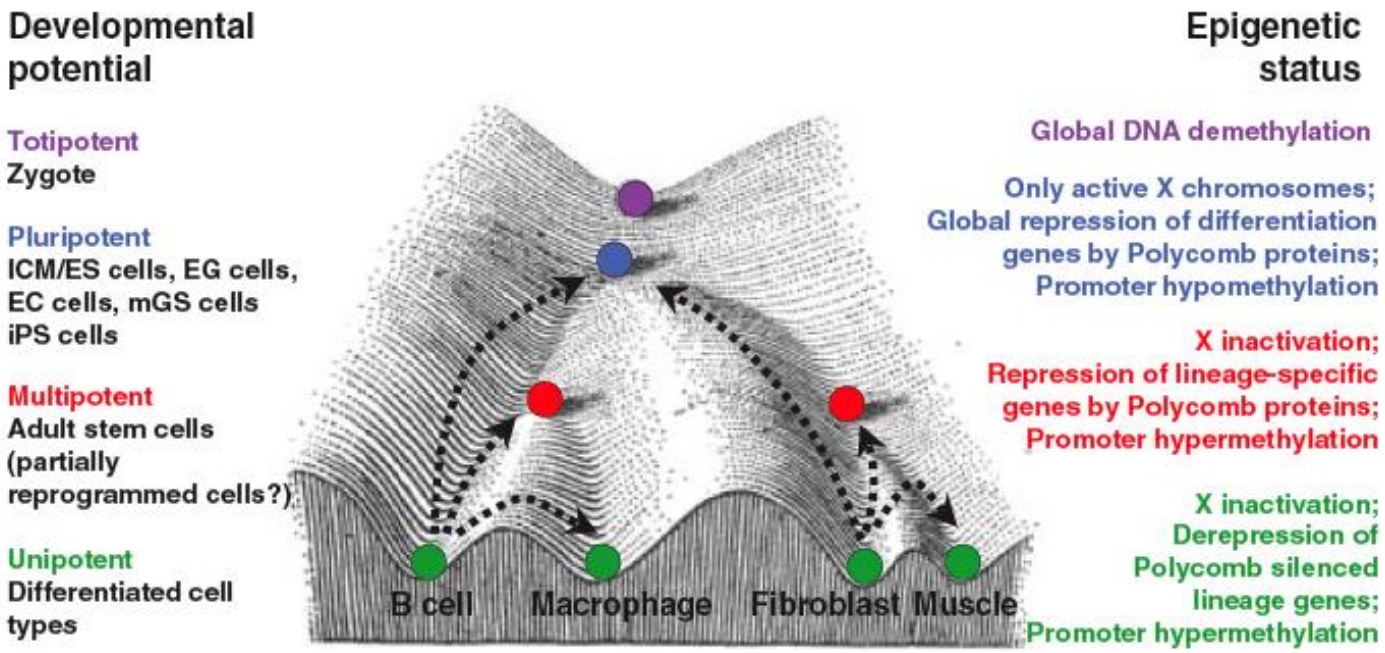
Tang, *Cell Res*. 2012

Phenotypic and developmental plasticity in CSCs and their progeny



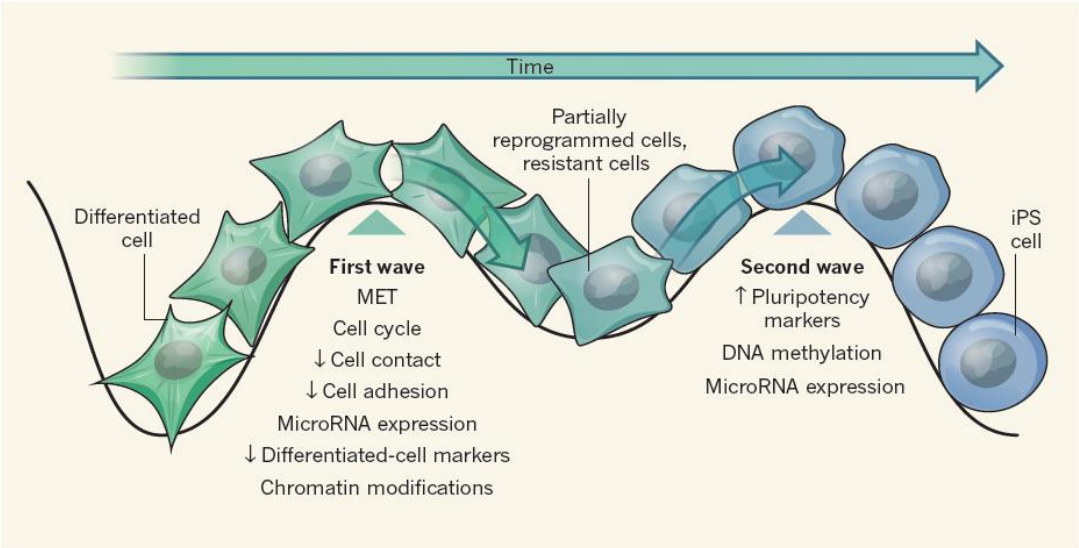
Tang, *Cell Res*. 2012

Hochedlinger 2009, Development 136, 509-523

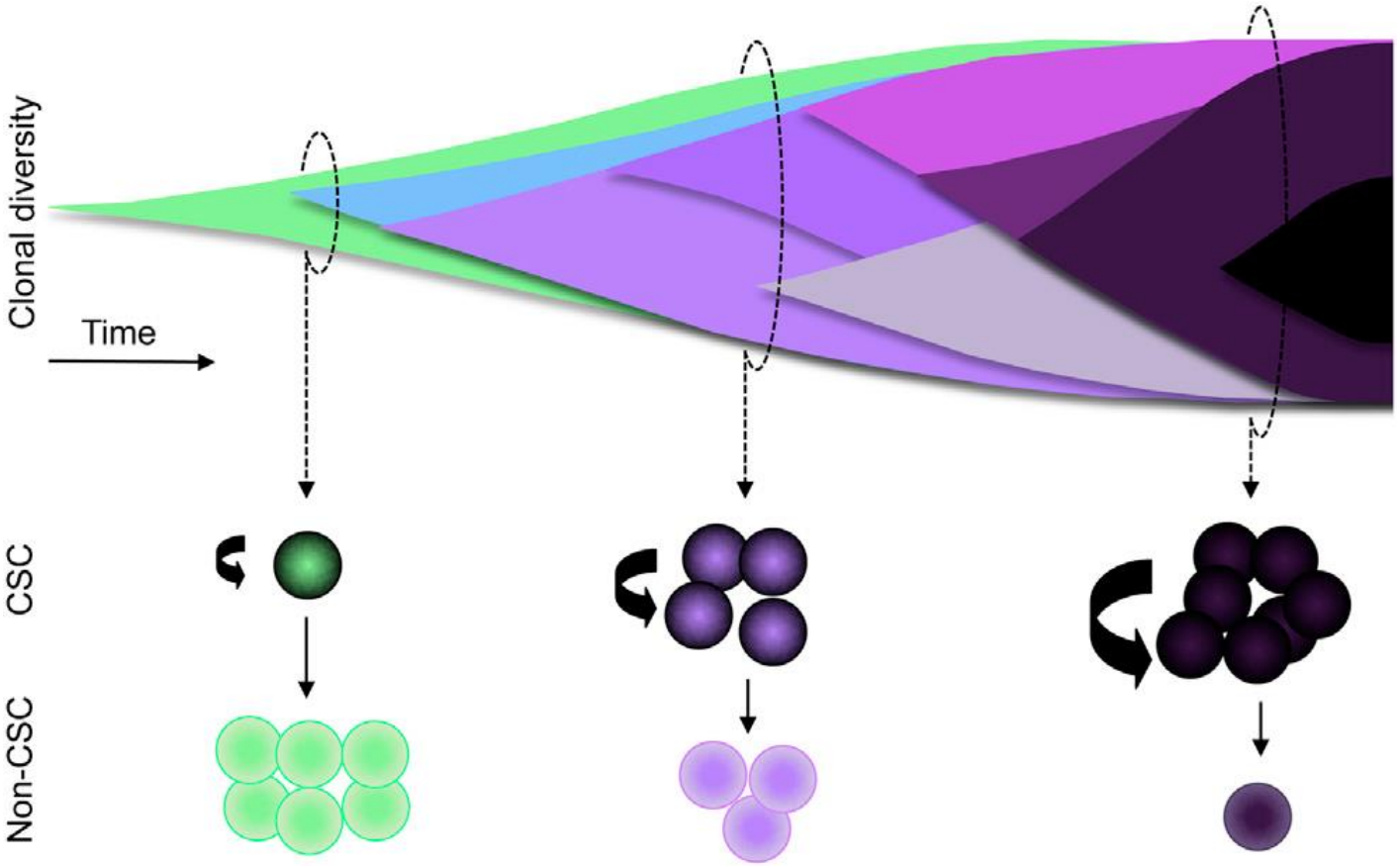


Early phase: c-Myc the driving force
Intermediate phases: Oct-4 & Sox2
Late (&early) phase: Klf4

Sancho-Martinez I & Izpisua Belmonte JC
Nature 493: 310-311, 2013.

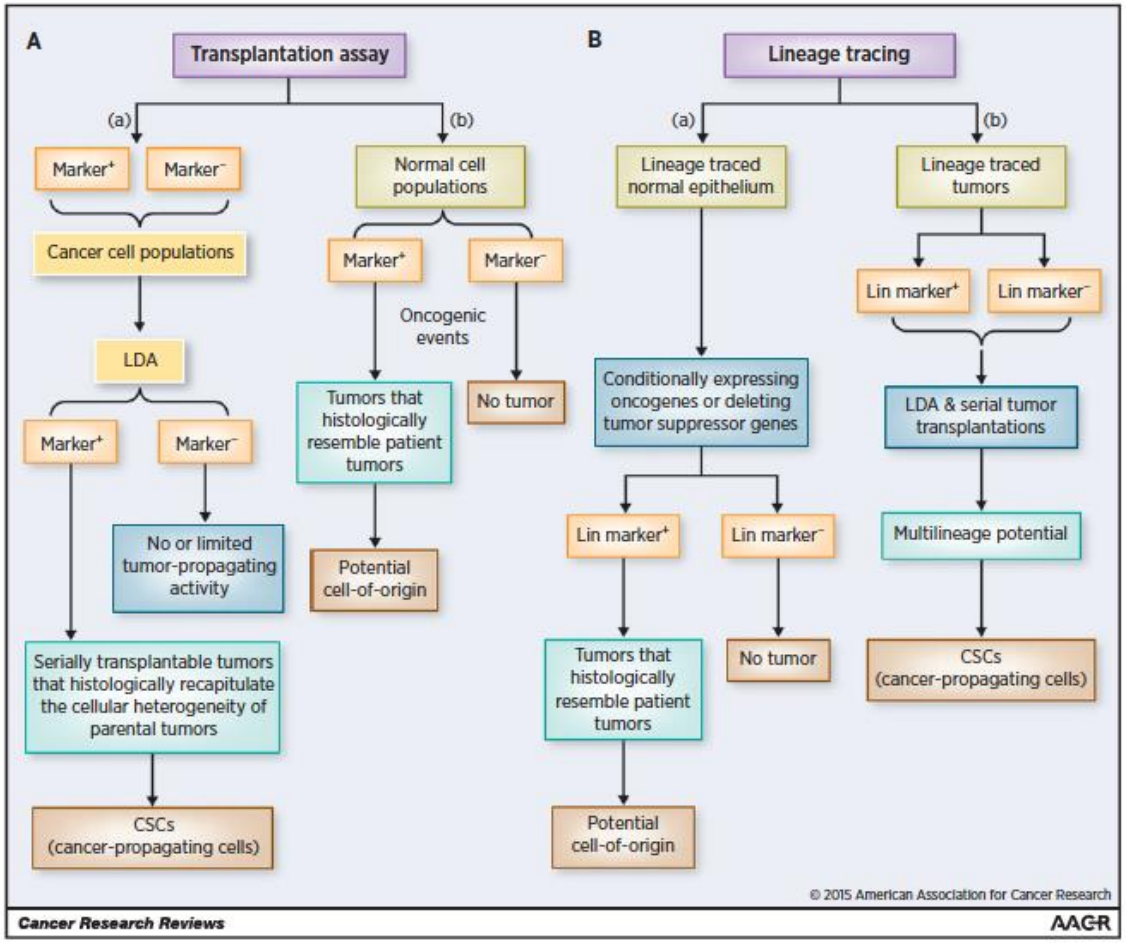


Cell-of-origin vs. CSCs



Kreso A & Dick JE. *Cell Stem Cell*, 2014
Rycaj K & Tang DG. *Cancer Res*, 2015

Functional Assays of Cancer Cell of Origin



Rycaj & Tang, *Cancer Res*, 2015

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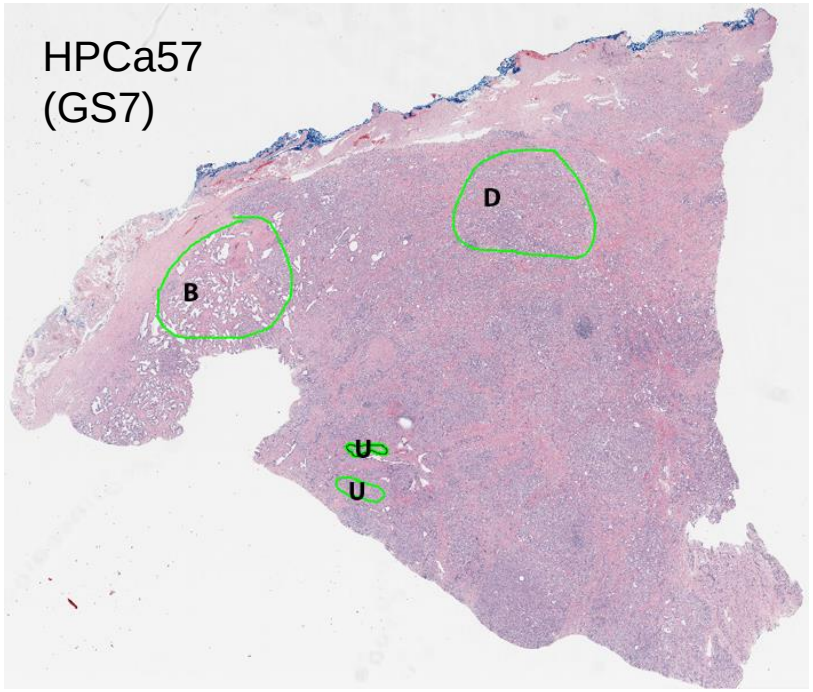
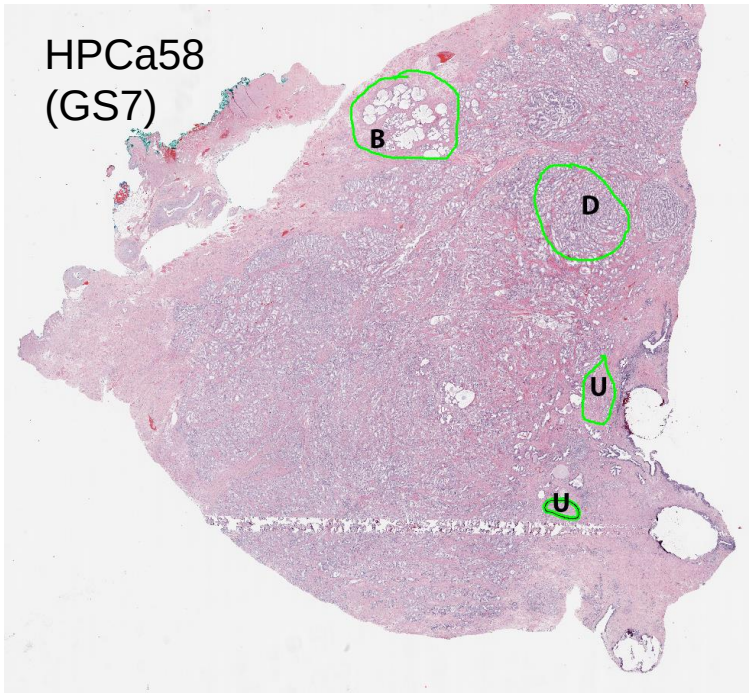

HPCa57
(GS7)
D
B
U
U


HPCa58
(GS7)
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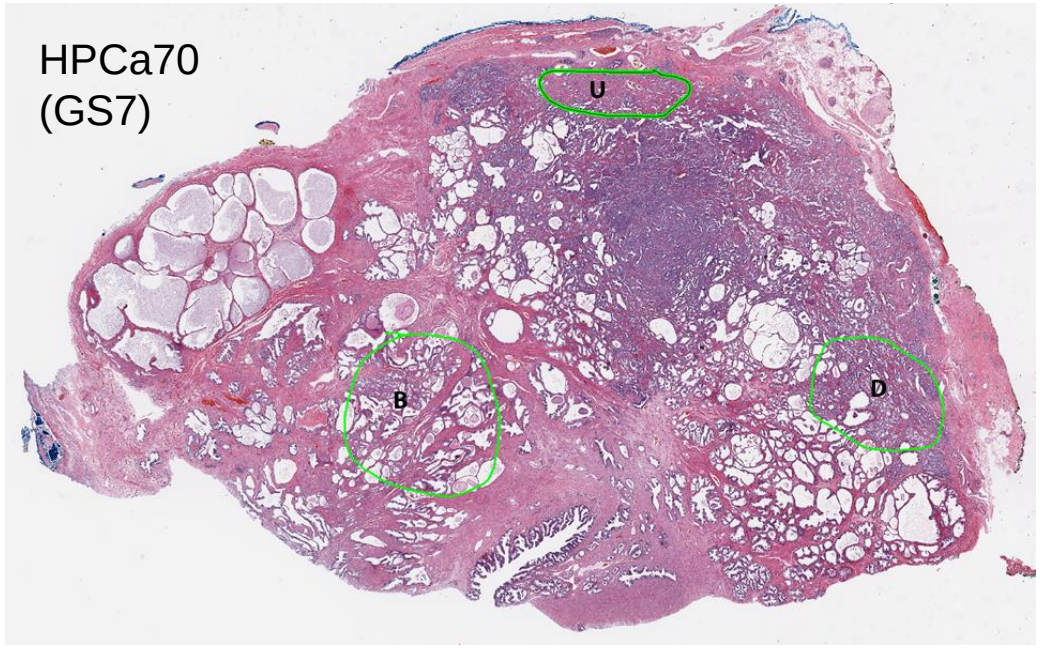
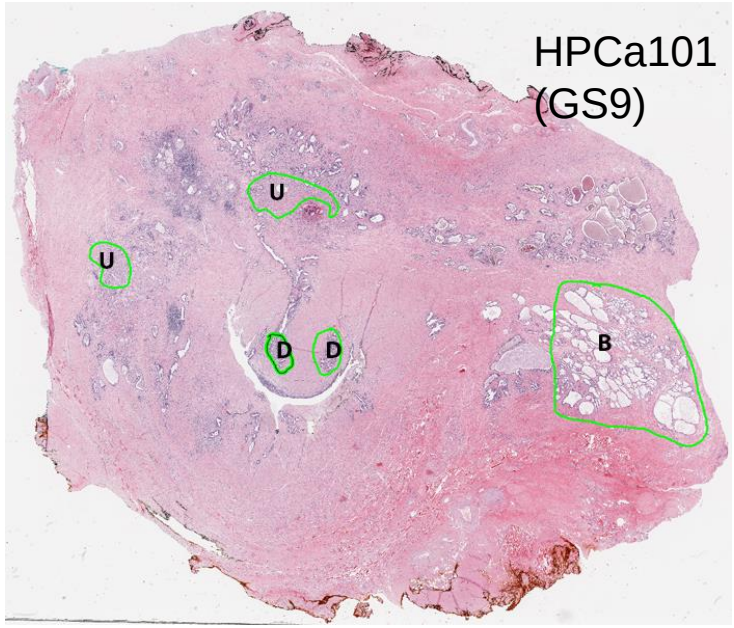
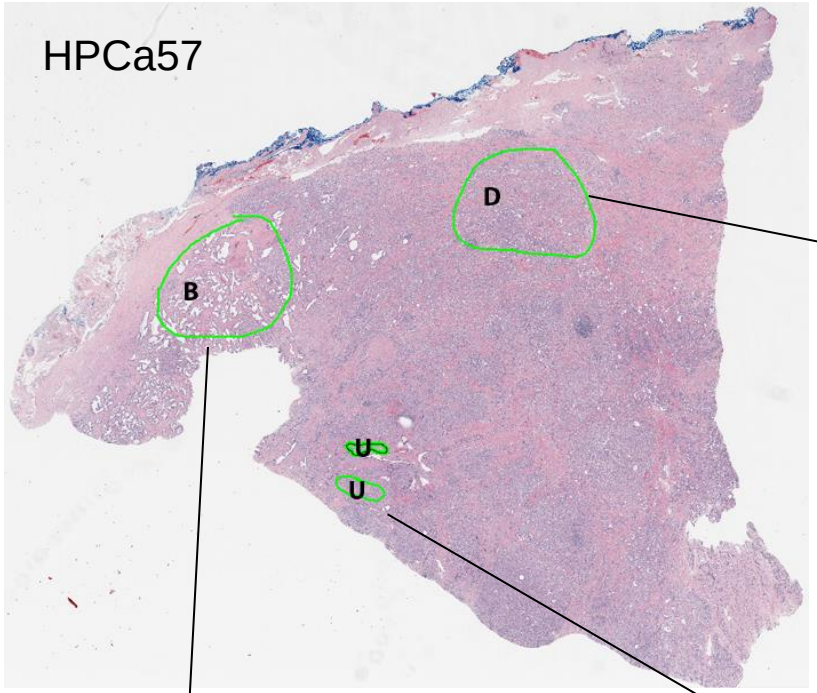
U
U


HPCa70
(GS7)
U
B
D


HPCa101
(GS9)
U
U
D
D
B


HPCa57
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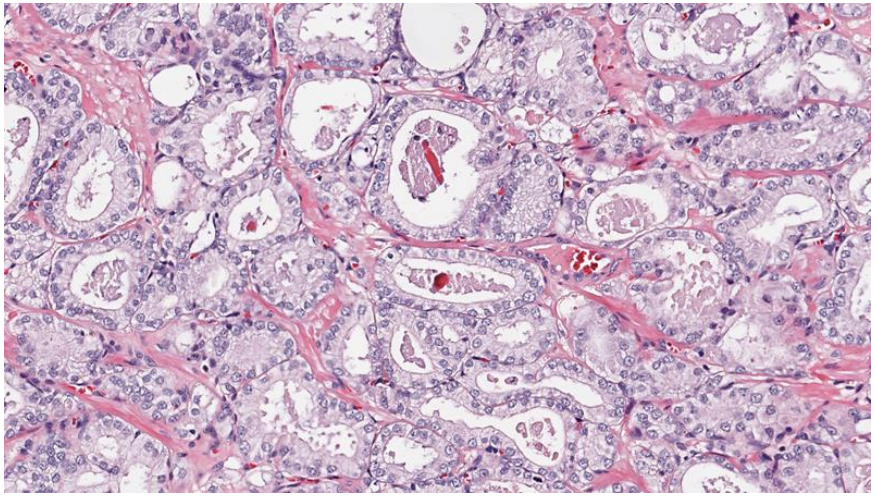
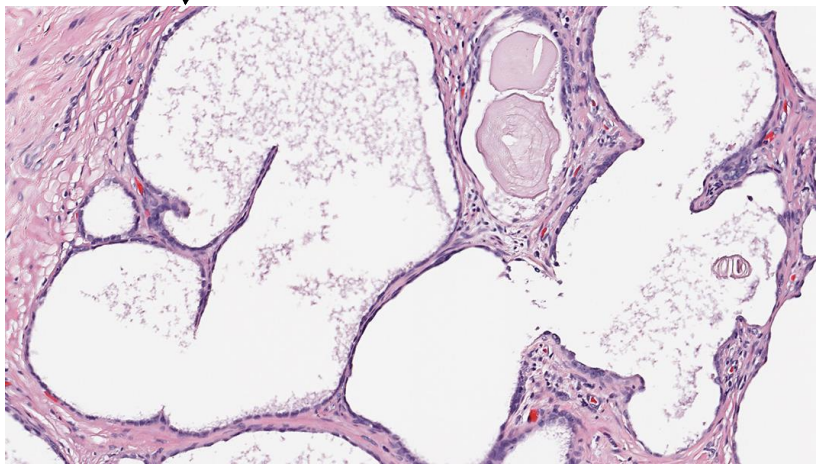
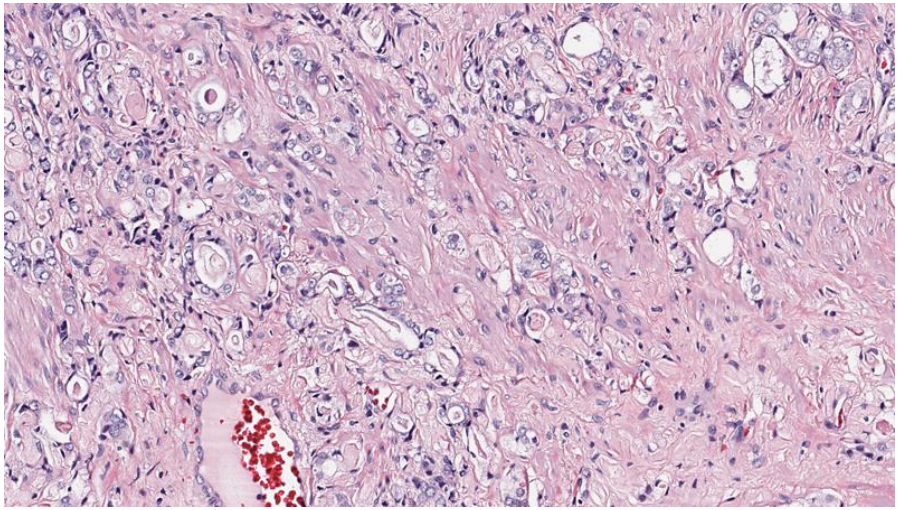


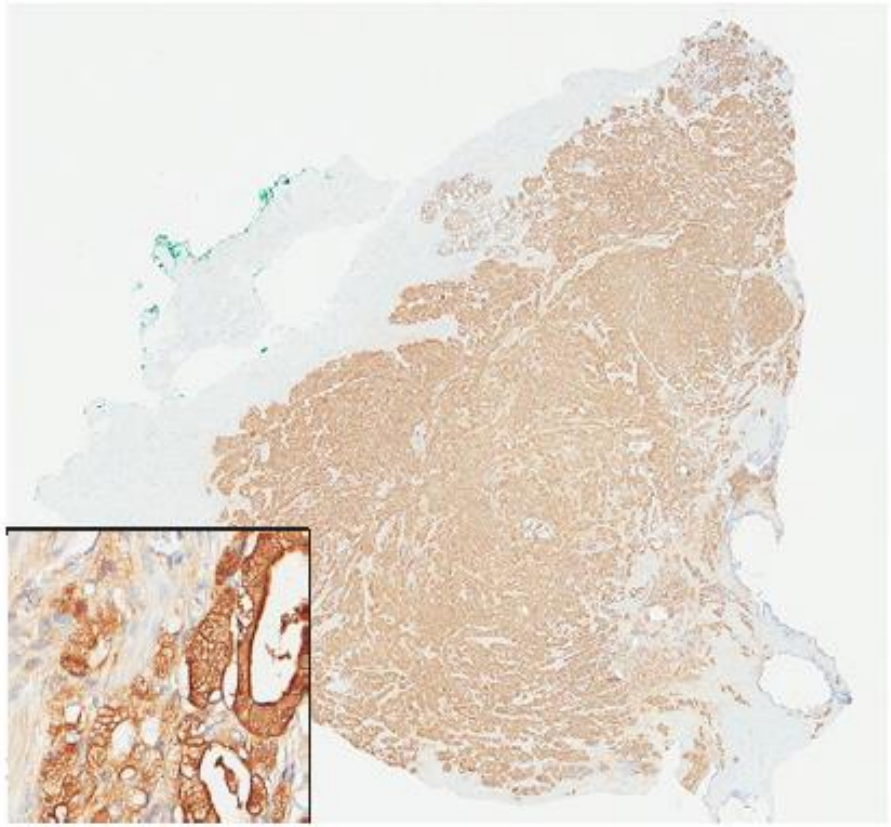


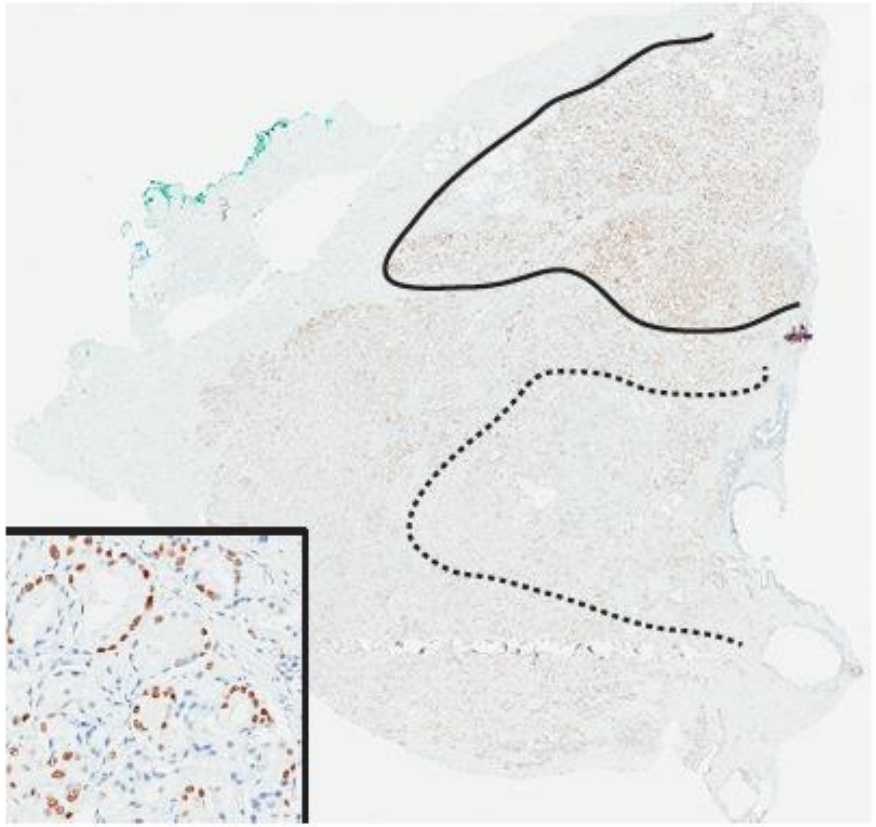


PSA

AR

HPCa57 (GS7)





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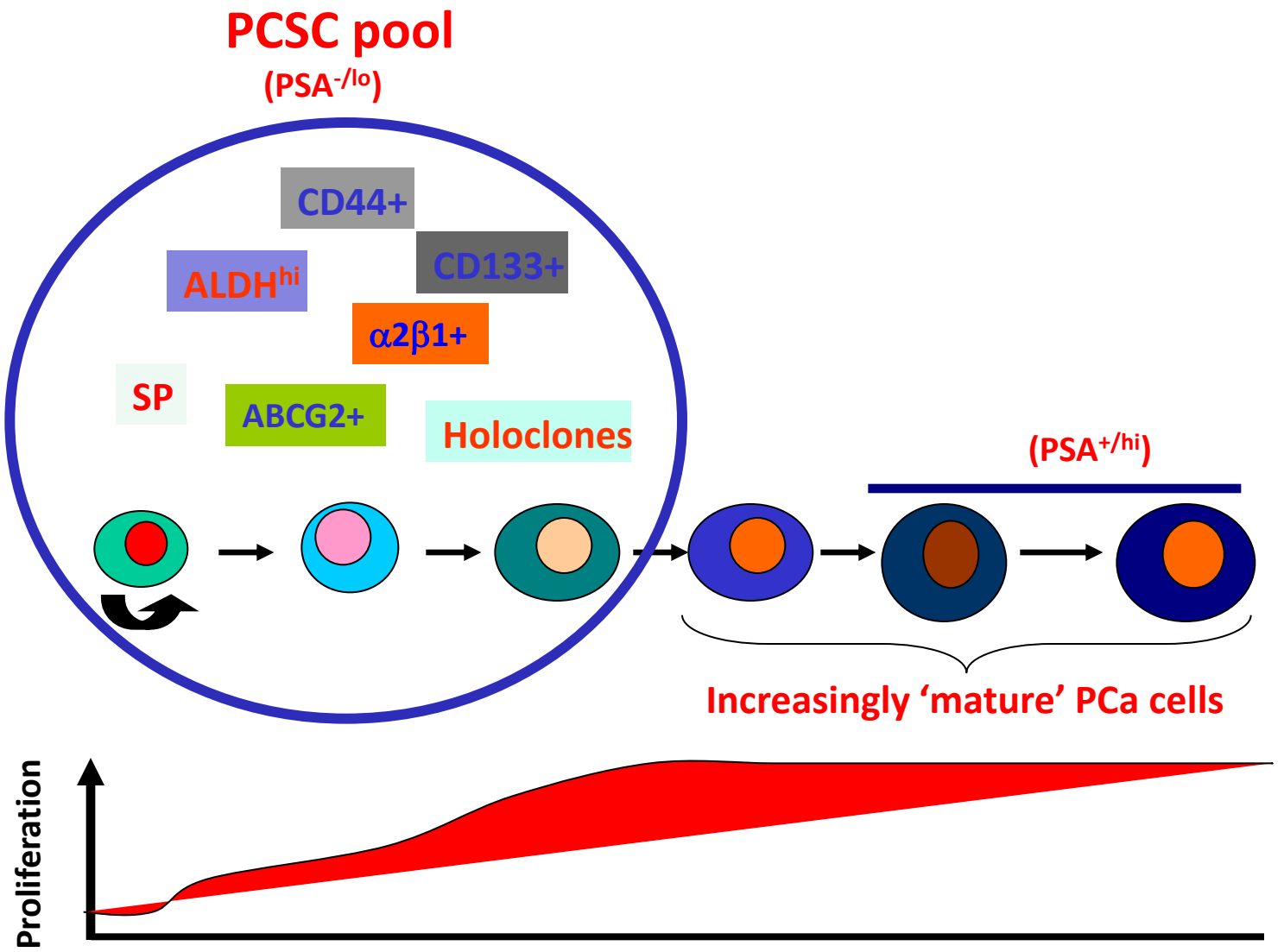
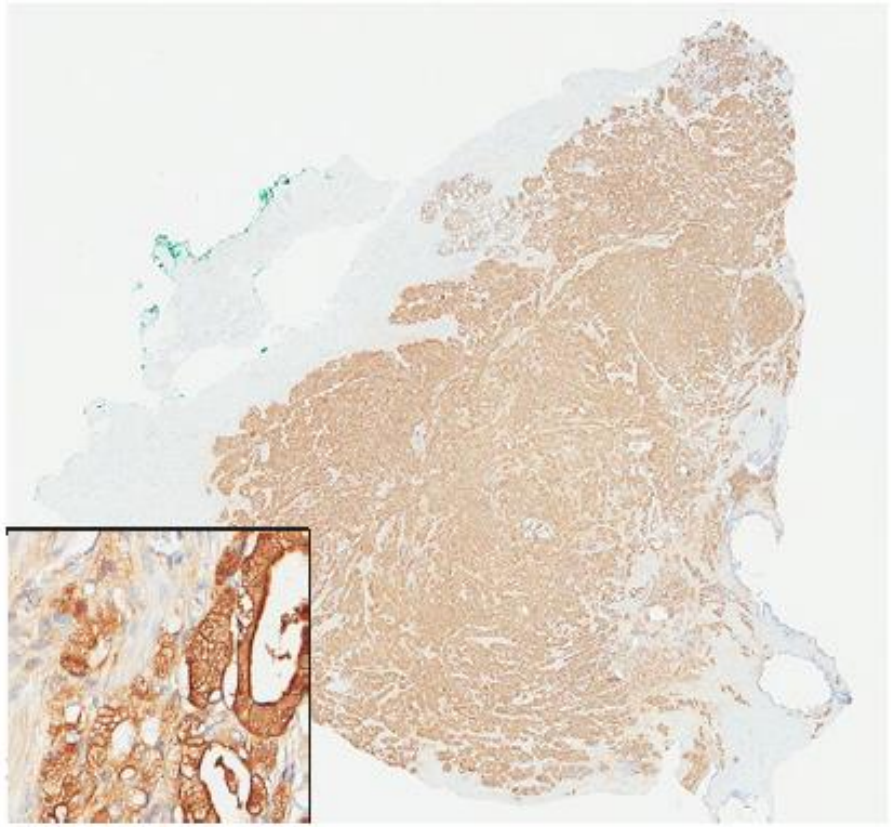
Phenotypic & Tumorigenic Heterogeneity of Human PCa cells

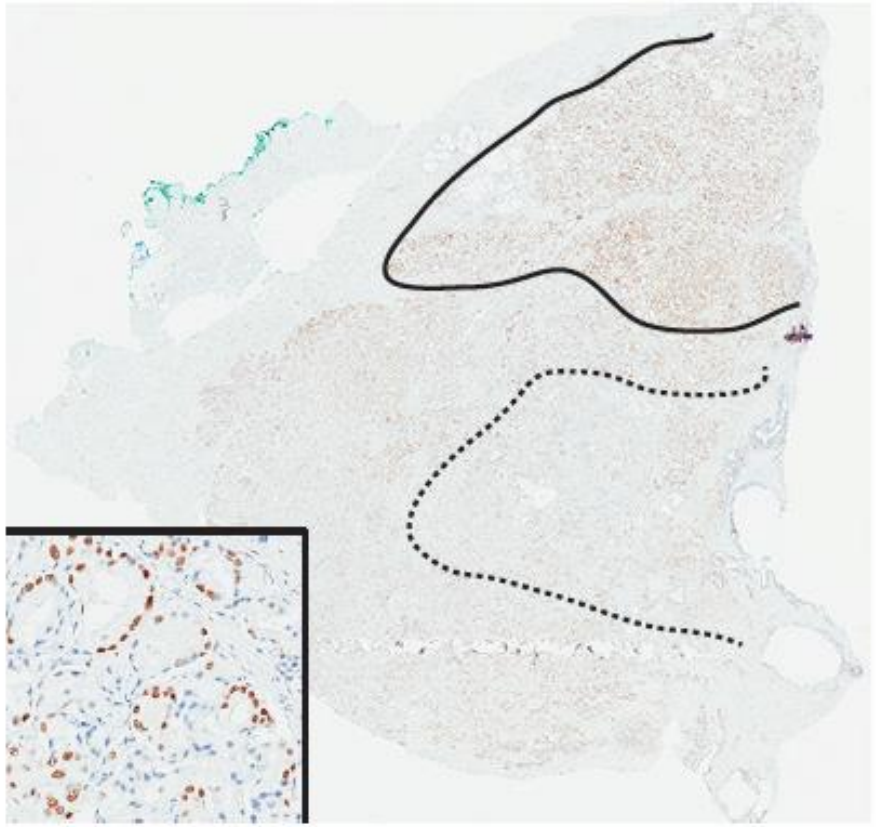


PSA

AR

HPCa57 (GS7)





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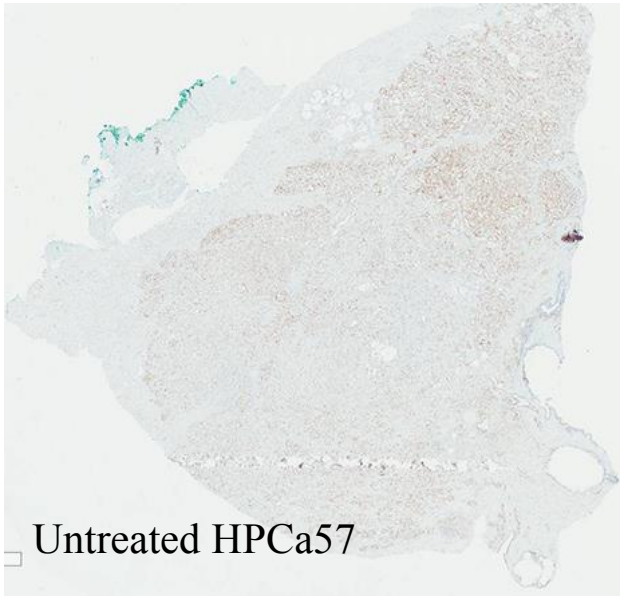
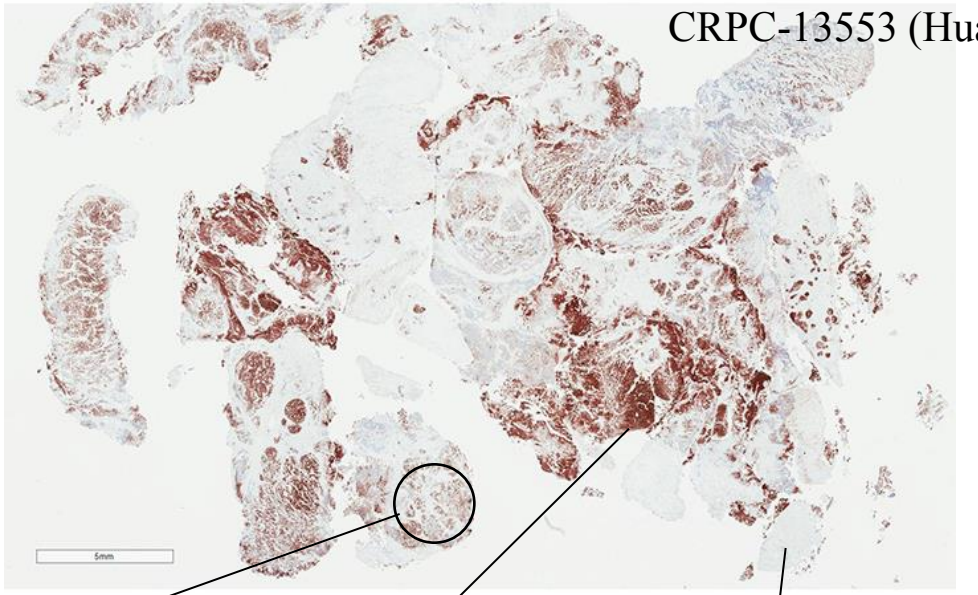
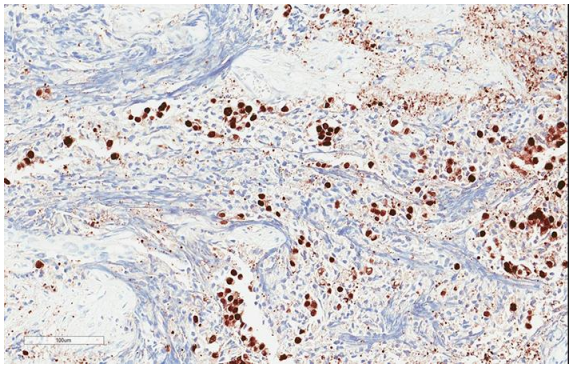
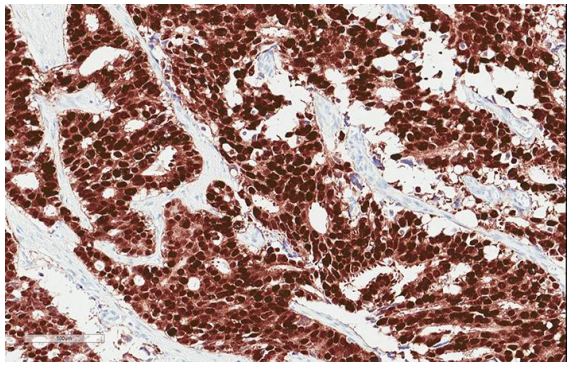
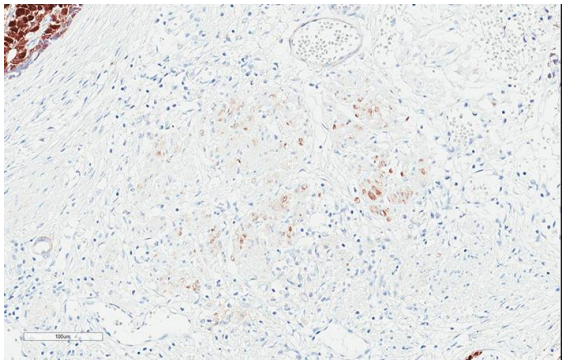
Heterogeneity of AR Expression in Untreated PCa & CRPC











Four CRPC models exhibit distinct AR heterogeneity

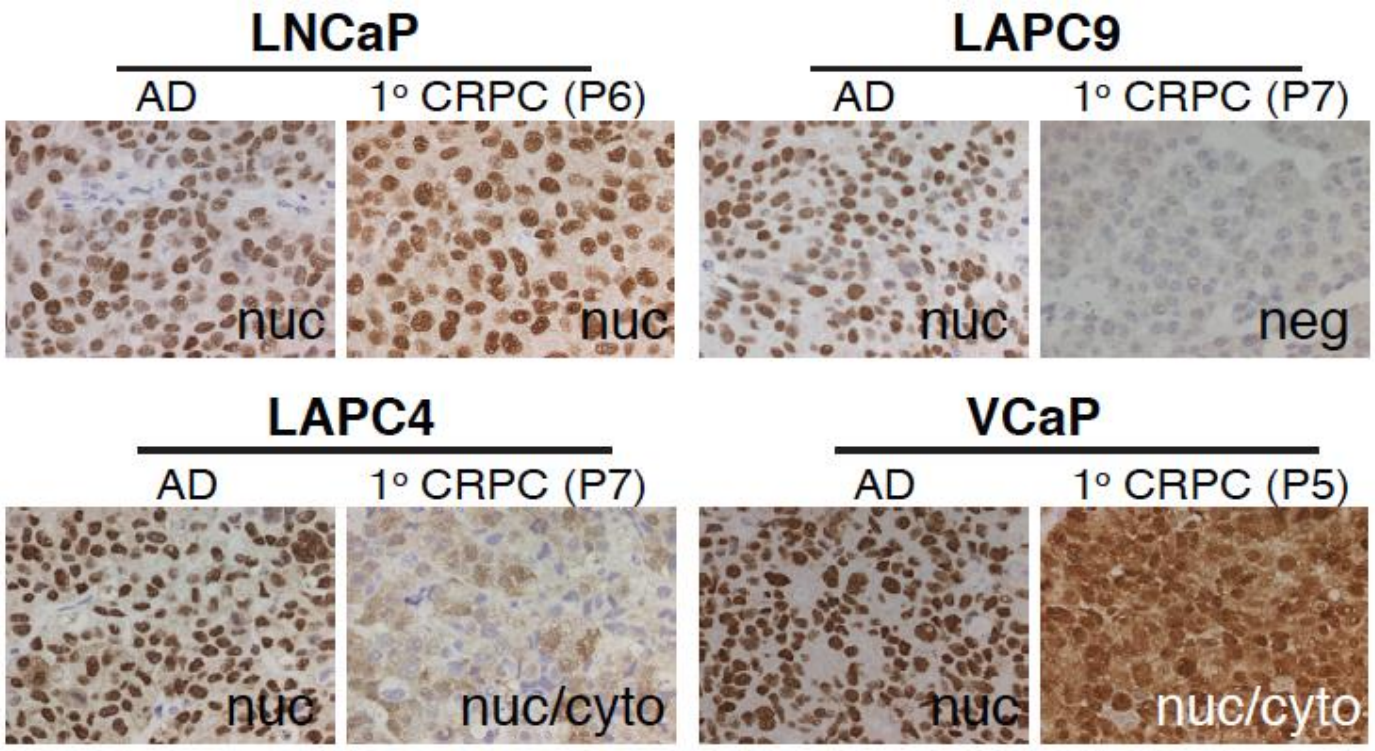
A

LNCaP, VCaP, LAPC4, LAPC9 tumors grown in intact male mice **(AD tumors)**

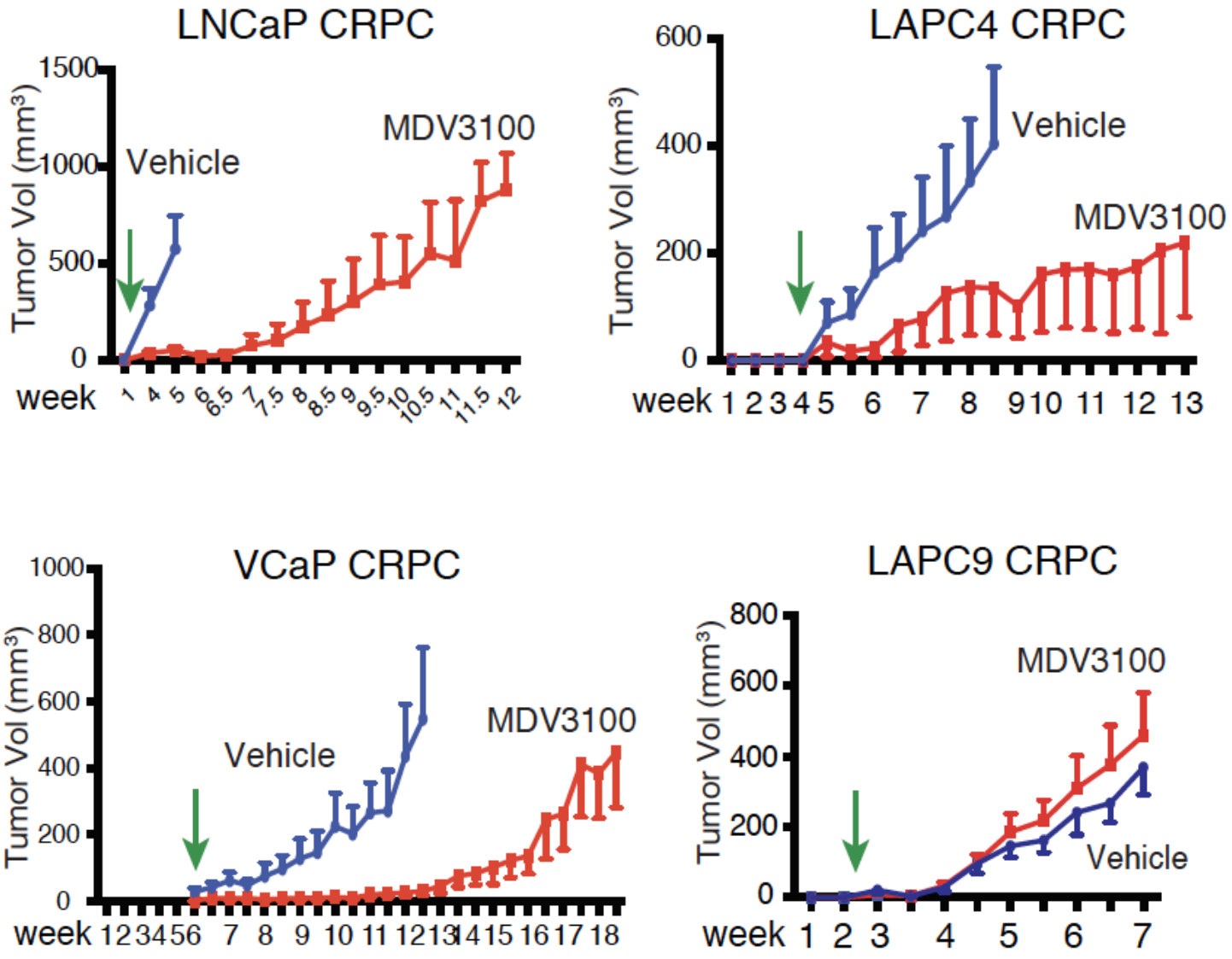
→ Serially passaged in castrated mice → **Primary (1°) CRPC**

→ Enzalutamide Tx in castrated mice → **Secondary (2°) CRPC**

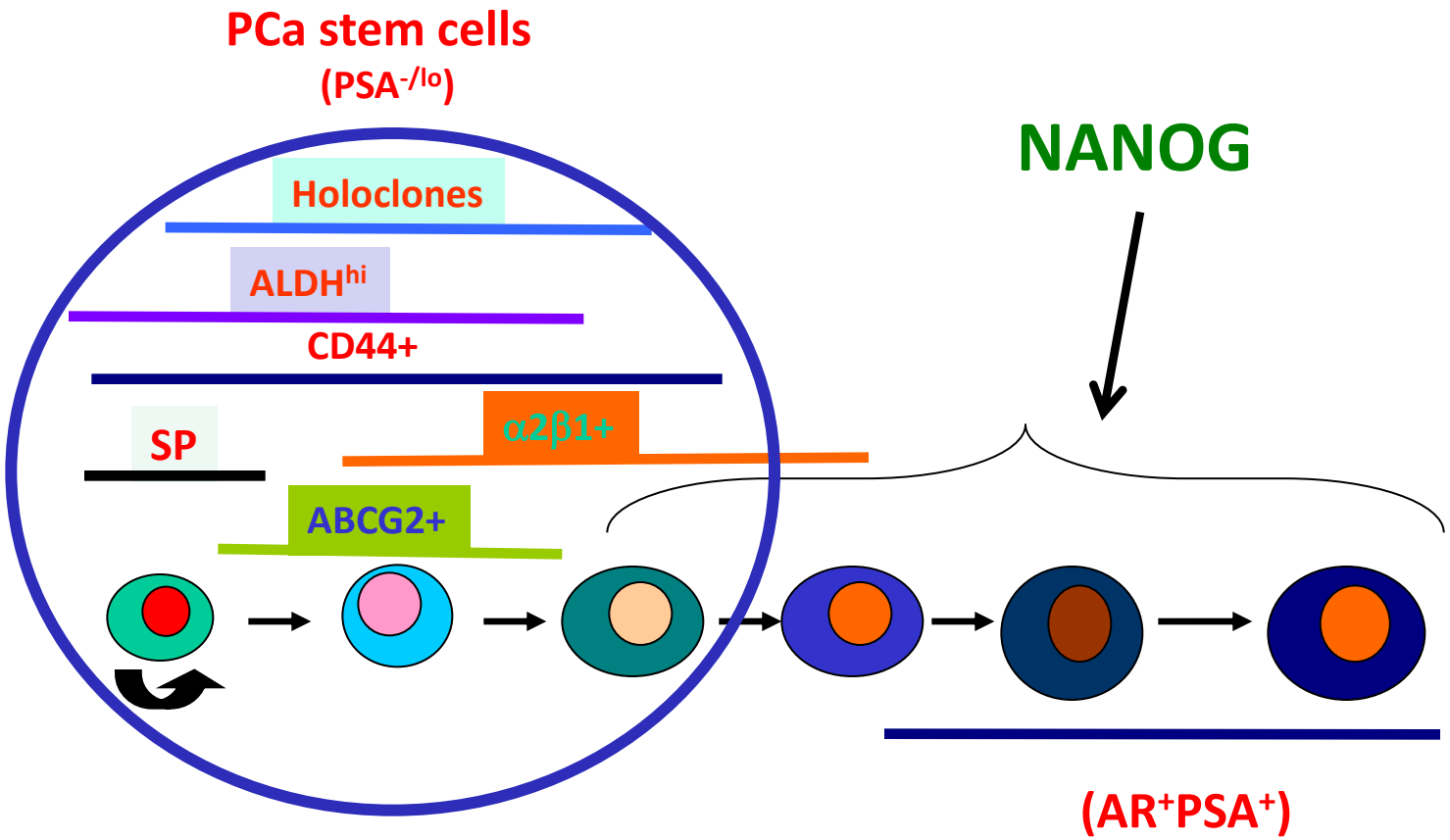
B



Four CRPCs respond differently to Enzalutamide

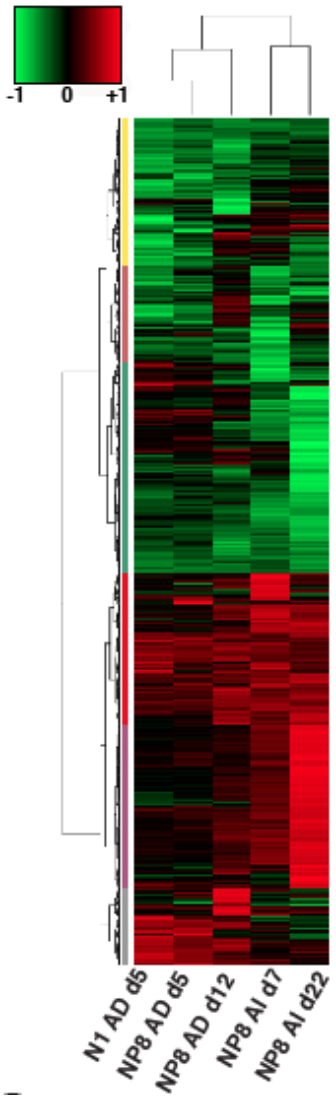


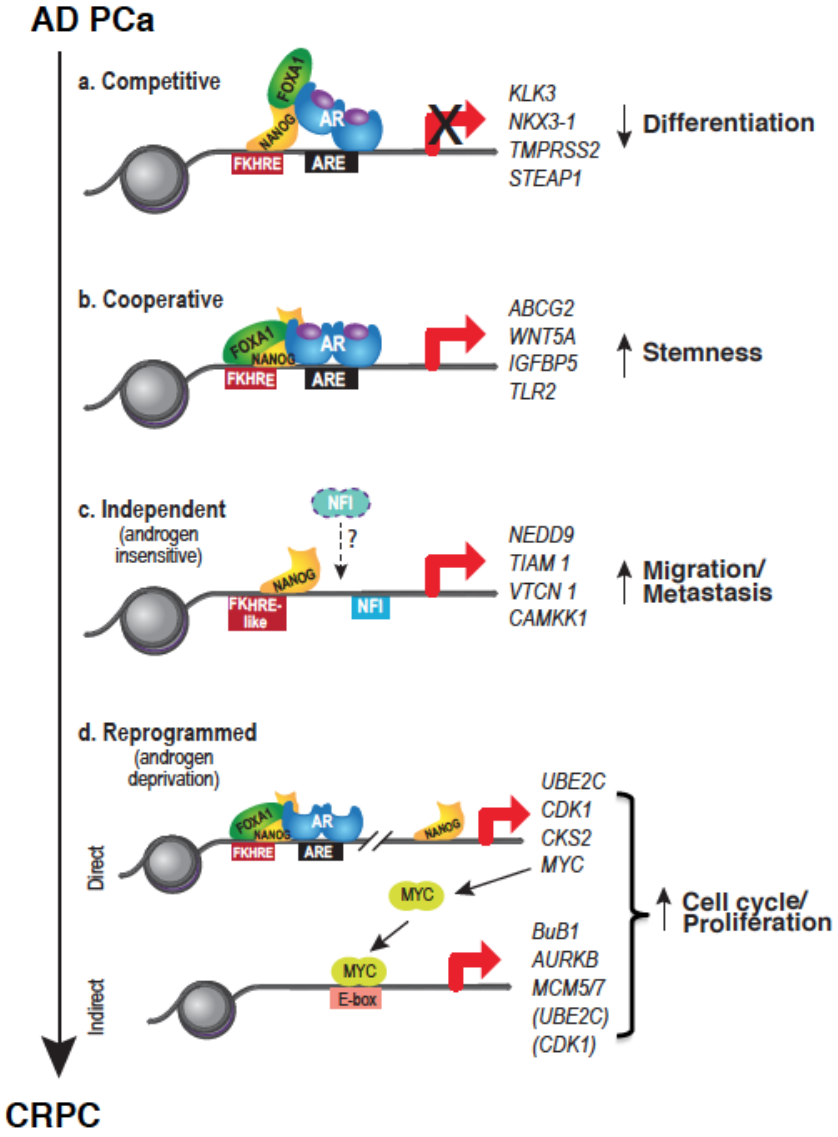
Prostate cancer cell plasticity: Reprogramming by NANOG



Jeter/Liu

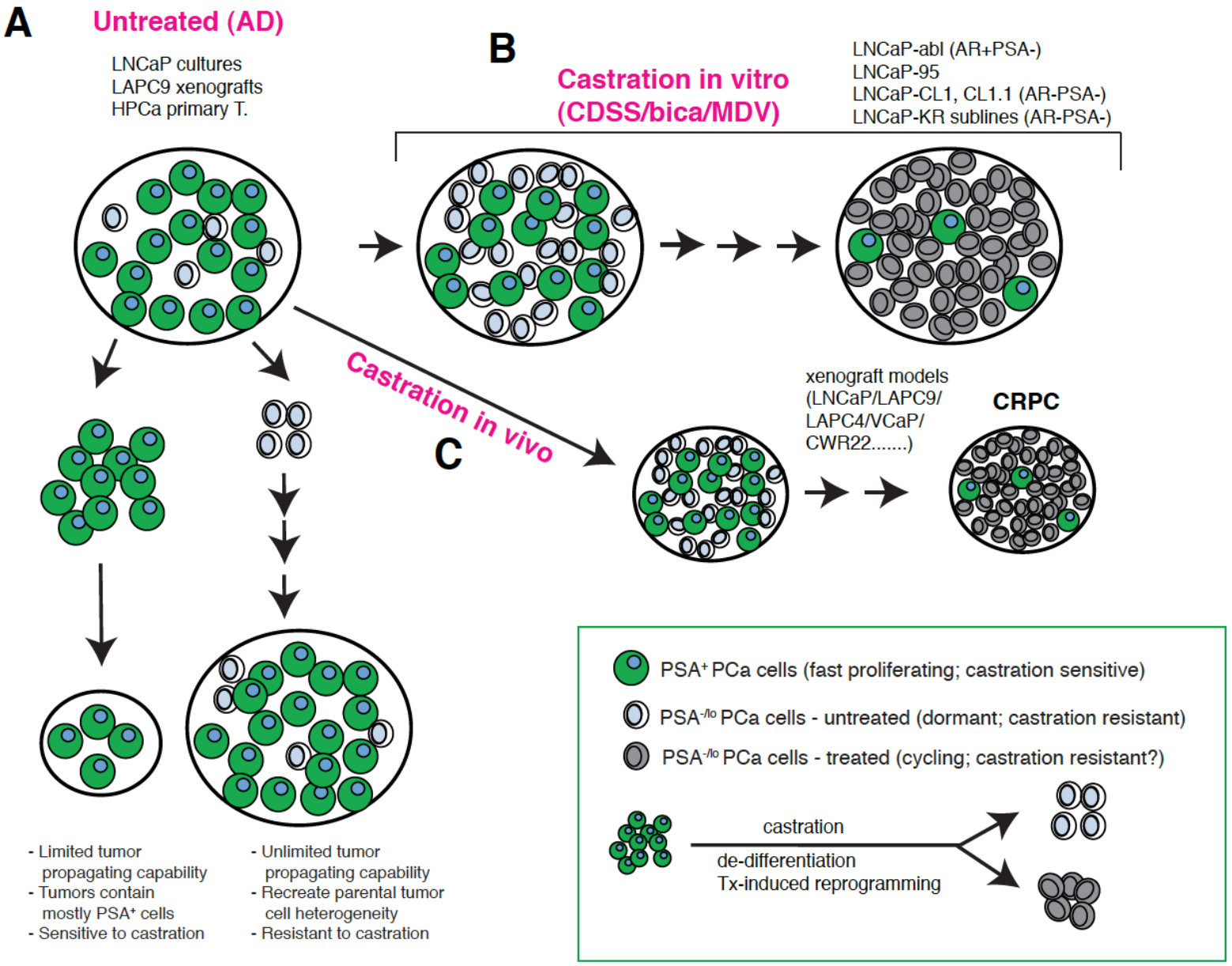
NANOG reprograms PSA^{+} PCa cells to PSA$^{-/lo}$, stem-like CRPC cells by dynamically repressing and engaging AR/FOXA1 signaling axis





Jeter C & Liu B et al., Cell Discovery, 2016

Understanding & Targeting Undifferentiated PCSCs



Combinatorial therapies targeting both AR+ bulk AND PCSCs to prevent cancer cell plasticity