Bladder and Prostate Cancer as Models of Urogenital Malignancies
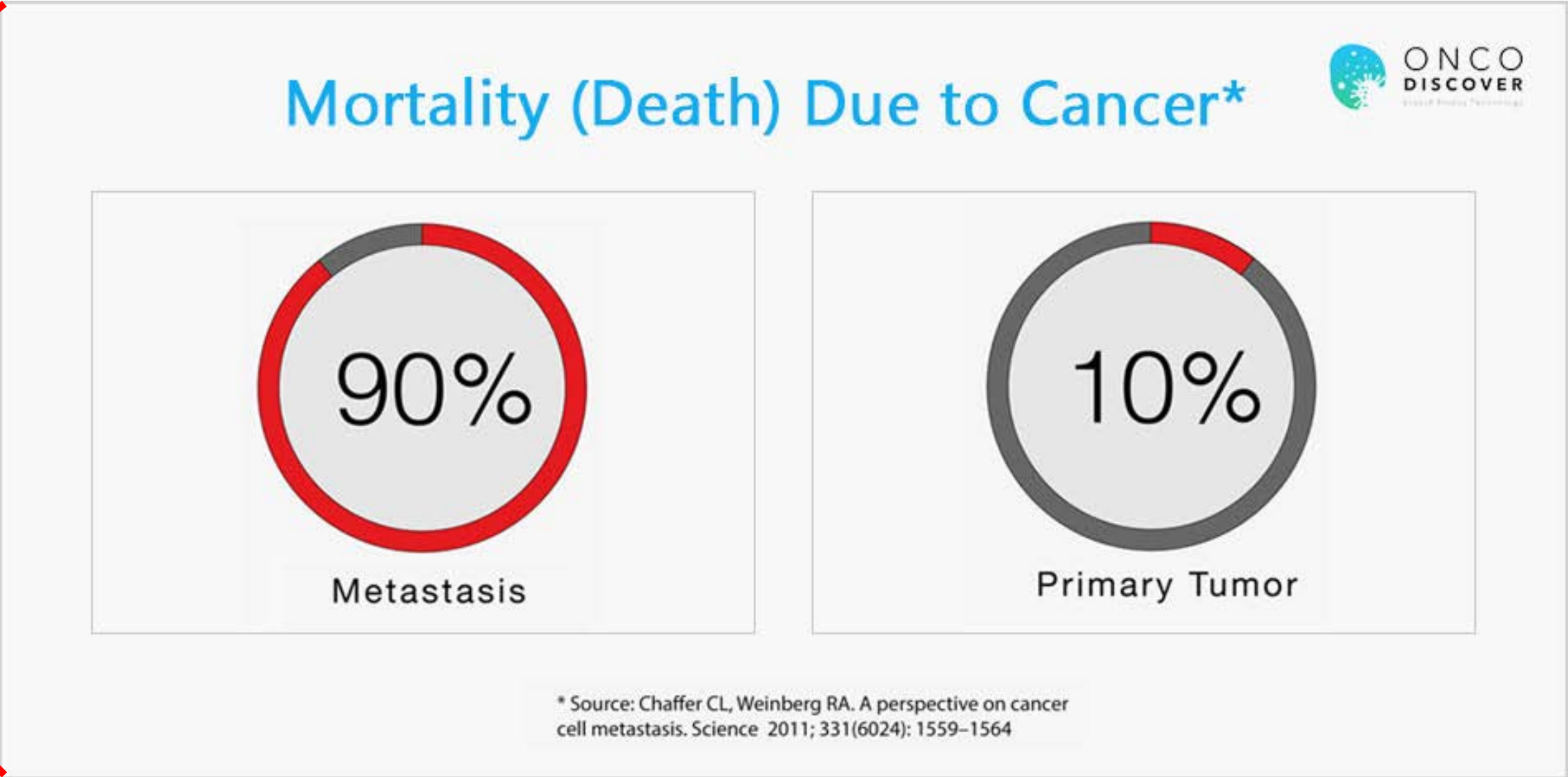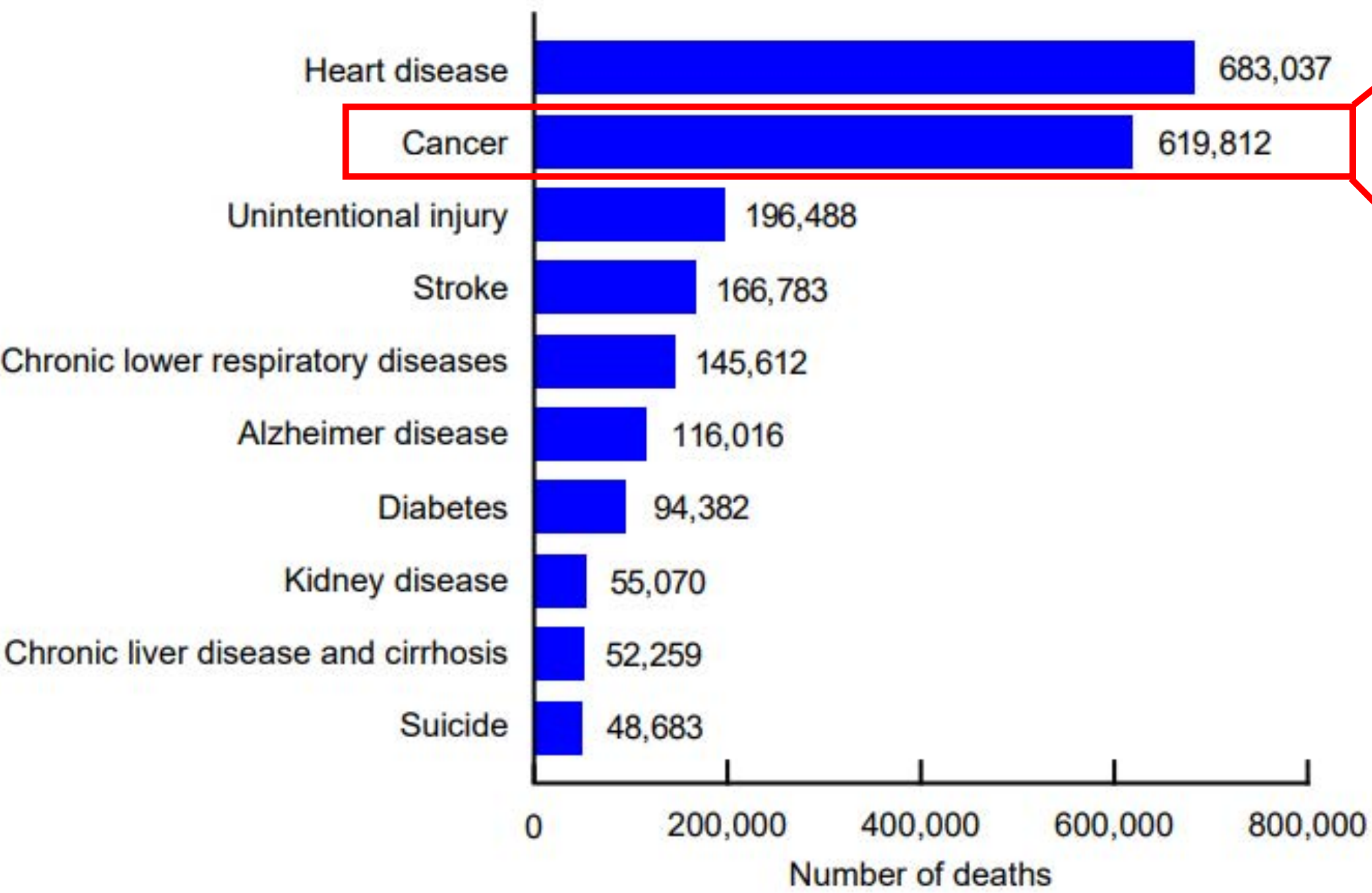
Cory Abate-Shen, PhD
Cancer Biology
December 8, 2025

Tumor metastasis is the leading cause of death among cancer patients
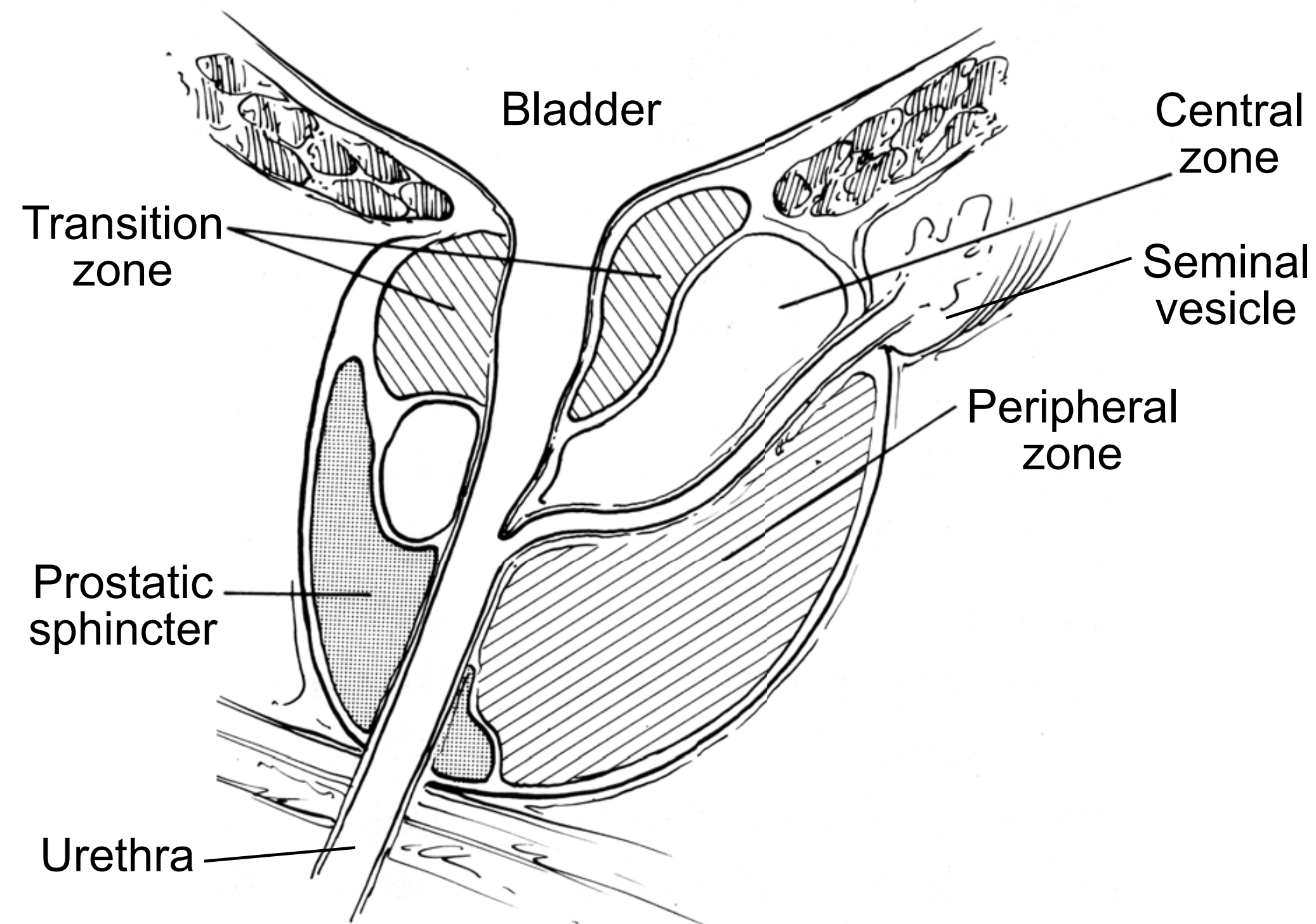
Leading underlying causes death: US,2024

Cause	Number of deaths
Heart disease	683,037
Cancer	619,812
Unintentional injury	196,488
Stroke	166,783
Chronic lower respiratory diseases	145,612
Alzheimer disease	116,016
Diabetes	94,382
Kidney disease	55,070
Chronic liver disease and cirrhosis	52,259
Suicide	48,683

Ahmad, Farida B. et al. (2025). Mortality in the United States: Provisional Data, 2024. (39).
https://dx.doi.org/10.15620/cdc/174621

Mortality (Death) Due to Cancer*

ONCO DISCOVER

90% Metastasis

10% Primary Tumor

* Source: Chaffer CL, Weinberg RA. A perspective on cancer cell metastasis. Science 2011; 331(6024): 1559–1564

Cancer metastasis accounts for 90% of cancer deaths.

Urogenital system

Human

Bladder

Central zone

Transition zone

Seminal vesicle

Peripheral zone

Prostatic sphincter

Urethra

Mouse

Seminal vesicle

Ductus deferens

Bladder

Anterior prostate
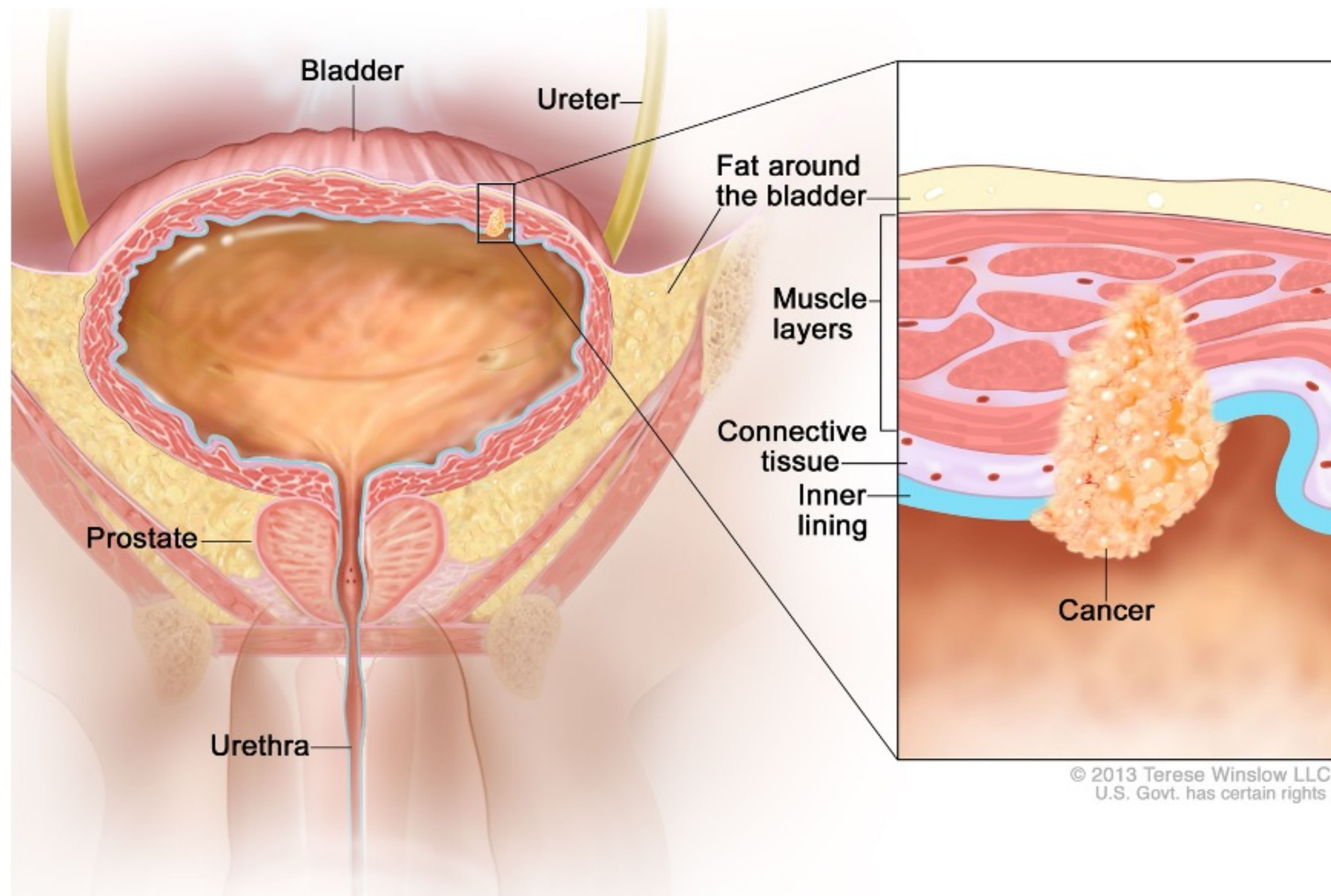
Ventral prostate

Lateral prostate

Dorsal prostate

Urethra
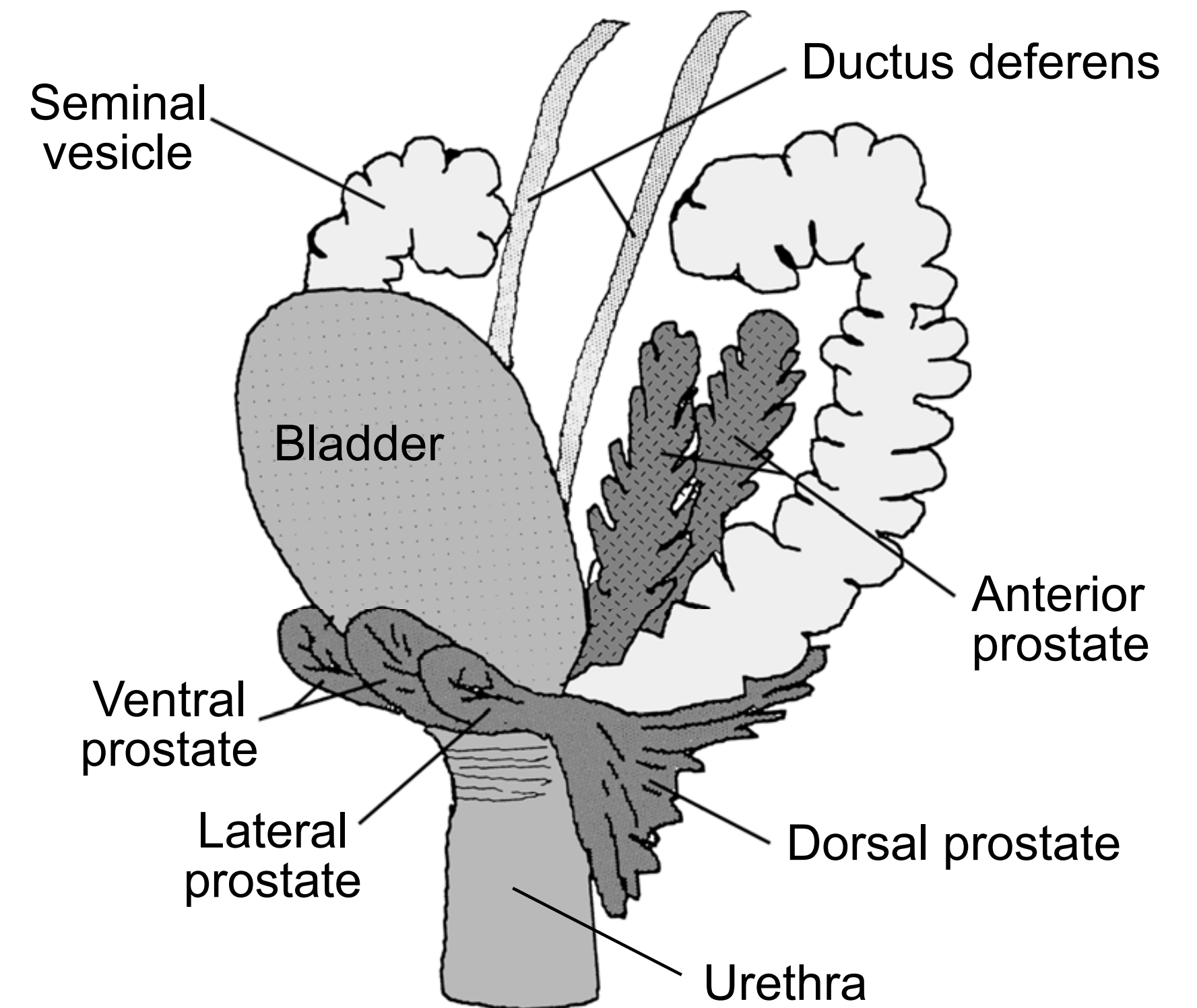
Adapted from Abate-Shen and Shen, Genes Dev 2000
Toivanen and Shen, *Development* 2017
Cunha et al., *Endocr Rev* 1987
McNeal, *Cancer* 1969

Bladder cancer

Bladder, Ureter, Fat around the bladder, Muscle layers, Connective tissue, Inner lining, Cancer, Prostate, Urethra

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U.S. Govt. has certain rights

- Arises from transitional epithelium of the urothelial tract (bladder, ureter, renal pelvis)

- Non-muscle invasive bladder cancer (75%)

- **Muscle invasive bladder cancer** (MIBC; 25%)

  - High recurrence rate

  - 50% 5-year overall survival

Bladder cancer

Aging and Gender

Smoking

Arsenic in water
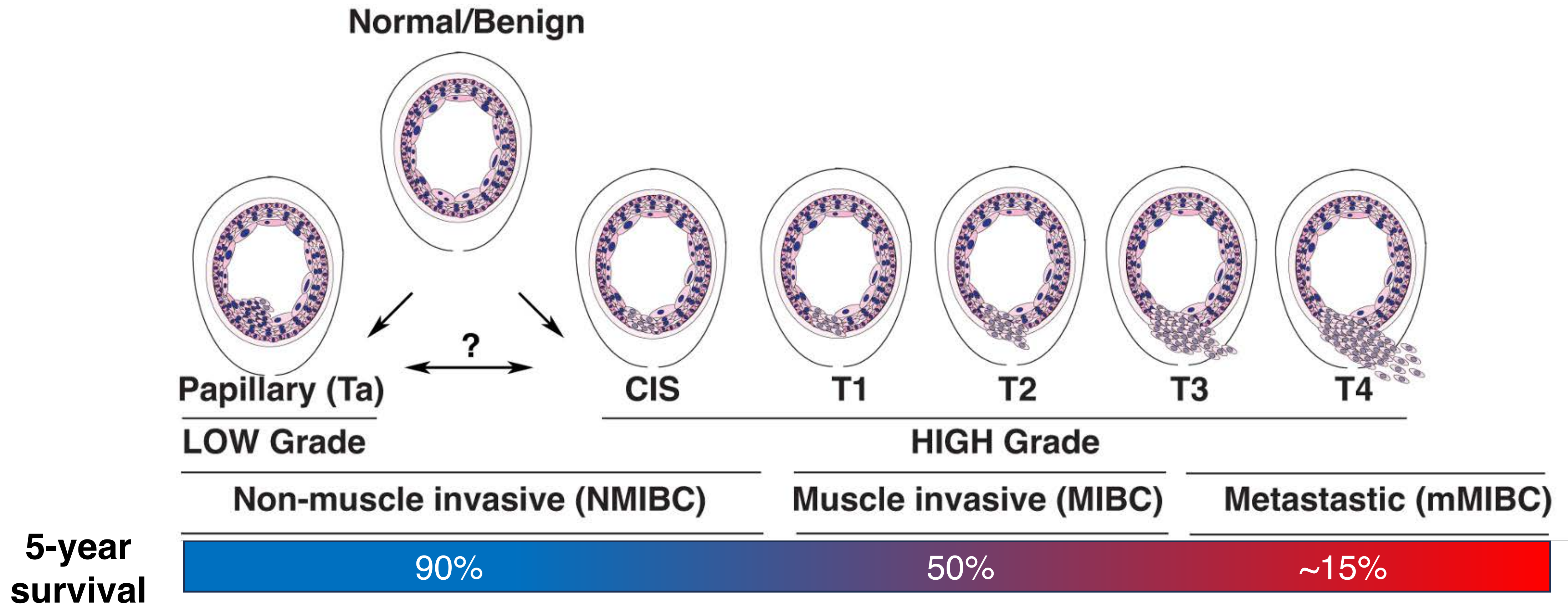
Chemical exposure

Chronic inflammation
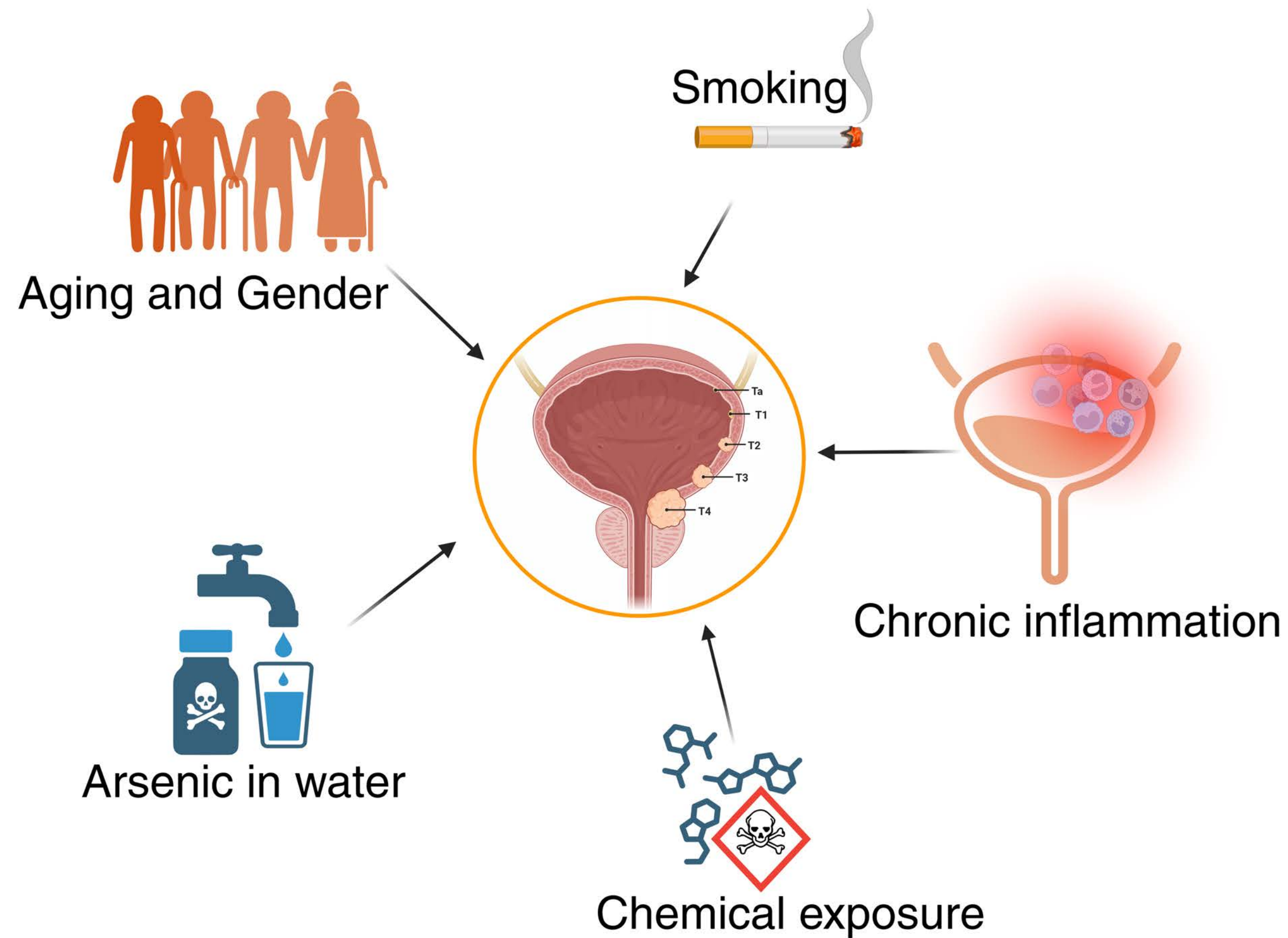
- 4th most common cancer in men

- Less common in women but more aggressive

- Smoking → ~50% of cases

- Aging: Median diagnosis at 70 years

- Chronic bladder inflammation

- Environmental & occupational hazards

Estimated New Cases

Male

Prostate	299,010	29%
Lung & bronchus	116,310	11%
Colon & rectum	81,540	8%
Urinary bladder	63,070	6%
Melanoma of the skin	59,170	6%
Kidney & renal pelvis	52,380	5%
Non-Hodgkin lymphoma	44,590	4%
Oral cavity & pharynx	41,510	4%
Leukemia	36,450	4%
Pancreas	34,530	3%
All sites	**1,029,080**	

Female

Breast	310,720	32%
Lung & bronchus	118,270	12%
Colon & rectum	71,270	7%
Uterine corpus	67,880	7%
Melanoma of the skin	41,470	4%
Non-Hodgkin lymphoma	36,030	4%
Pancreas	31,910	3%
Thyroid	31,520	3%
Kidney & renal pelvis	29,230	3%
Leukemia	26,320	3%
All sites	**972,060**	

Estimated Deaths

Male

Lung & bronchus	65,790	20%
Prostate	35,250	11%
Colon & rectum	28,700	9%
Pancreas	27,270	8%
Liver & intrahepatic bile duct	19,120	6%
Leukemia	13,640	4%
Esophagus	12,880	4%
Urinary bladder	12,290	4%
Non-Hodgkin lymphoma	11,780	4%
Brain & other nervous system	10,690	3%
All sites	**322,800**	

Female

Lung & bronchus	59,280	21%
Breast	42,250	15%
Pancreas	24,480	8%
Colon & rectum	24,310	8%
Uterine corpus	13,250	5%
Ovary	12,740	4%
Liver & intrahepatic bile duct	10,720	4%
Leukemia	10,030	3%
Non-Hodgkin lymphoma	8,360	3%
Brain & other nervous system	8,070	3%
All sites	**288,920**	

Estimates are rounded to the nearest 10, and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder. Estimates do not include Puerto Rico or other US territories. Ranking is based on modeled projections and may differ from the most recent observed data.
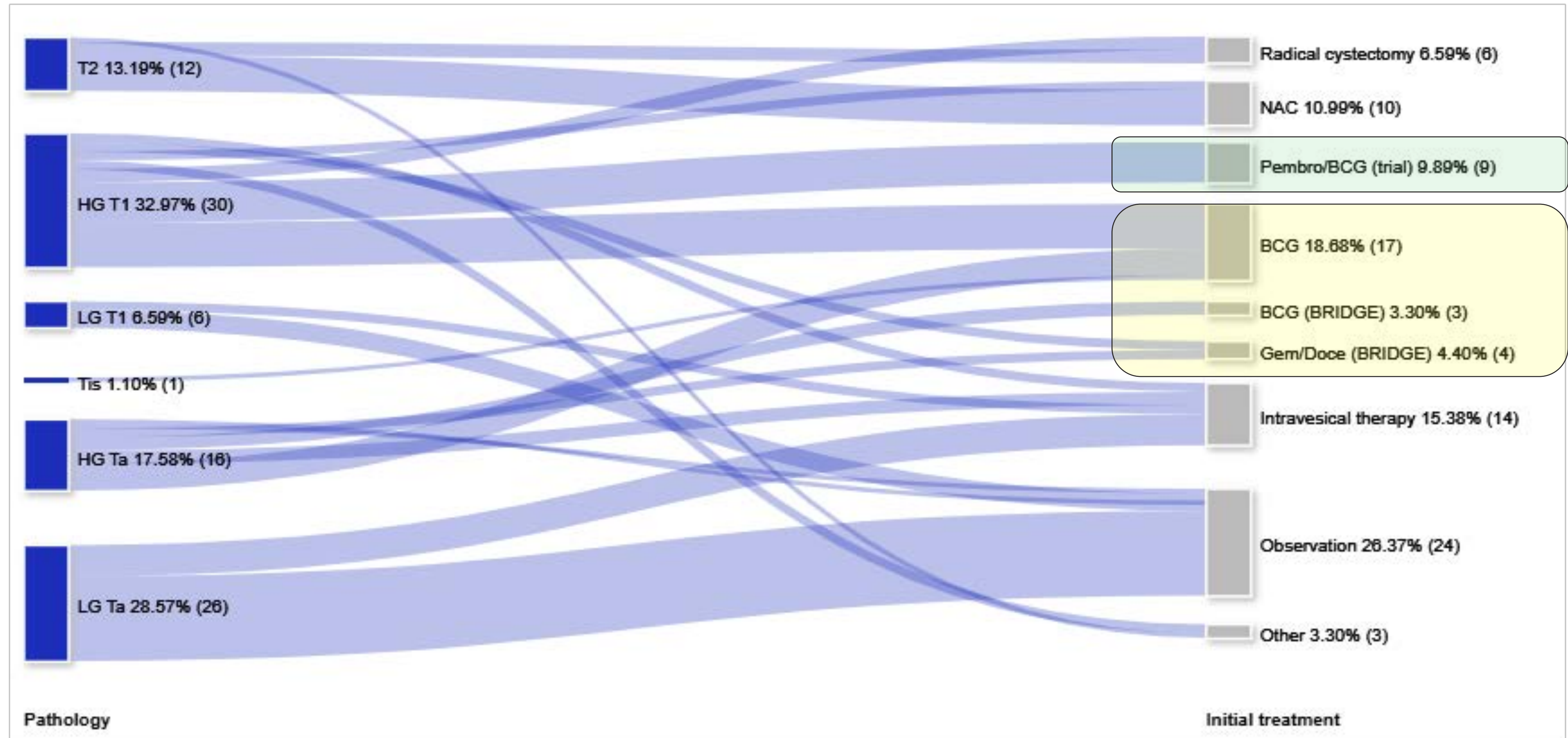
©2024, American Cancer Society, Inc., Surveillance and Health Equity Science

Bladder Cancer Progression

Adapted from Kobayashi… Abate-Shen, Nat Rev Cancer (2015)

Treating bladder cancer by stage

MIBC

HG NMIBC

LG NMIBC

T2 13.19% (12)

HG T1 32.97% (30)

LG T1 6.59% (6)

Tis 1.10% (1)

HG Ta 17.58% (16)

LG Ta 28.57% (26)

Pathology

Radical cystectomy 6.59% (6)

NAC 10.99% (10)

Pembro/BCG (trial) 9.89% (9)

BCG 18.68% (17)

BCG (BRIDGE) 3.30% (3)

Gem/Doce (BRIDGE) 4.40% (4)

Intravesical therapy 15.38% (14)

Observation 26.37% (24)

Other 3.30% (3)

Initial treatment

Cansu Yol.

8

Comprehensive Molecular Characterization of Muscle-Invasive Bladder Cancer

Cell 2017;171(3):540-556.e25

A. Gordon Robertson,[1,25] Jaegil Kim,[2,25] Hikmat Al-Ahmadie,[3] Joaquim Bellmunt,[4] Guangwu Guo,[5] Andrew D. Cherniack,[2] Toshinori Hinoue,[6] Peter W. Laird,[6] Katherine A. Hoadley,[7] Rehan Akbani,[8] Mauro A.A. Castro,[9] Ewan A. Gibb,[1] Rupa S. Kanchi,[8] Dmitry A. Gordenin,[10] Sachet A. Shukla,[5] Francisco Sanchez-Vega,[11] Donna E. Hansel,[12] Bogdan A. Czerniak,[13] Victor E. Reuter,[3] Xiaoping Su,[8] Benilton de Sa Carvalho,[14] Vinicius S. Chagas,[9] Karen L. Mungall,[1] Sara Sadeghi,[1] Chandra Sekhar Pedamallu,[2] Yiling Lu,[15] Leszek J. Klimczak,[16] Jiexin Zhang,[8] Caleb Choo,[1] Akinyemi I. Ojesina,[17] Susan Bullman,[2] Kristen M. Leraas,[18] Tara M. Lichtenberg,[18] Catherine J. Wu,[19] Nicholaus Schultz,[11] Gad Getz,[2] Matthew Meyerson,[20] Gordon B. Mills,[15] David J. McConkey,[21] TCGA Research Network, John N. Weinstein,[8,22,*] David J. Kwiatkowski,[23,*] and Seth P. Lerner[24,26,*]
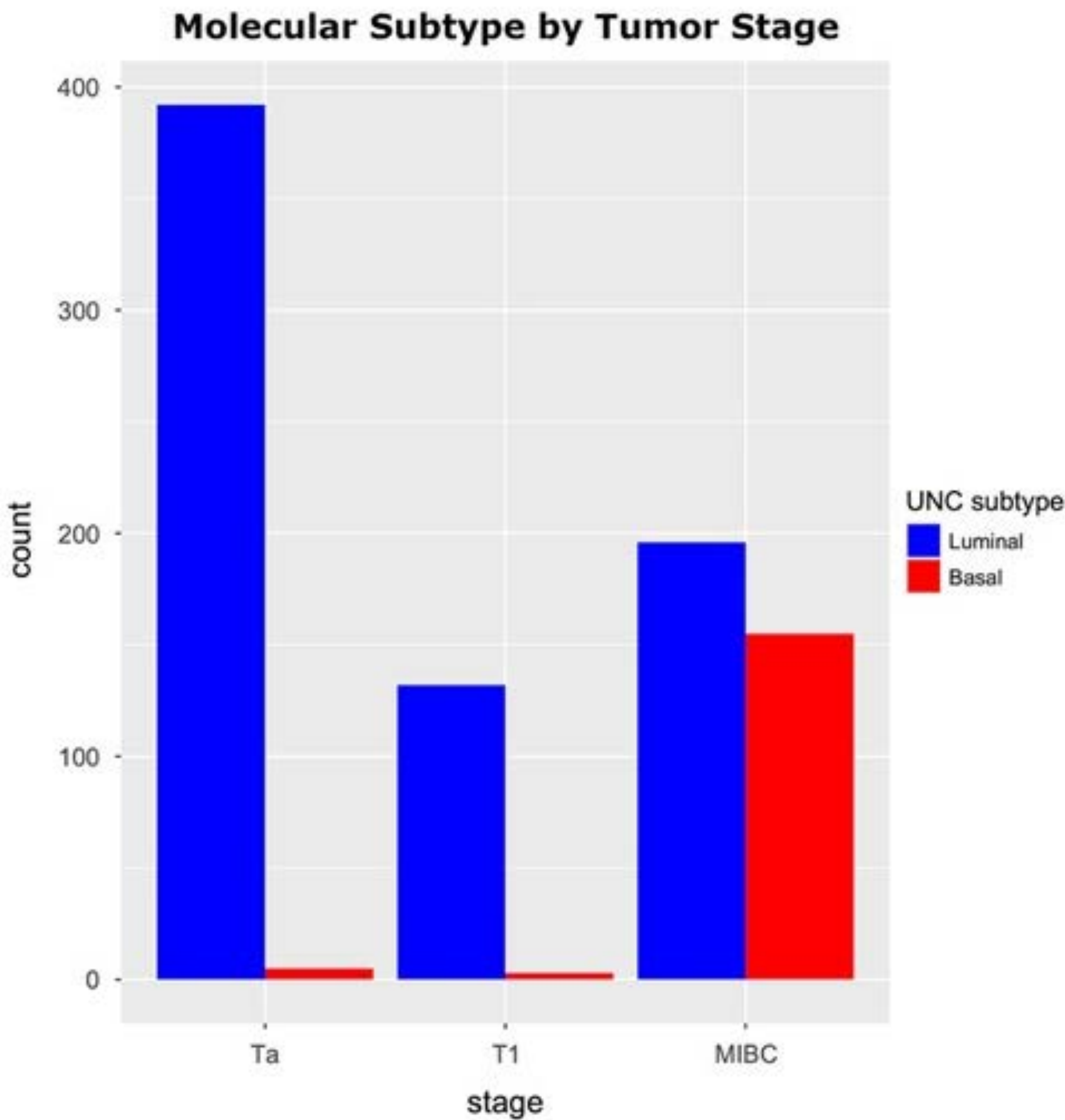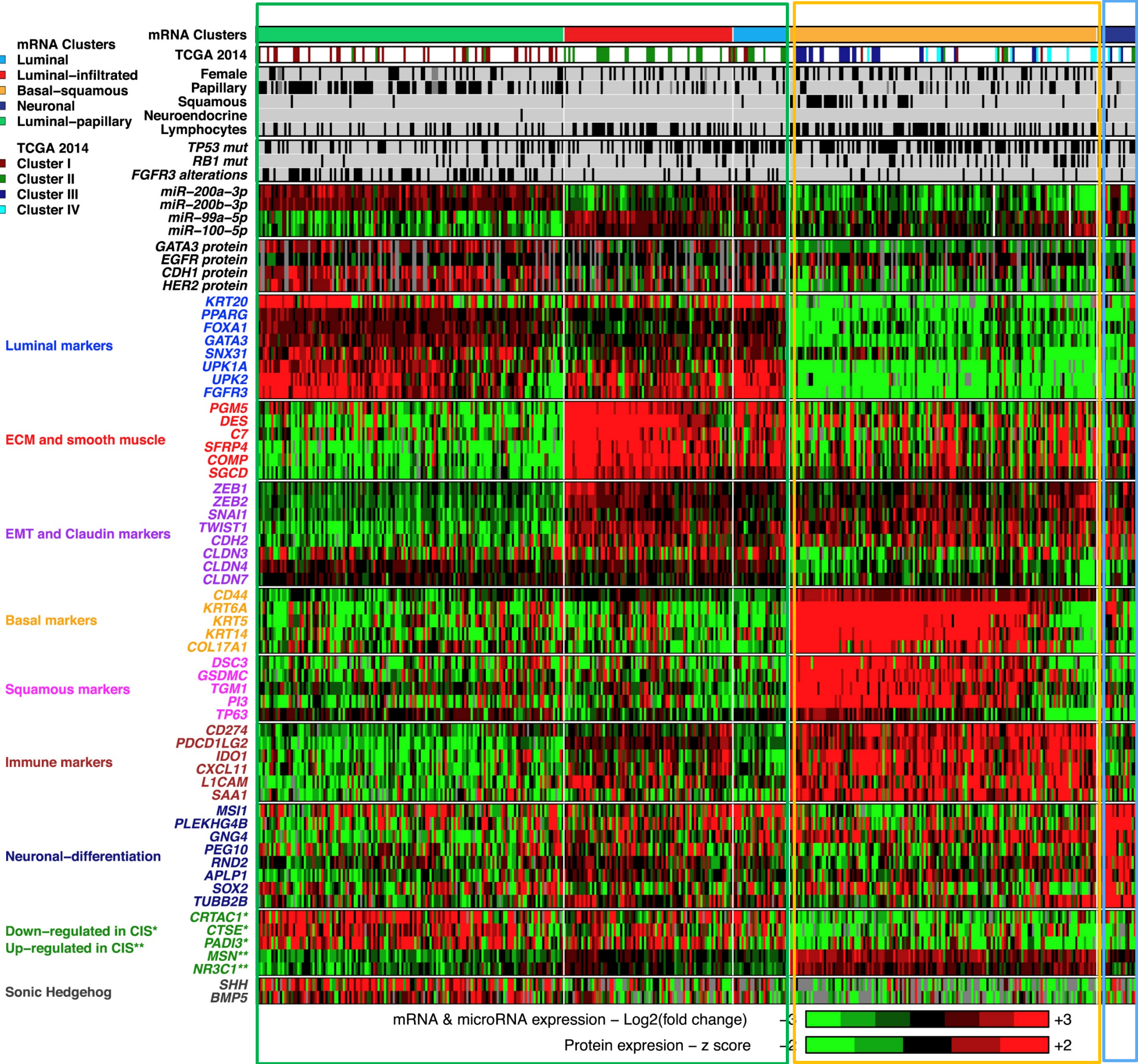
Warrick et al. Am J Surg Pathol 2024

Bladder cancer subtypes
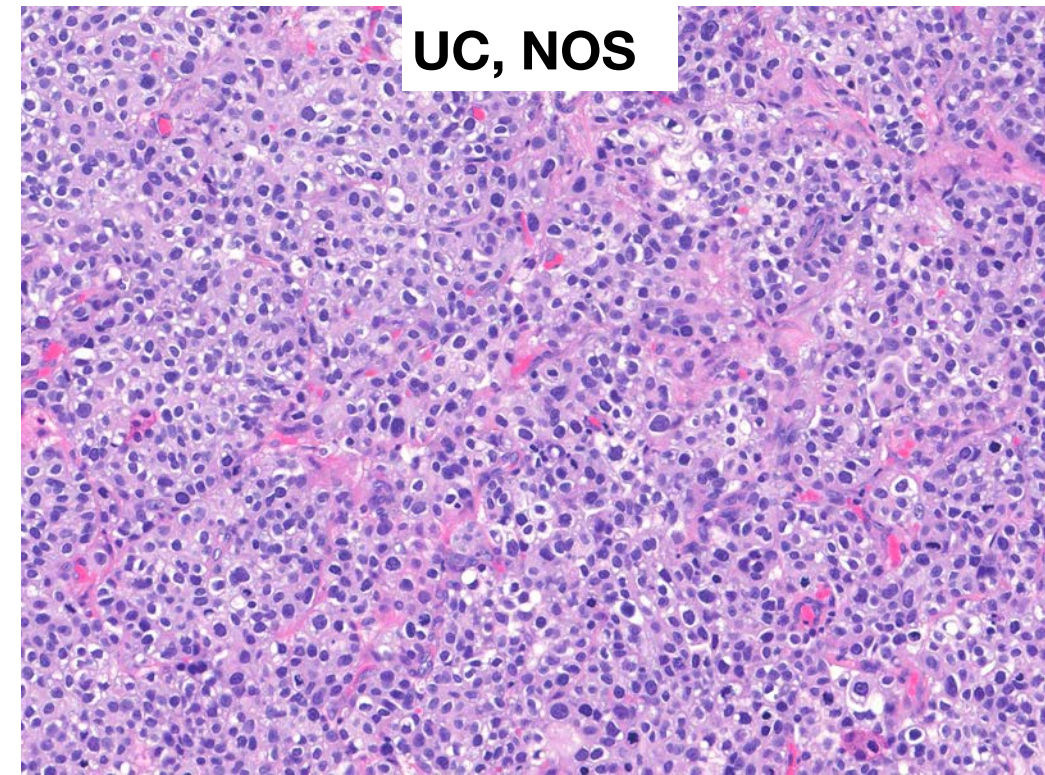
UC, NOS
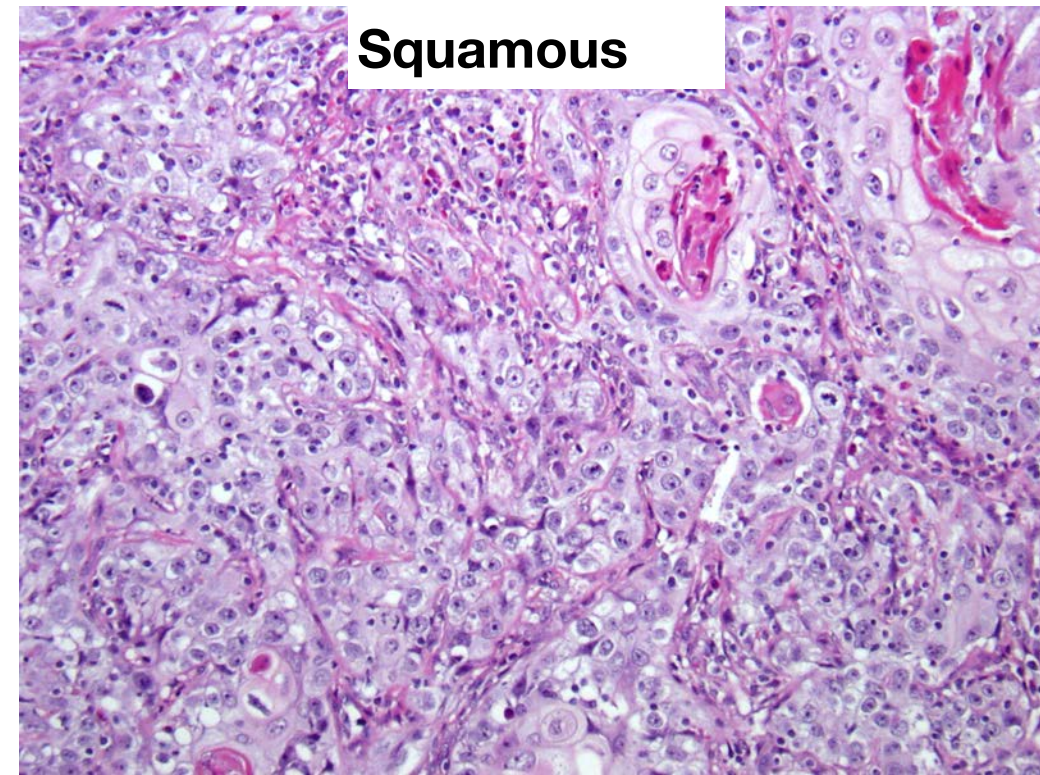
Squamous
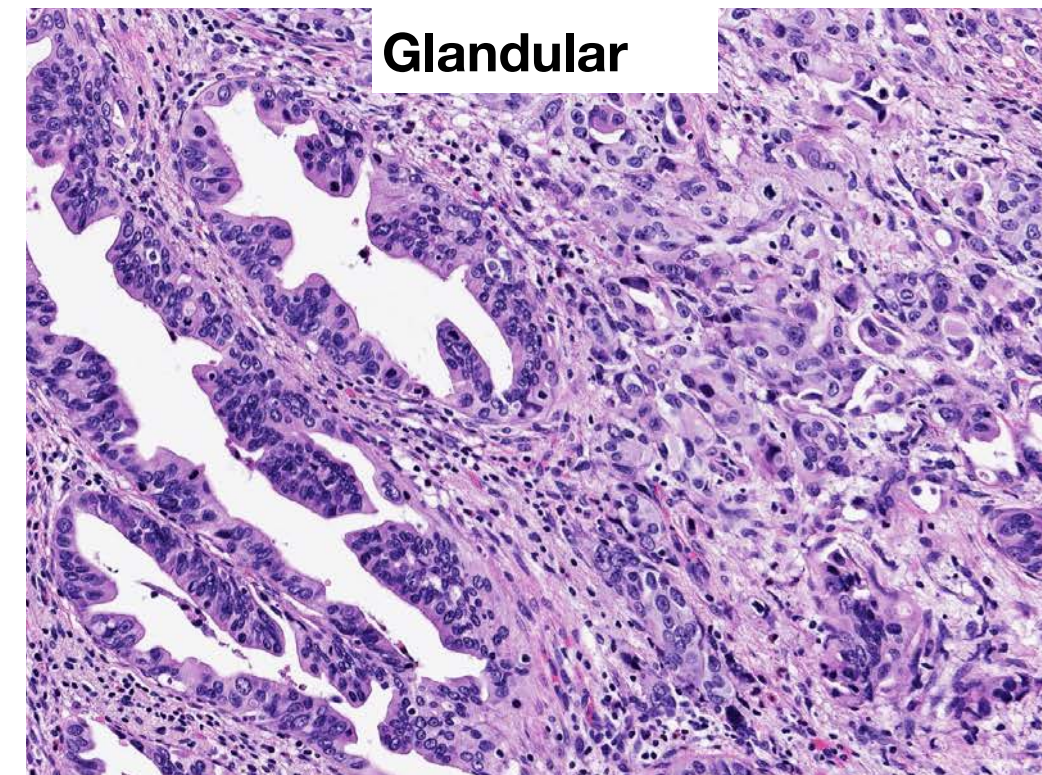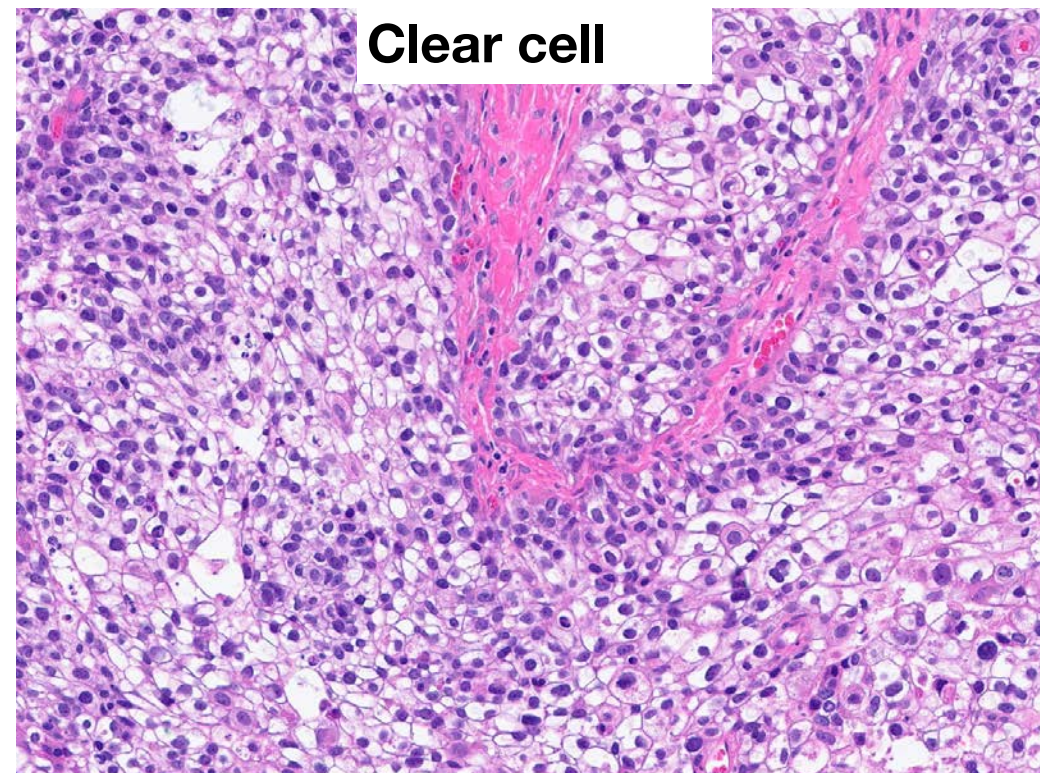
Glandular
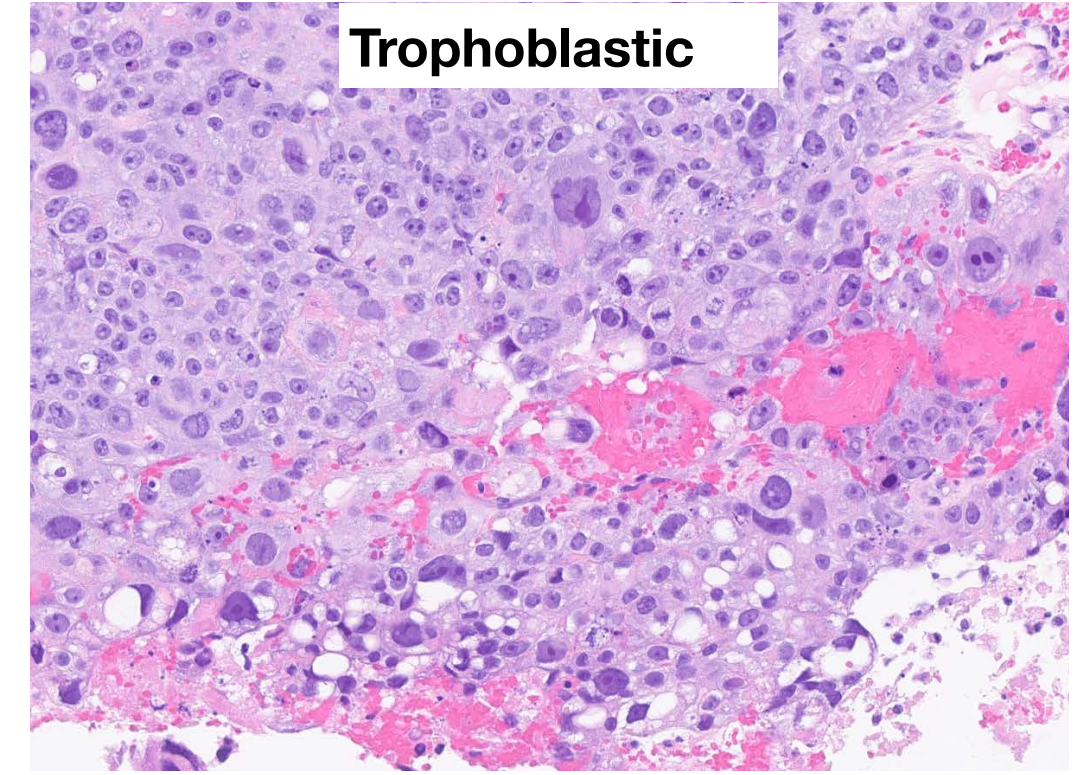
Trophoblastic
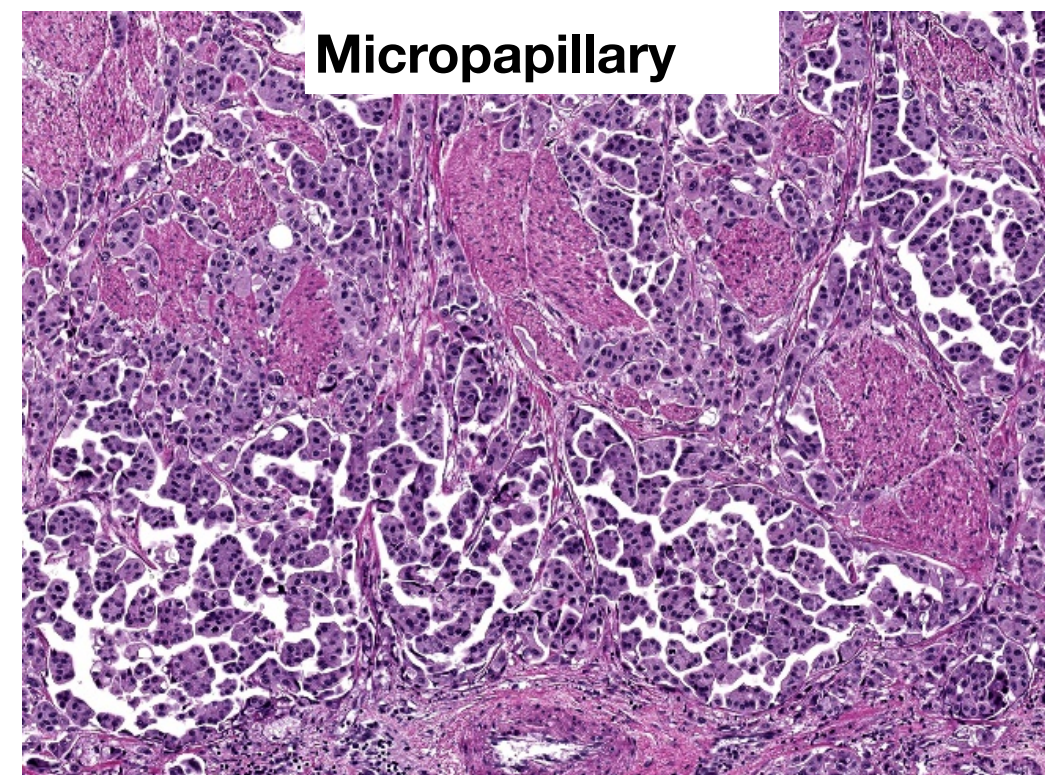
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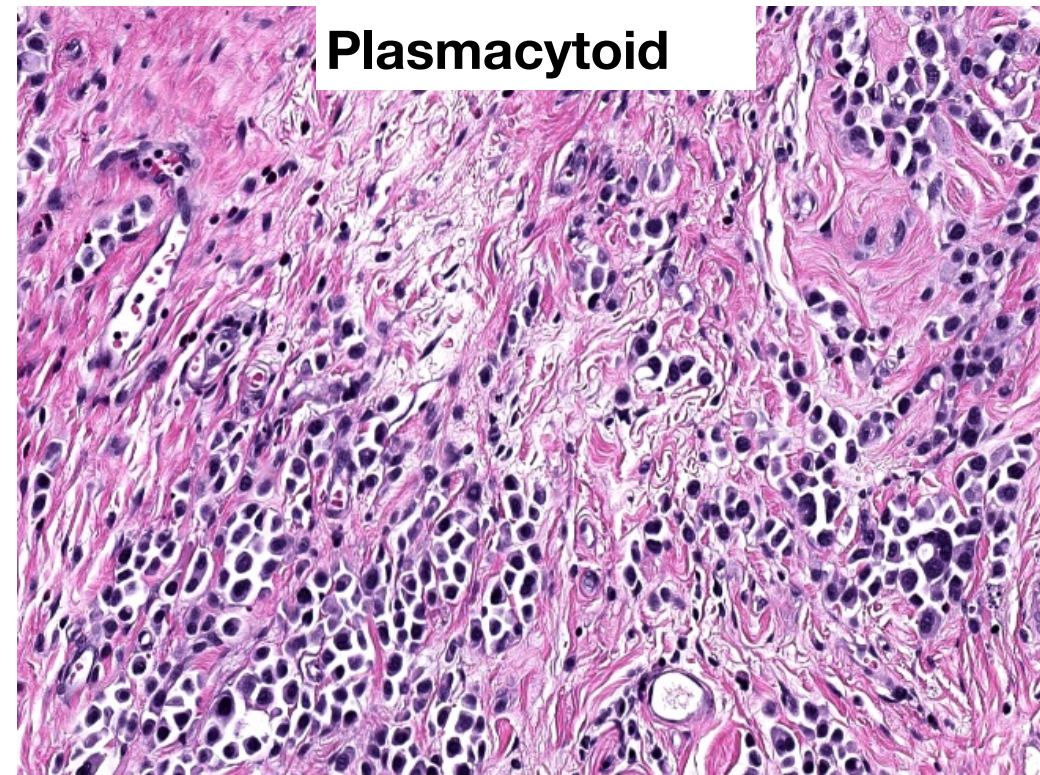
Plasmacytoid
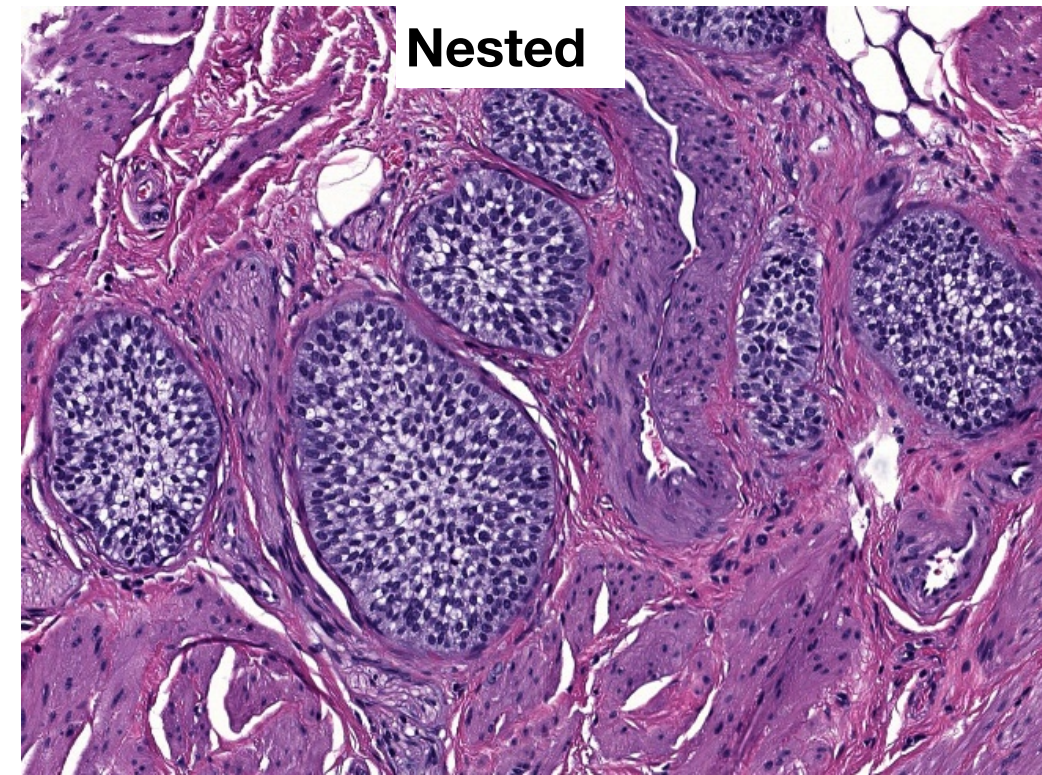
Nested
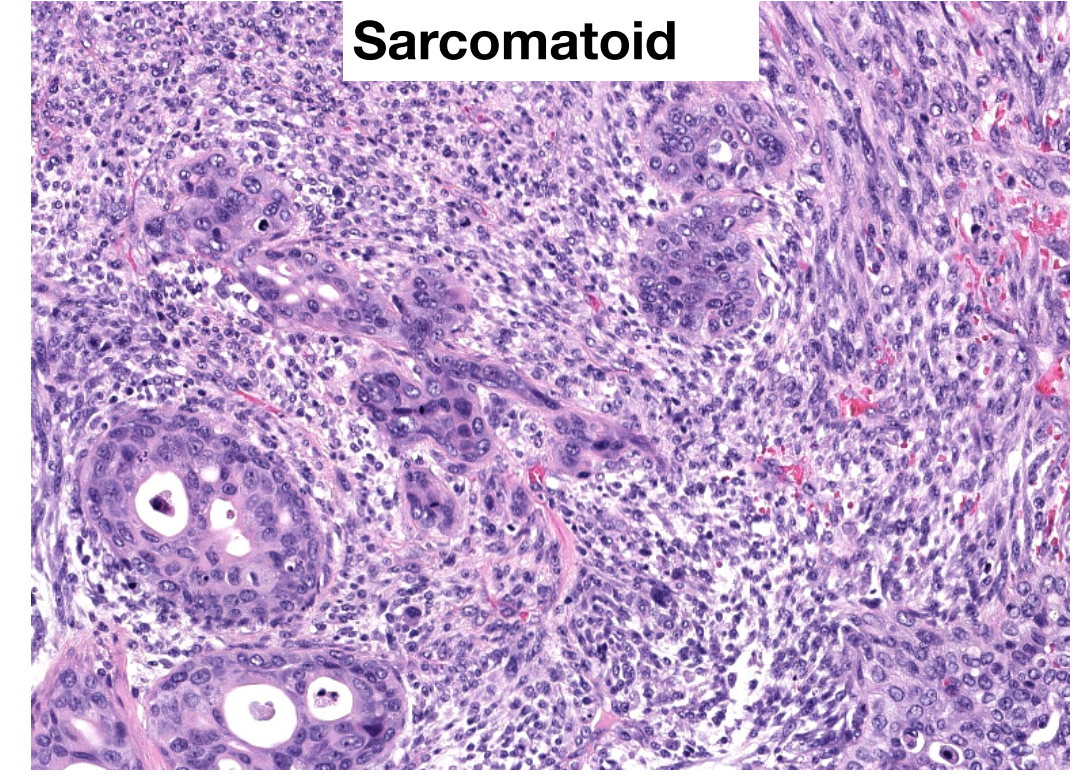
Sarcomatoid
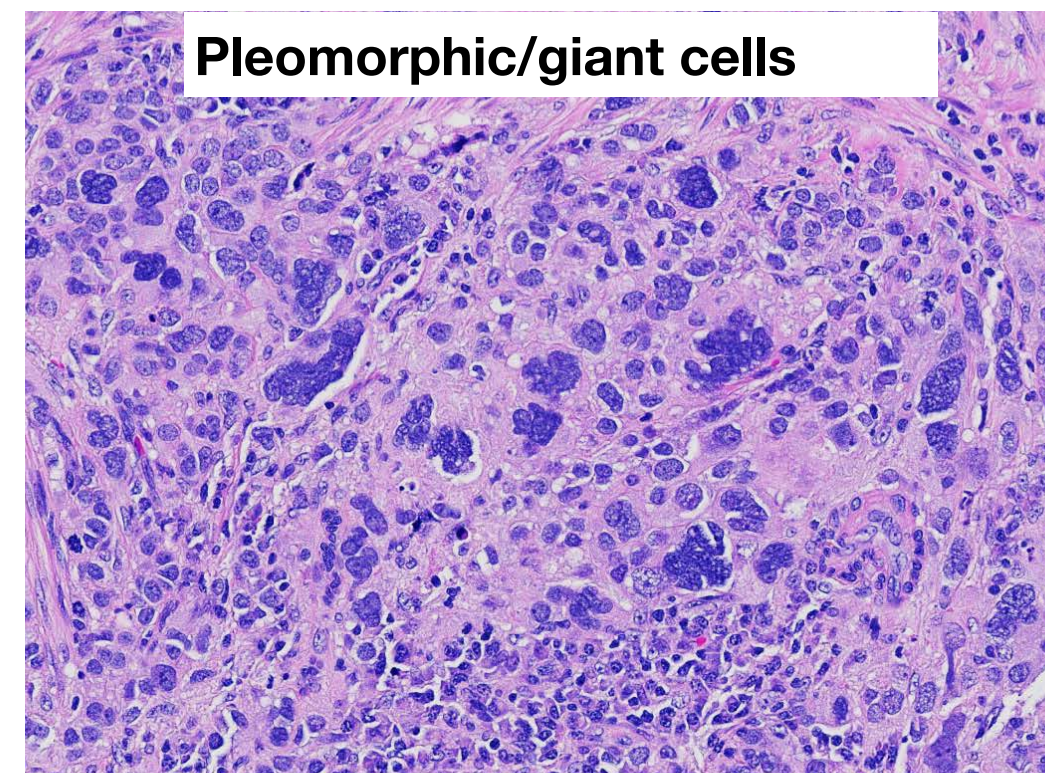
Pleomorphic/giant cells
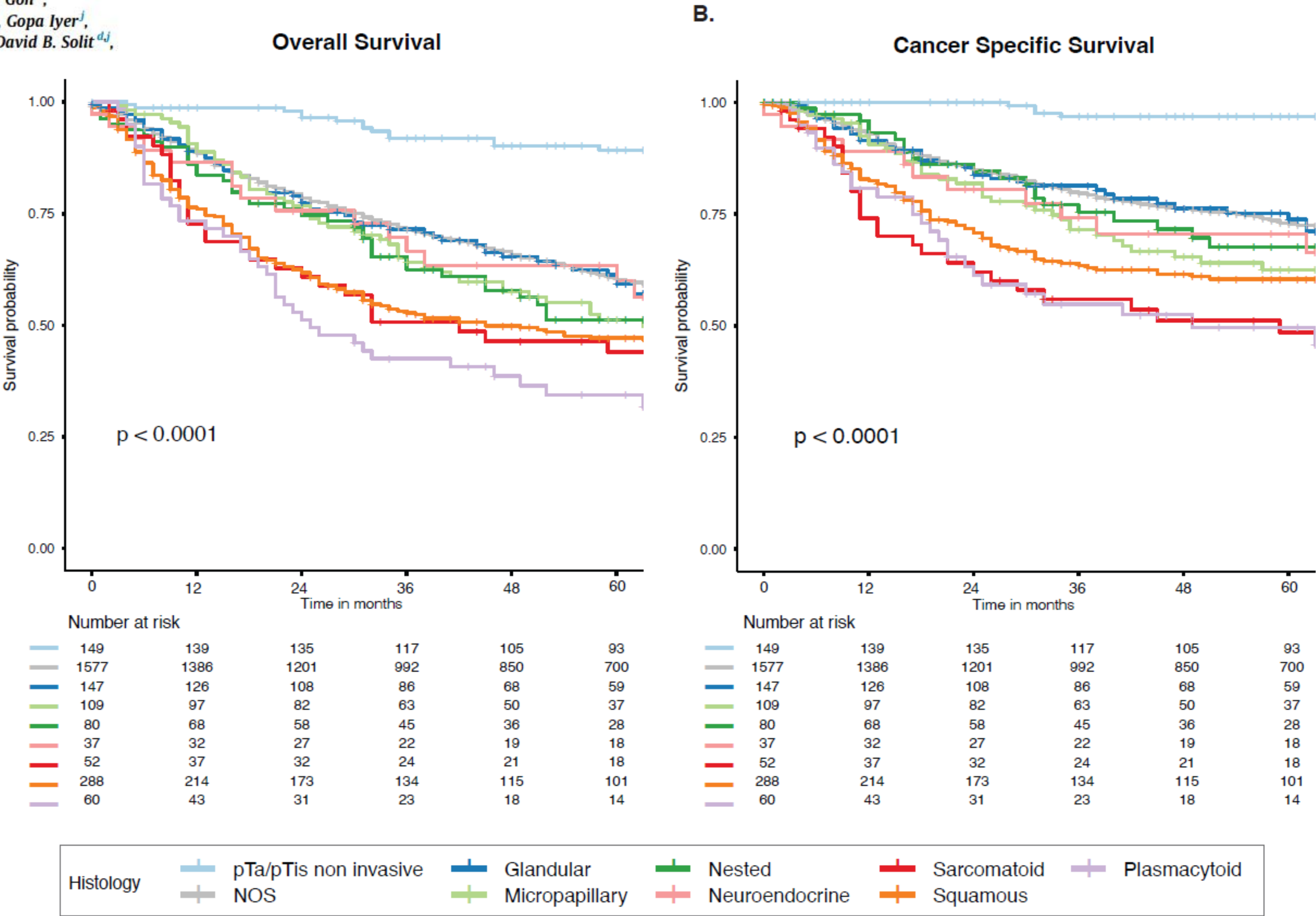
Clear cell
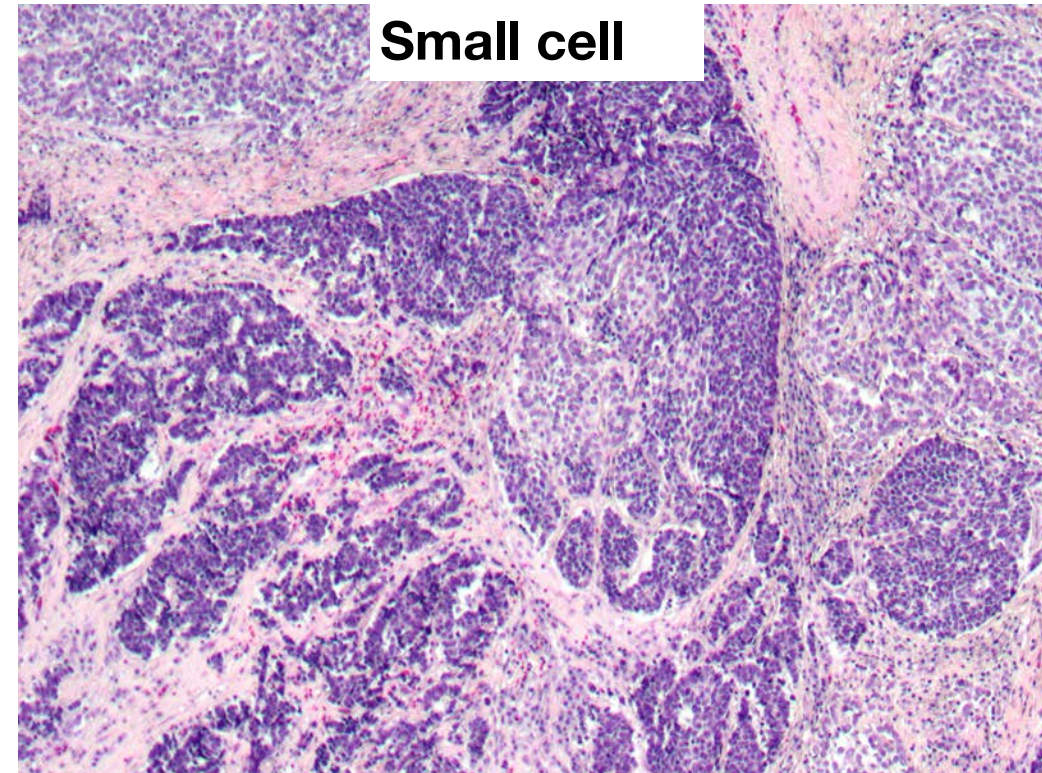
Small cell

Adenocarcinoma

Hikmat Al-Ahamadie (MSK)
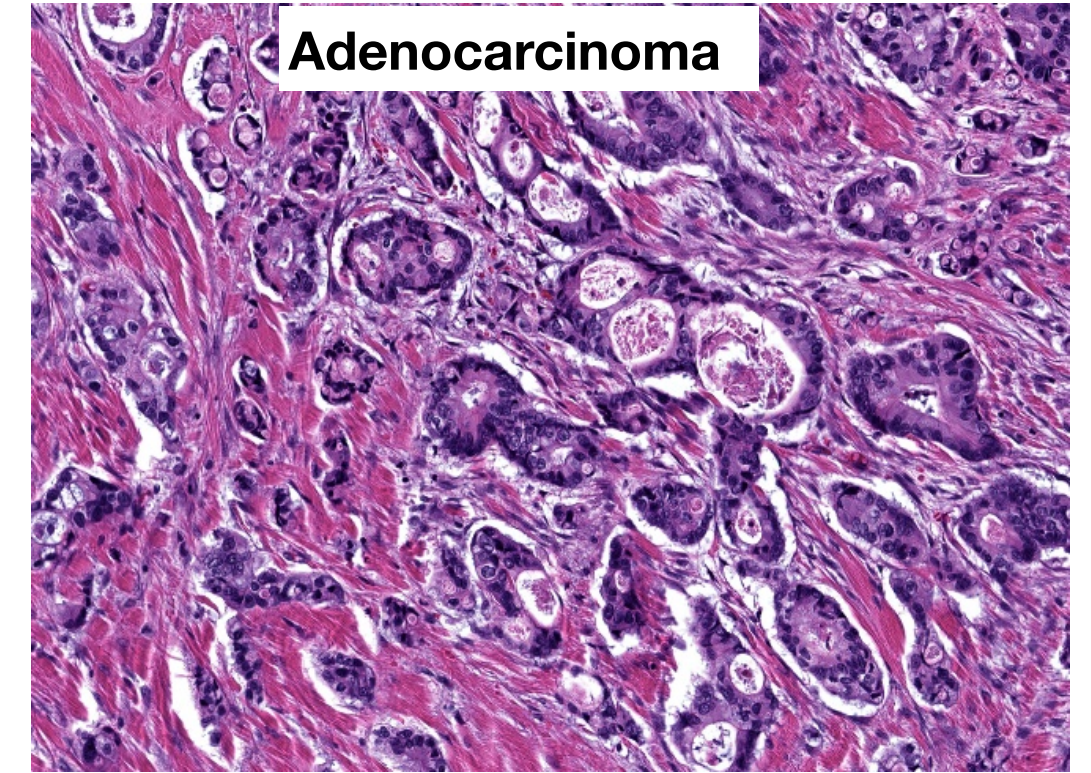
Clinical Outcomes, Genomic Heterogeneity, and Therapeutic Considerations Across Histologic Subtypes of Urothelial Carcinoma

Carissa E. Chu [a,b], Ziyu Chen [c,d], Karissa Whiting [e], Irina Ostrovnaya [e], Andrew T. Lenis [f],
Timothy N. Clinton [g], Rayan Rammal [h], Gamze Gokturk Ozcan [h], Dilara Akbulut [i], Merve Basar [h],
Jie-Fu Chen [h], Ying-Bei Chen [h], Anuradha Gopalan [h], Samson W. Fine [h], Satish K. Tickoo [h],
Maria Arcila [h], A. Rose Brannon [h], Michael F. Berger [d,h], Eugene K. Cha [b], Alvin C. Goh [b],
Timothy F. Donahue [b], Dean F. Bajorin [j], Min Yuen Teo [j], Jonathan E. Rosenberg [j], Gopa Iyer [j],
Eugene J. Pietzak [b], Bernard H. Bochner [b], Victor E. Reuter [h], Judy Sarungbam [h], David B. Solit [d,j],
Hikmat Al-Ahmadie [h,*]

Treating bladder cancer by stage

Cansu Yol.

BCG is the Original Cancer Immunotherapy

THE JOURNAL OF UROLOGY
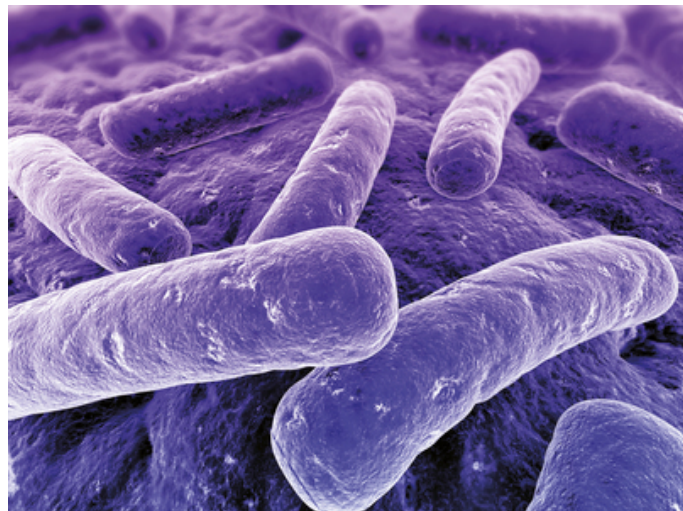Copyright © 1976 by The Williams & Wilkins Co.

Vol. 116, August
Printed in U.S.A.

INTRACAVITARY BACILLUS CALMETTE-GUERIN IN THE TREATMENT OF SUPERFICIAL BLADDER TUMORS

A. MORALES,* D. EIDINGER AND A. W. BRUCE

From the Departments of Urology, and Microbiology and Immunology, Queen's University, Kingston, Ontario, Canada

SWOG 8216
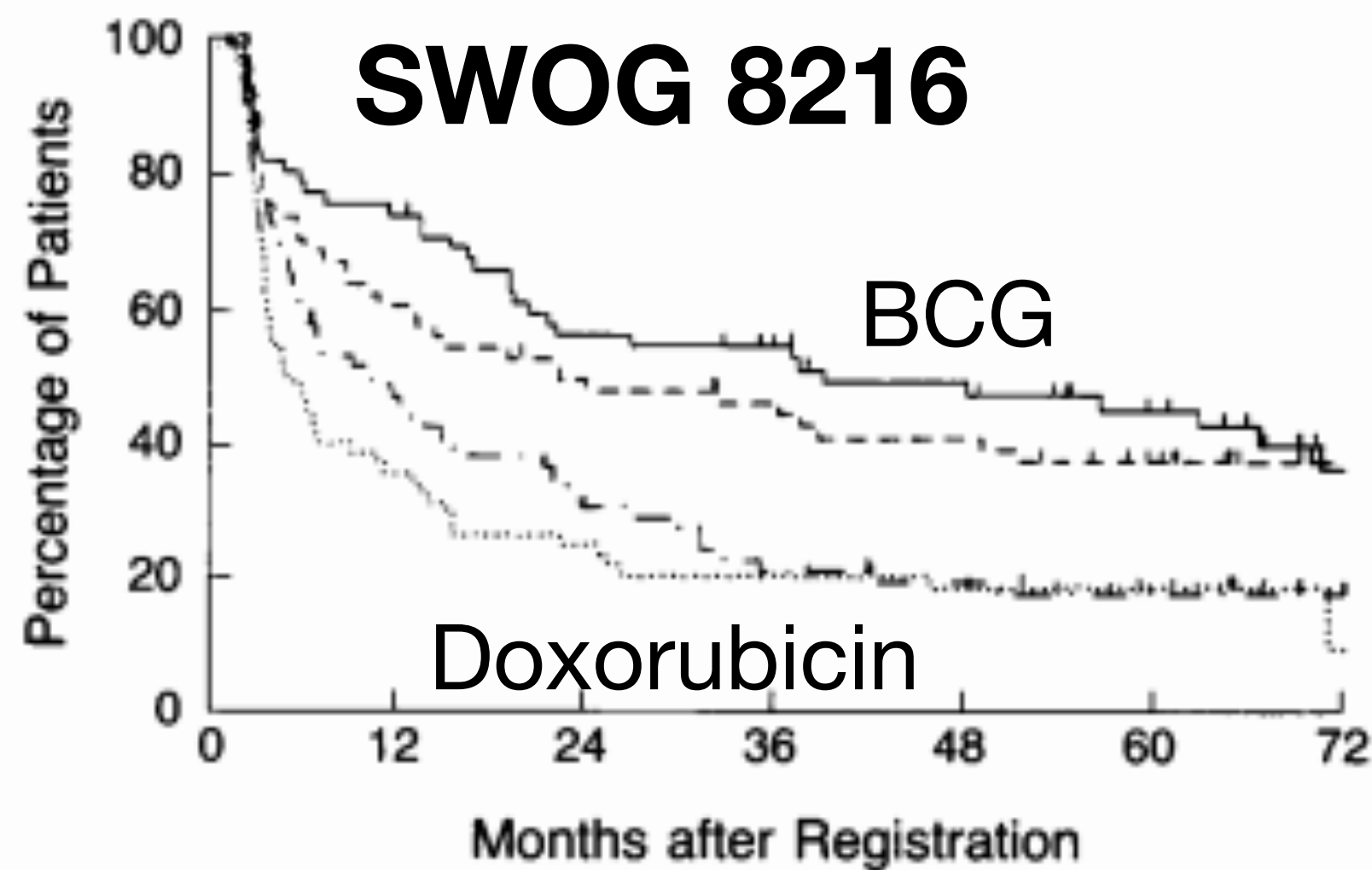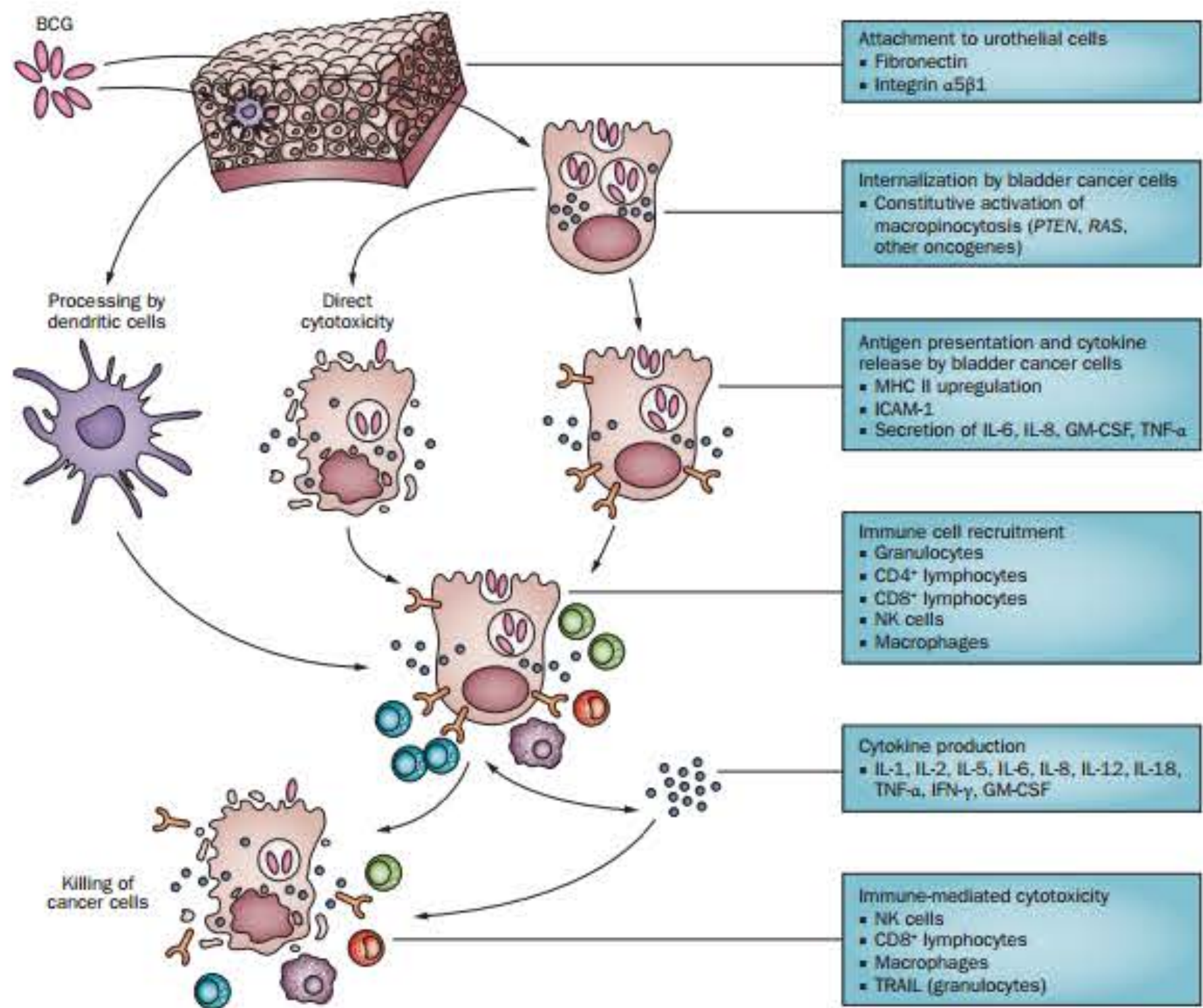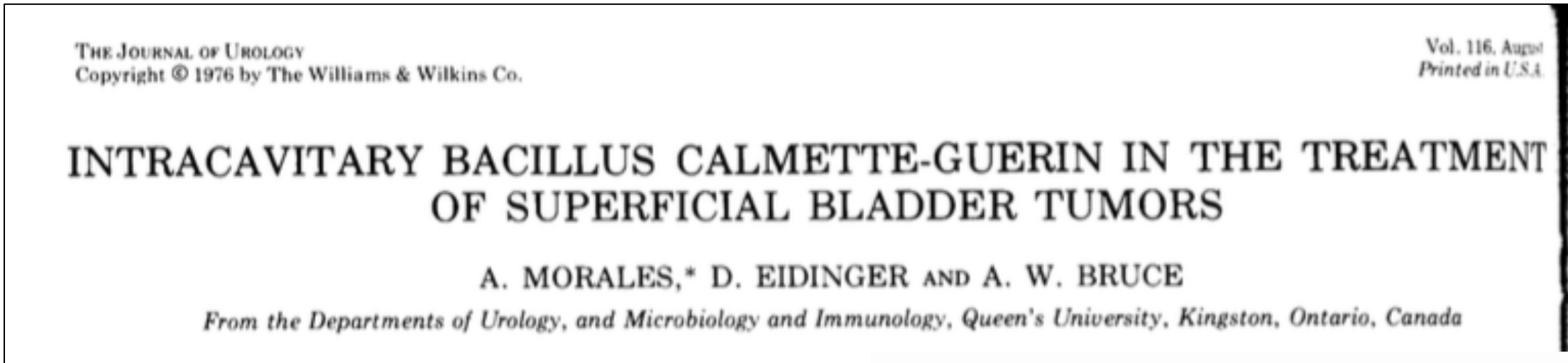
Figure 1. Kaplan–Meier Plots of the Time to Treatment Failure for Patients with Carcinoma in Situ Treated with BCG (Solid Line) or Doxorubicin (Dotted Line) and for Patients with Stage Ta and T1 Transitional-Cell Carcinoma Treated with BCG (Dashed Line) or Doxorubicin (Dotted-and-Dashed Line).

The apparent flattening of the curves for patients treated with BCG at a level well above that of the curves for patients treated with doxorubicin suggests that the benefits of BCG immunotherapy are long-lasting.

Lamm NEJM 1991

Redelman-Sidi, Glickman, Bochner, Nature Reviews Urology 2014

Treating bladder cancer by stage

MIBC

HG
NMIBC

LG
NMIBC

T2 13.19% (12)

HG T1 32.97% (30)

LG T1 6.59% (6)

Tis 1.10% (1)

HG Ta 17.58% (16)

LG Ta 28.57% (26)

Pathology

Radical cystectomy 6.59% (6)

NAC 10.99% (10)

Pembro/BCG (trial) 9.89% (9)

BCG 18.68% (17)

BCG (BRIDGE) 3.30% (3)

Gem/Doce (BRIDGE) 4.40% (4)

Intravesical therapy 15.38% (14)

Observation 26.37% (24)

Other 3.30% (3)

Initial treatment

Cansu Yol.
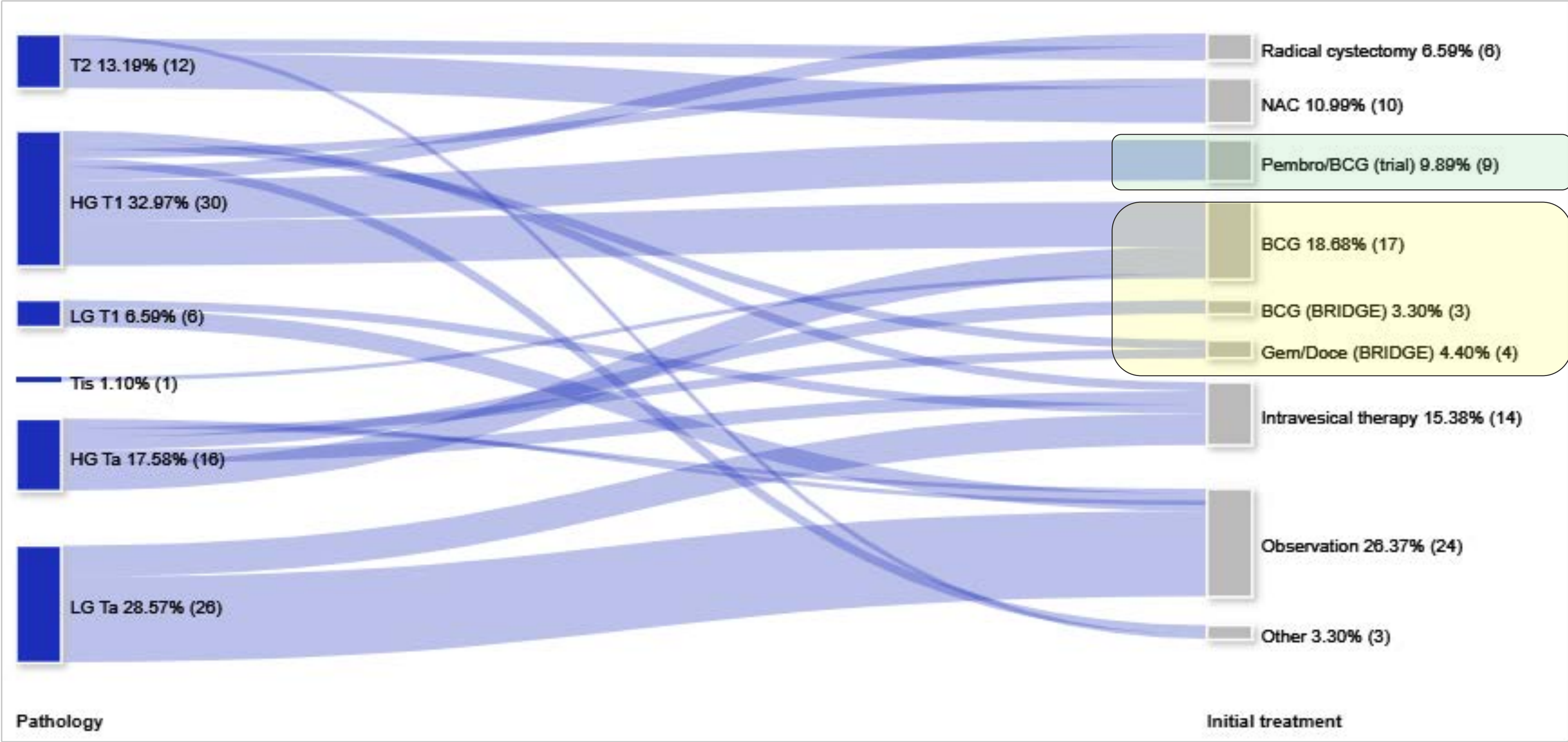
Antibody Drug Conjugates (ADCs) emerge as a new standard of care for bladder cancer

ESTABLISHED IN 1812   MARCH 7, 2024   VOL. 390   NO. 10

Enfortumab Vedotin and Pembrolizumab in Untreated Advanced Urothelial Cancer

T. Powles, B.P. Valderrama, S. Gupta, J. Bedke, E. Kikuchi, J. Hoffman-Censits, G. Iyer, C. Vulsteke, S.H. Park, S.J. Shin, D. Castellano, G. Fornarini, J.-R. Li, M. Gümüş, N. Mar, Y. Loriot, A. Fléchon, I. Duran, A. Drakaki, S. Narayanan, X. Yu, S. Gorla, B. Homet Moreno, and M.S. van der Heijden, for the EV-302 Trial Investigators*

Progression-free Survival

	No. of Events/ No. of Patients	Median Progression-free Survival (95% CI)
		mo
Enfortumab Vedotin–Pembrolizumab	223/442	12.5 (10.4–16.6)
Chemotherapy	307/444	6.3 (6.2–6.5)

Hazard ratio, 0.45 (95% CI, 0.38–0.54)
Two-sided P<0.001

No. at Risk

Enfortumab vedotin–pembrolizumab	442	409	361	303	253	204	167	132	102	73	45	33	17	6	3	1
Chemotherapy	444	380	297	213	124	78	56	41	30	19	8	6	5	3	2	1	1
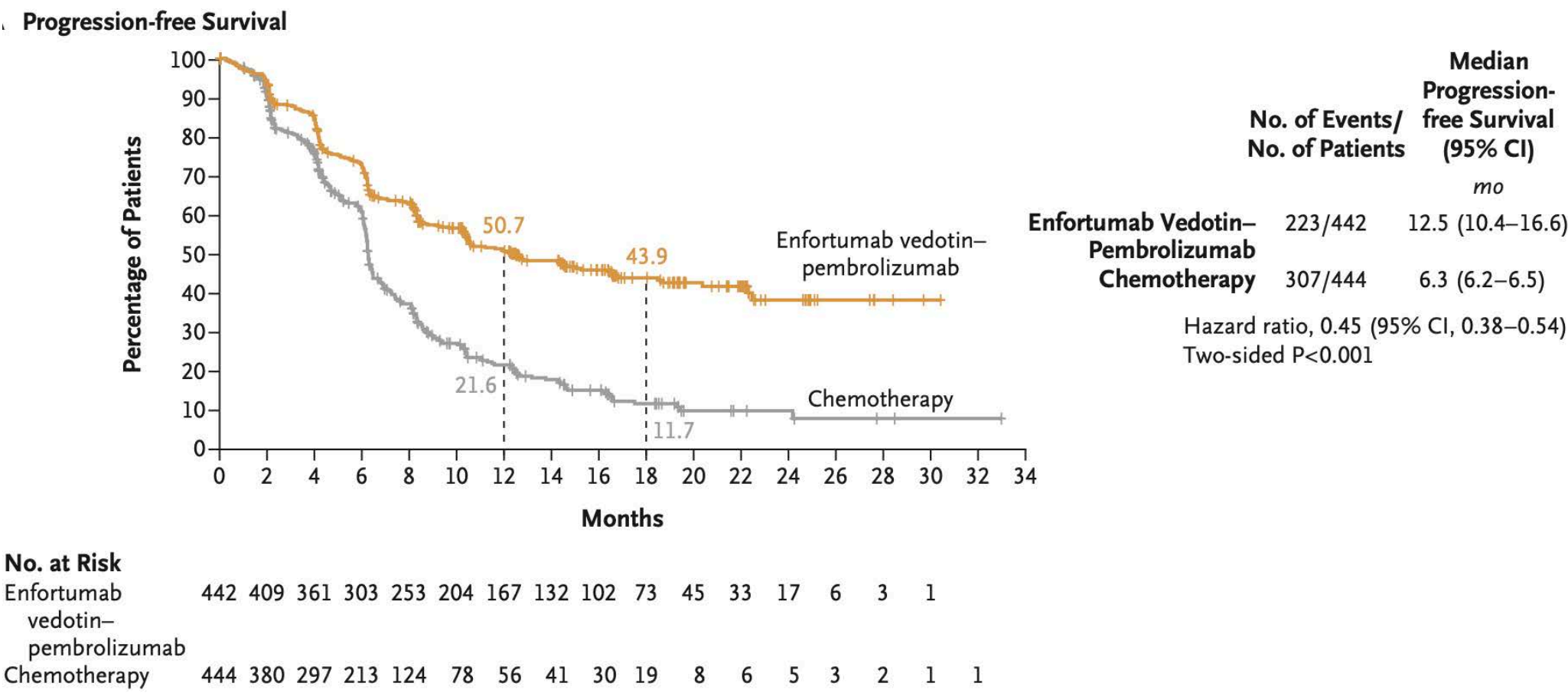
ORIGINAL ARTICLE

Disitamab Vedotin plus Toripalimab in HER2-Expressing Advanced Urothelial Cancer

X. Sheng,[1] G. Zeng,[2] C. Zhang,[3] Q. Zhang,[4] J. Bian,[5] H. Niu,[6] J. Li,[7] Y. Shi,[8] K. Yao,[8] B. Hu,[9] Z. Liu,[10] H. Liao,[11] Z. Yu,[12] B. Jin,[13] P. Zhao,[13] T. Yang,[14] X. Liu,[15] Y. Qin,[16] X. Xue,[17] X. Gou,[18] J. Huang,[19] J. Gu,[20] X. Qi,[21] L. Zhang,[22] G. Ma,[22] B. Liu,[22] J. Fang,[23] S. Jiang,[2] Z. He,[3] A. Zhou,[24] and J. Guo,[1] for the RC48-C016 Trial Investigators*

Progression-free Survival

	No. of Events	Median Progression-free Survival (95% CI)
		mo
DV+T	126	13.1 (11.1–16.7)
Chemotherapy	149	6.5 (5.7–7.4)

Hazard ratio for disease progression or death, 0.36 (95% CI, 0.28–0.46)
P<0.001 by log-rank test
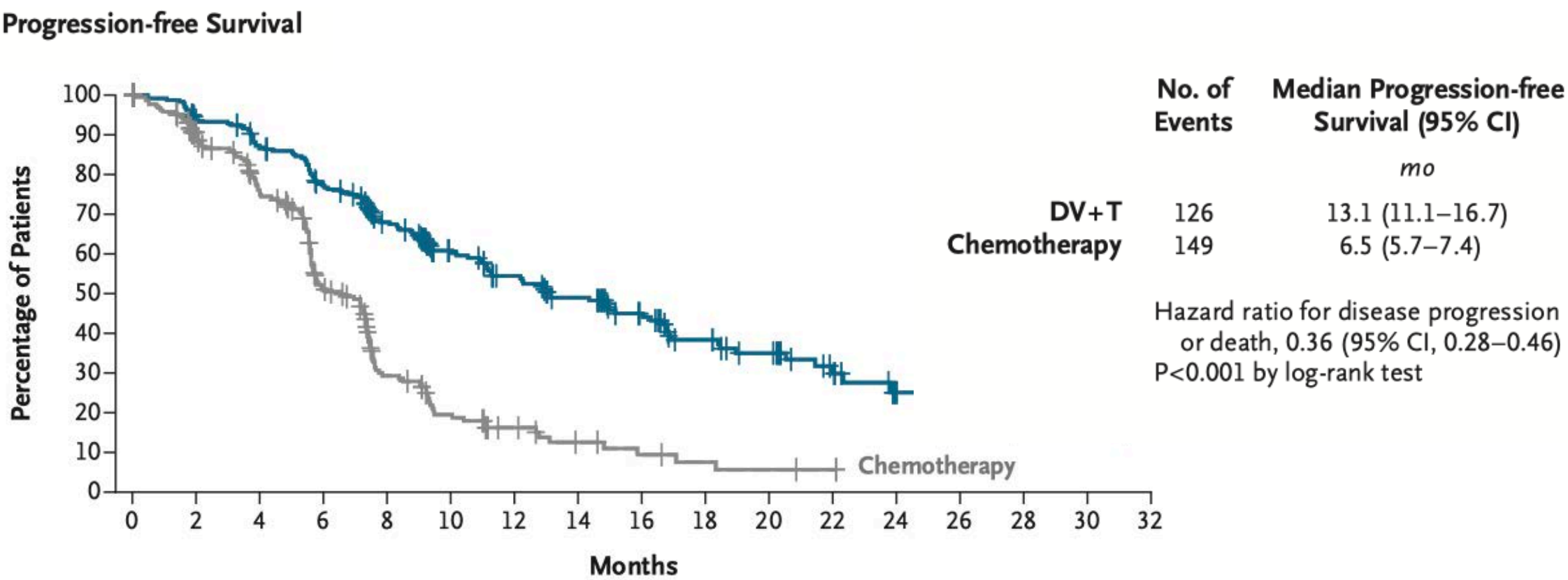
Common genetic alterations in bladder cancer
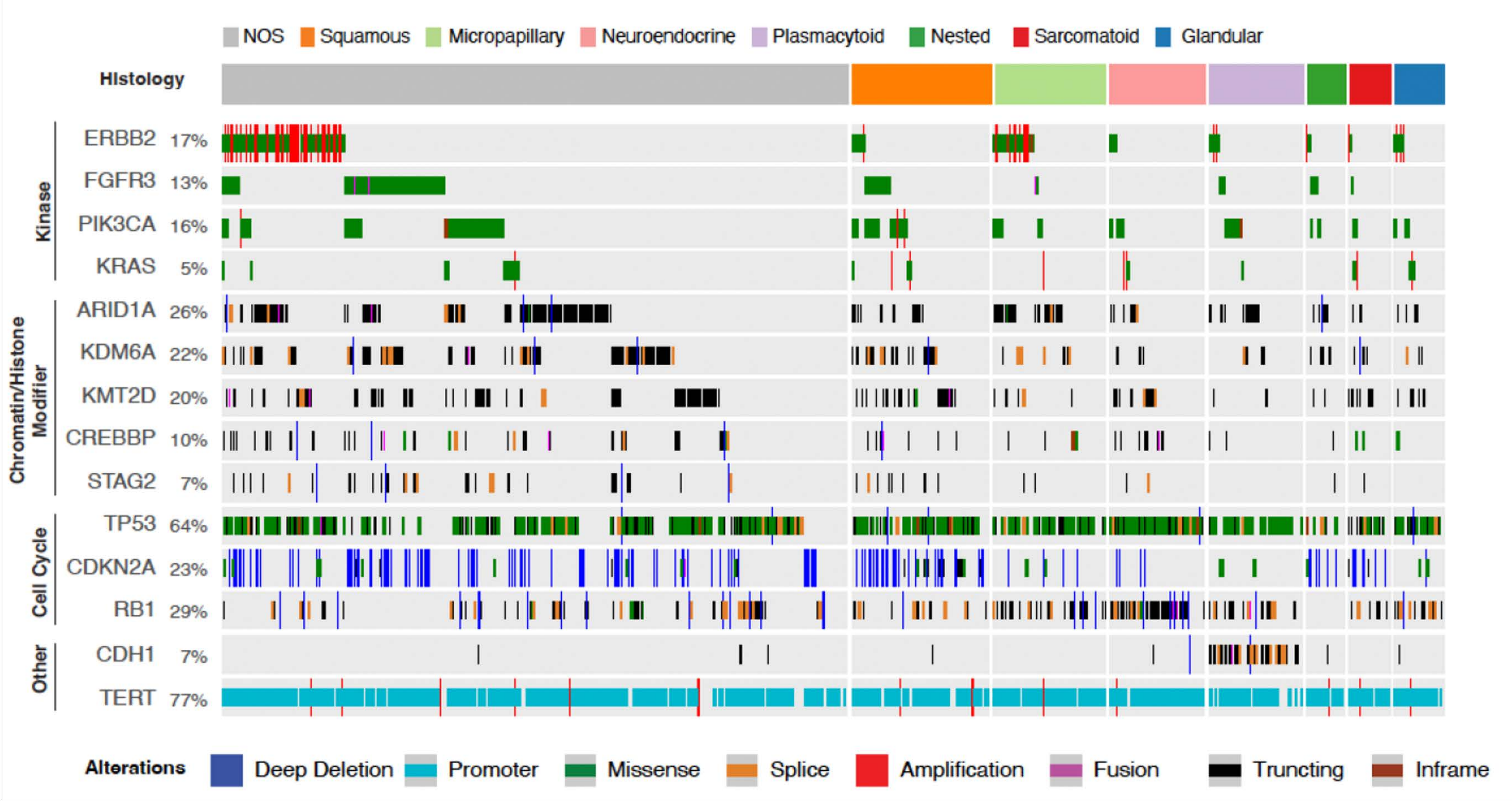
Establishment of patient-derived bladder organoids
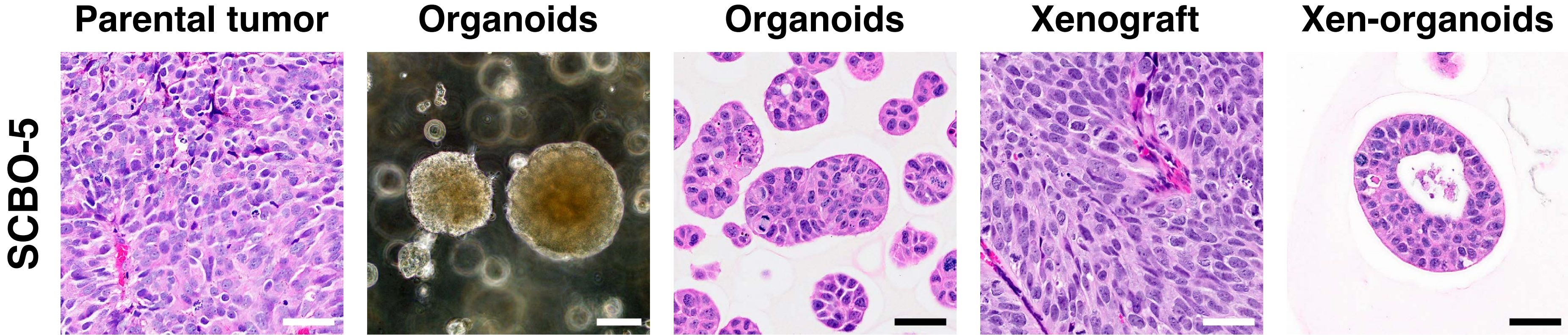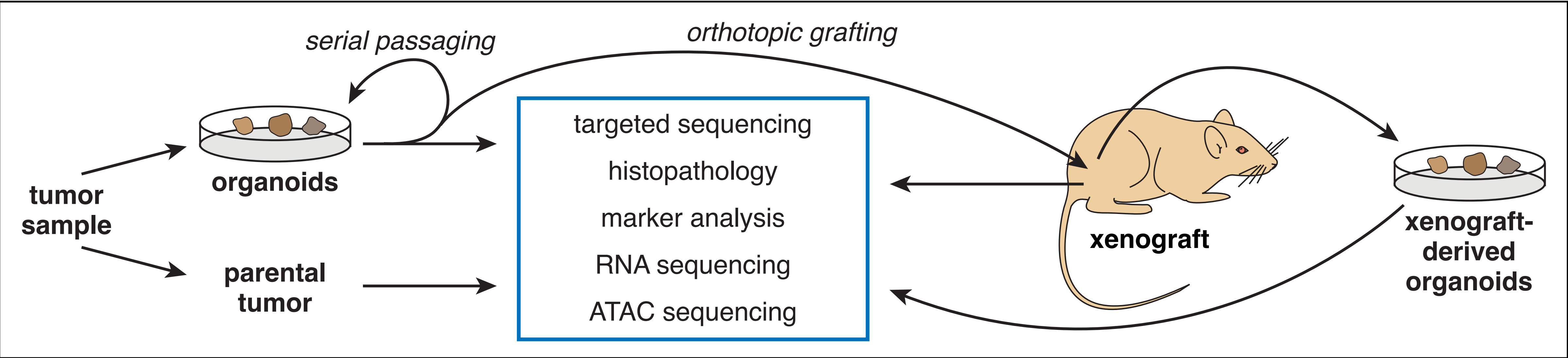
A living urothelial tumor organoid biobank
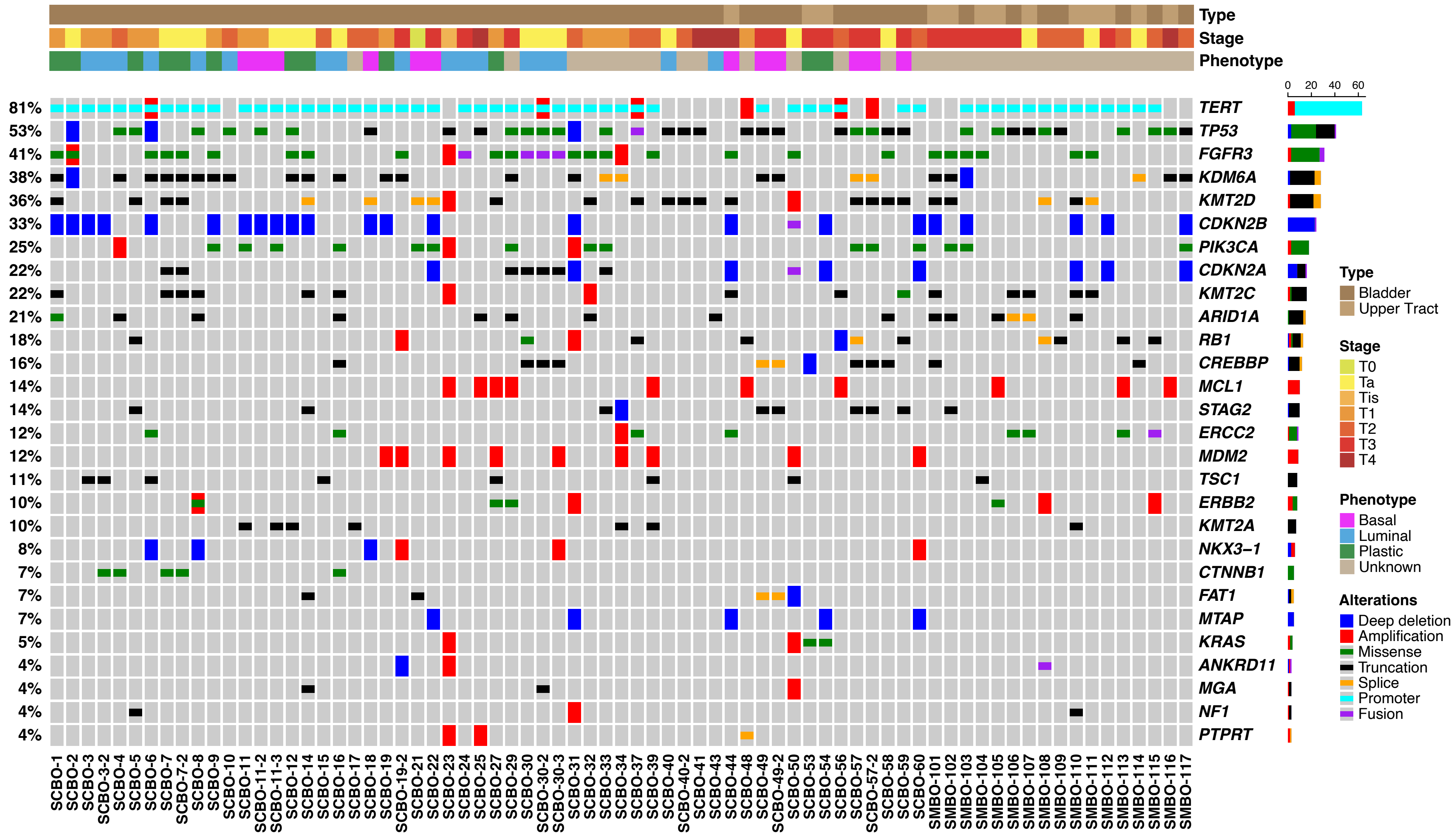
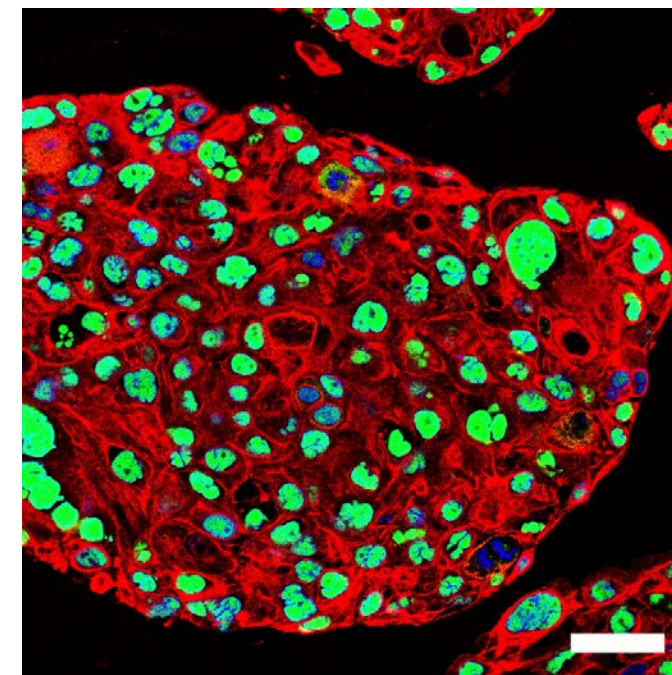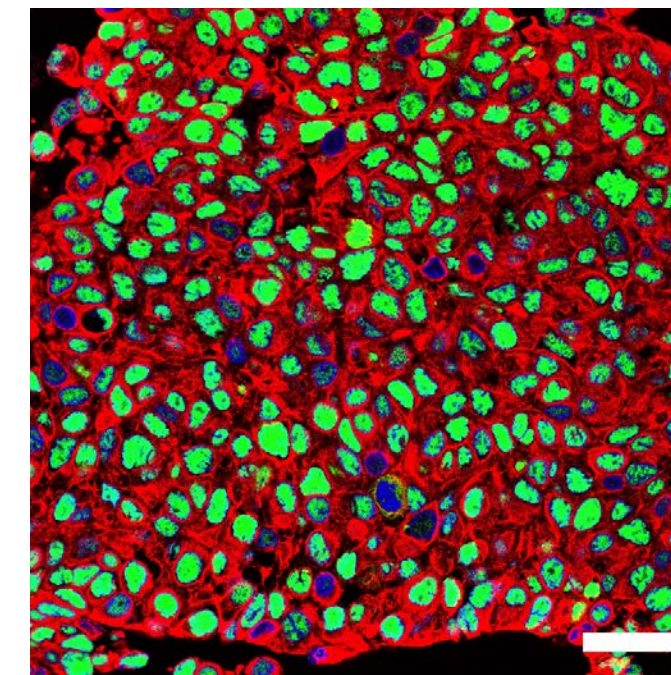# Luminal-basal plasticity in organoids

SCBO-10
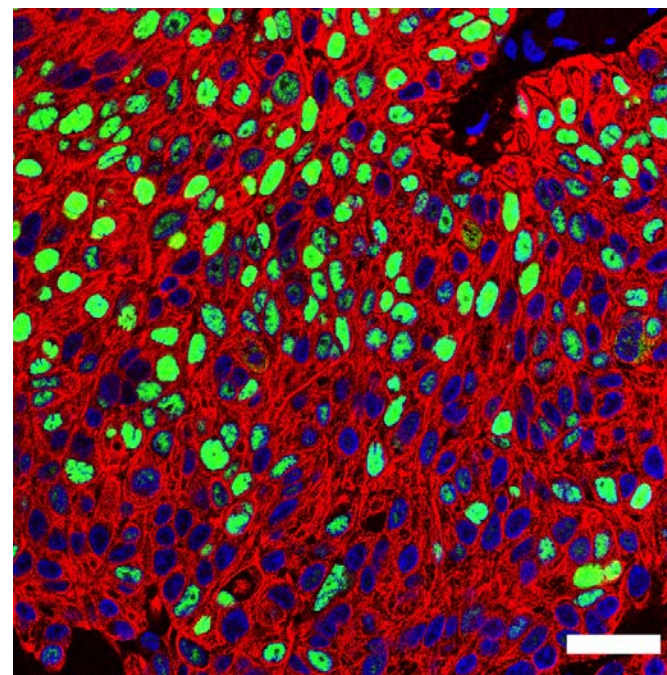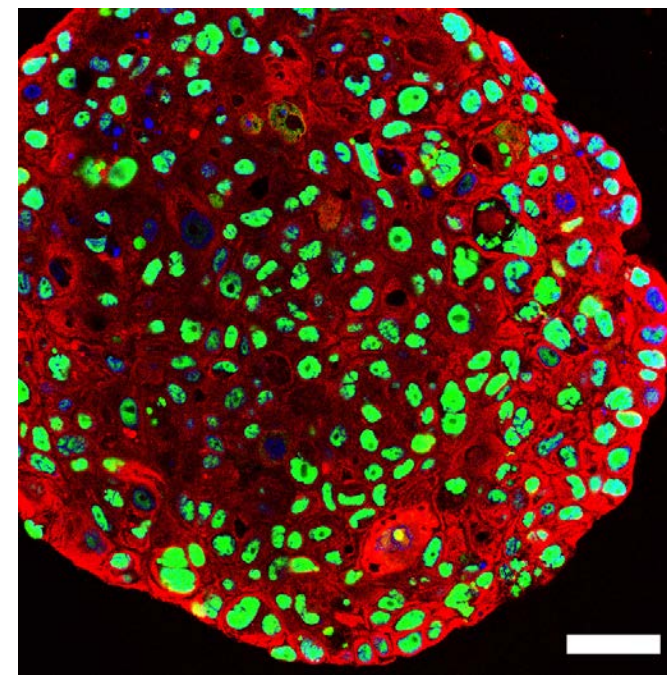
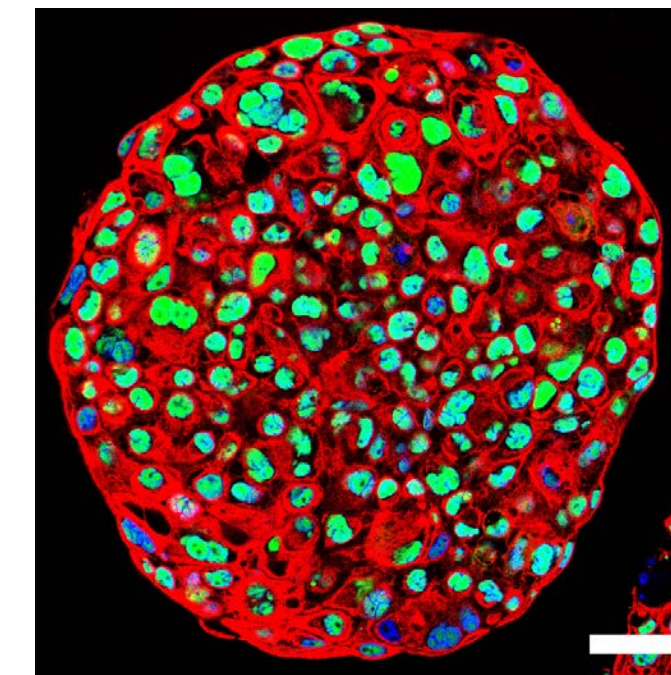| Parental tumor | Organoids P0 | Organoids P5 | Xenograft | Xen-organoids P4 |

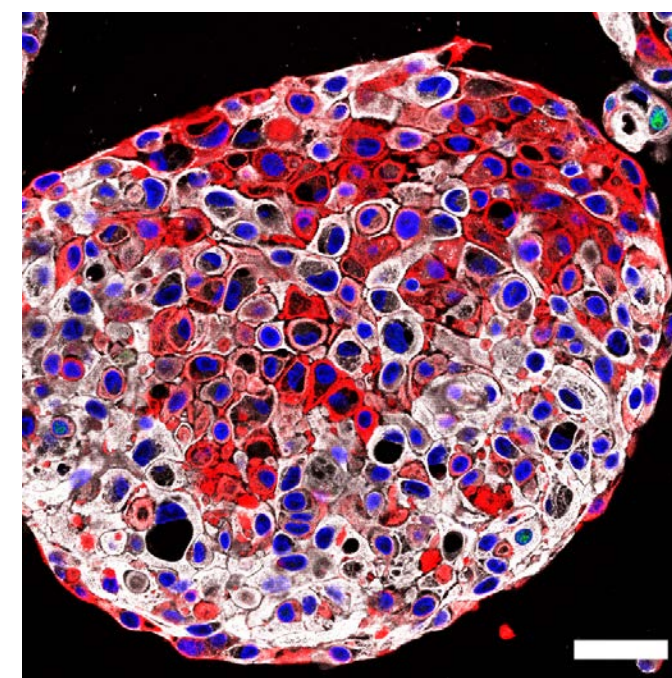p53 CK8 CK5 DAPI
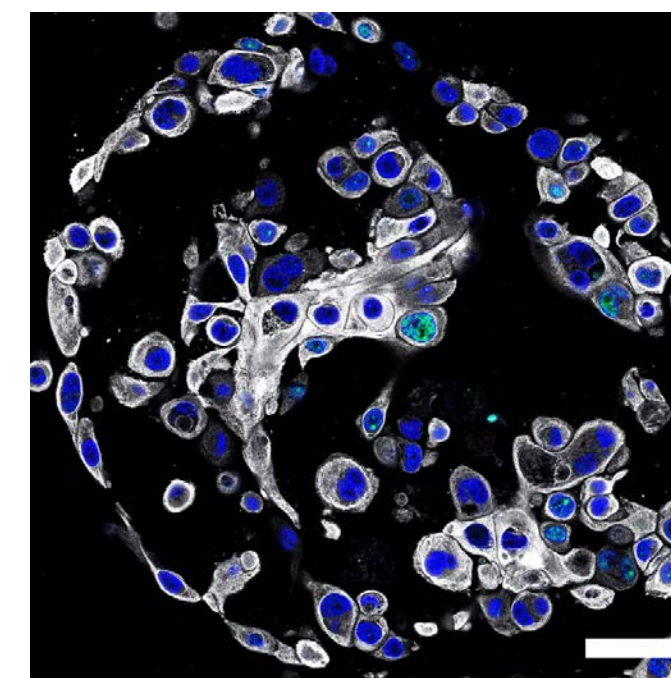
Stable luminal

SCBO-7
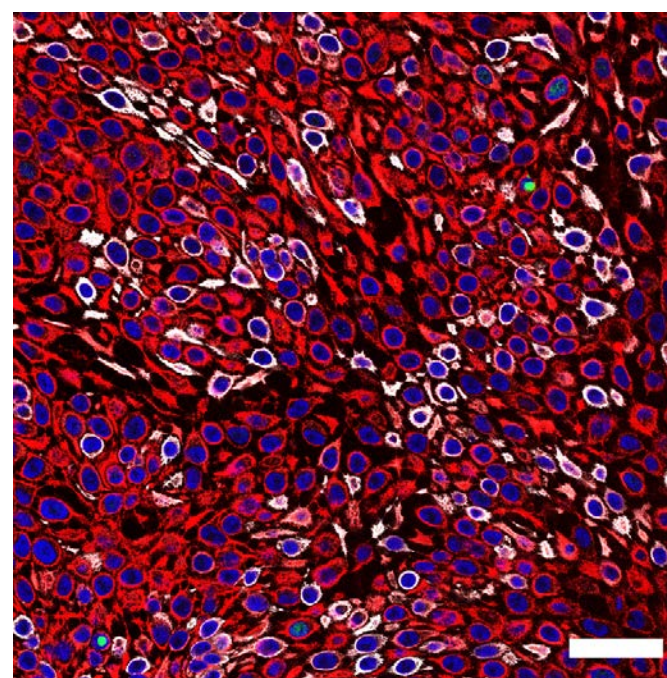
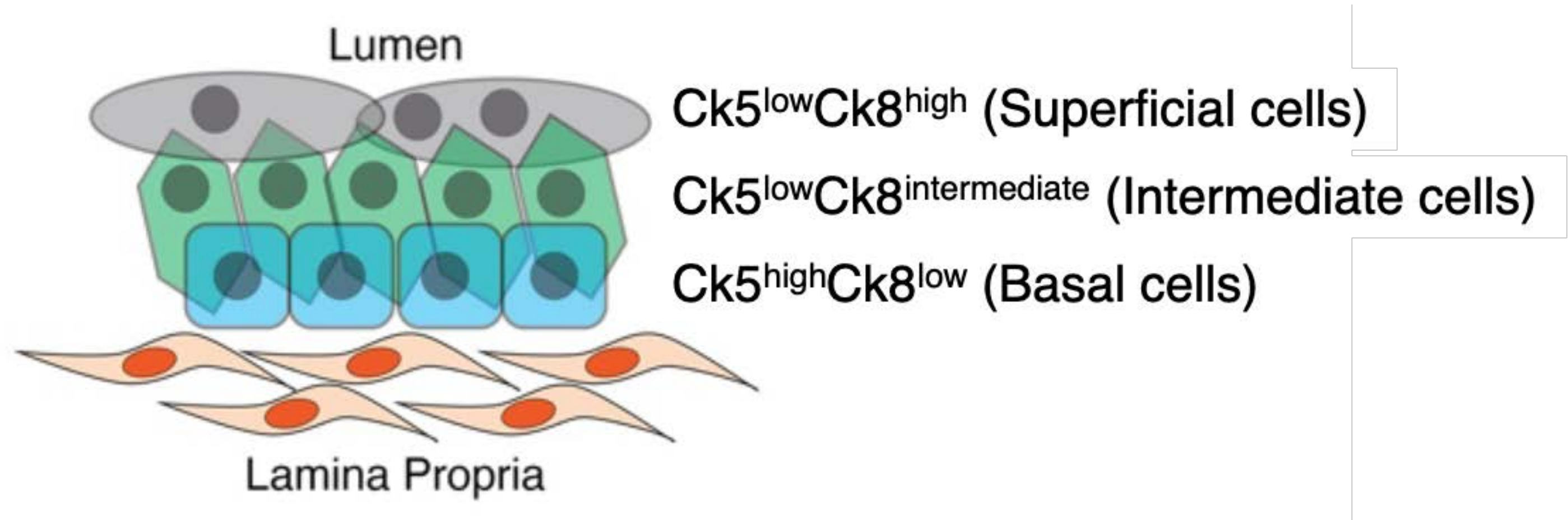| Parental tumor | Organoids P0 d7 | Organoids P0 d21 | Organoids P7 | Xenograft | Xen-organoids P3 |
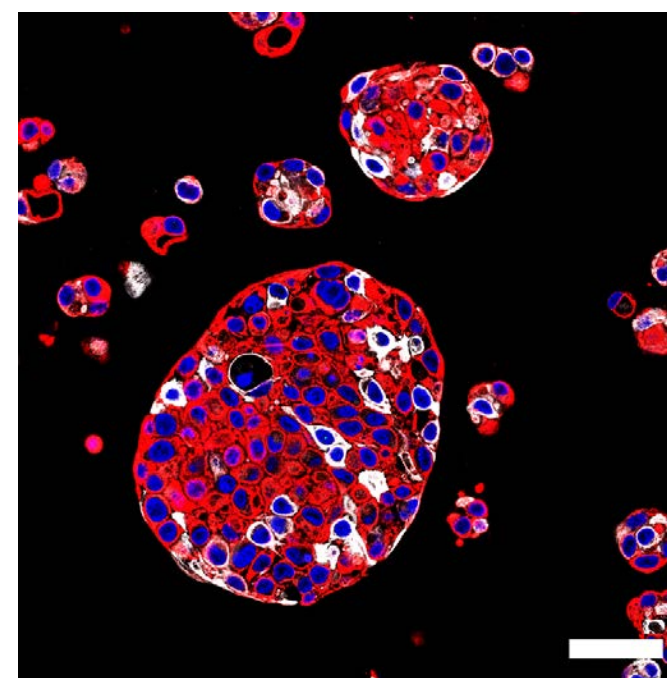
p53 CK8 CK5 DAPI

Plastic

Lee *et al.* (2018) *Cell* 173: 515-528
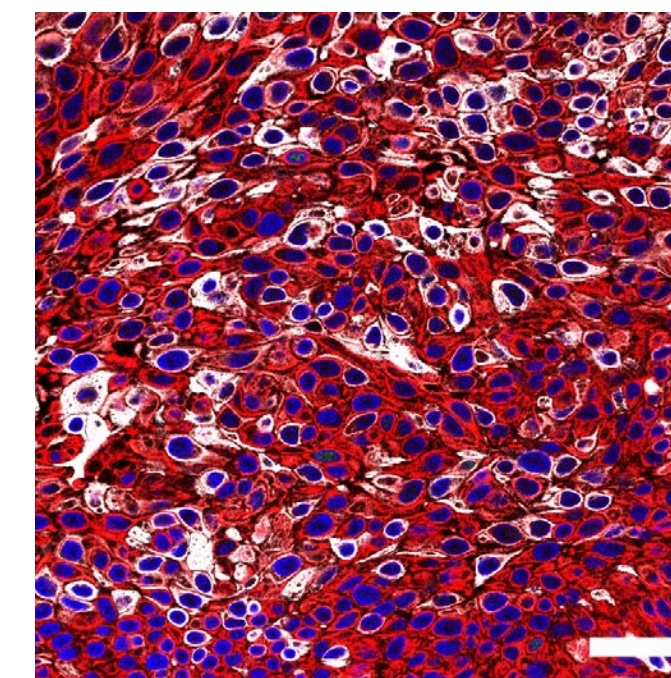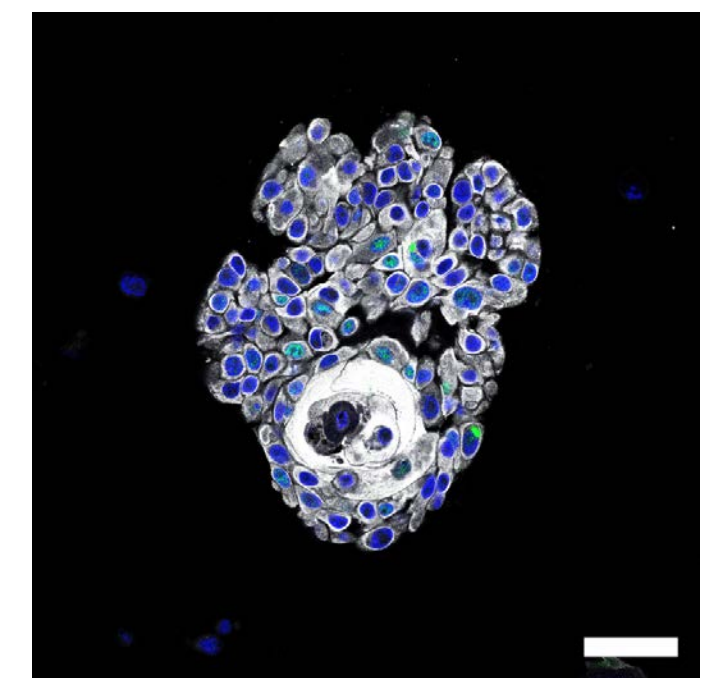
Biology of Bladder Urothelium

Lumen

Ck5^{low}Ck8^{high} (Superficial cells)

Ck5^{low}Ck8^{intermediate} (Intermediate cells)

Ck5^{high}Ck8^{low} (Basal cells)

Lamina Propria

Ck5/Ck18/DAPI   p63/Ck8/DAPI

Human

Mouse

Challenges

○ Unclear what cell types to target
○ Limited options to target bladder urothelium directly
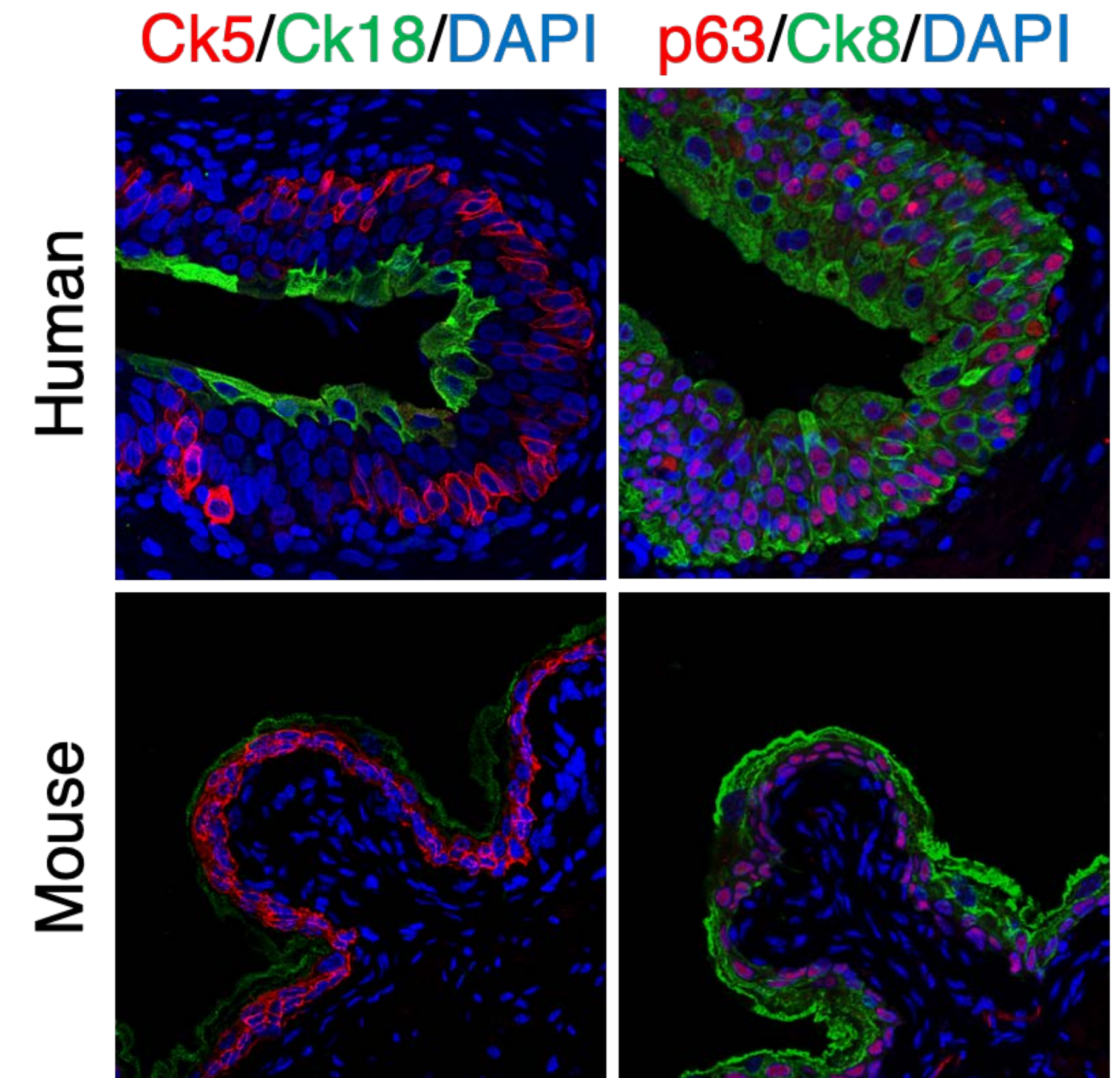
Bladder-specific Gene Recombination
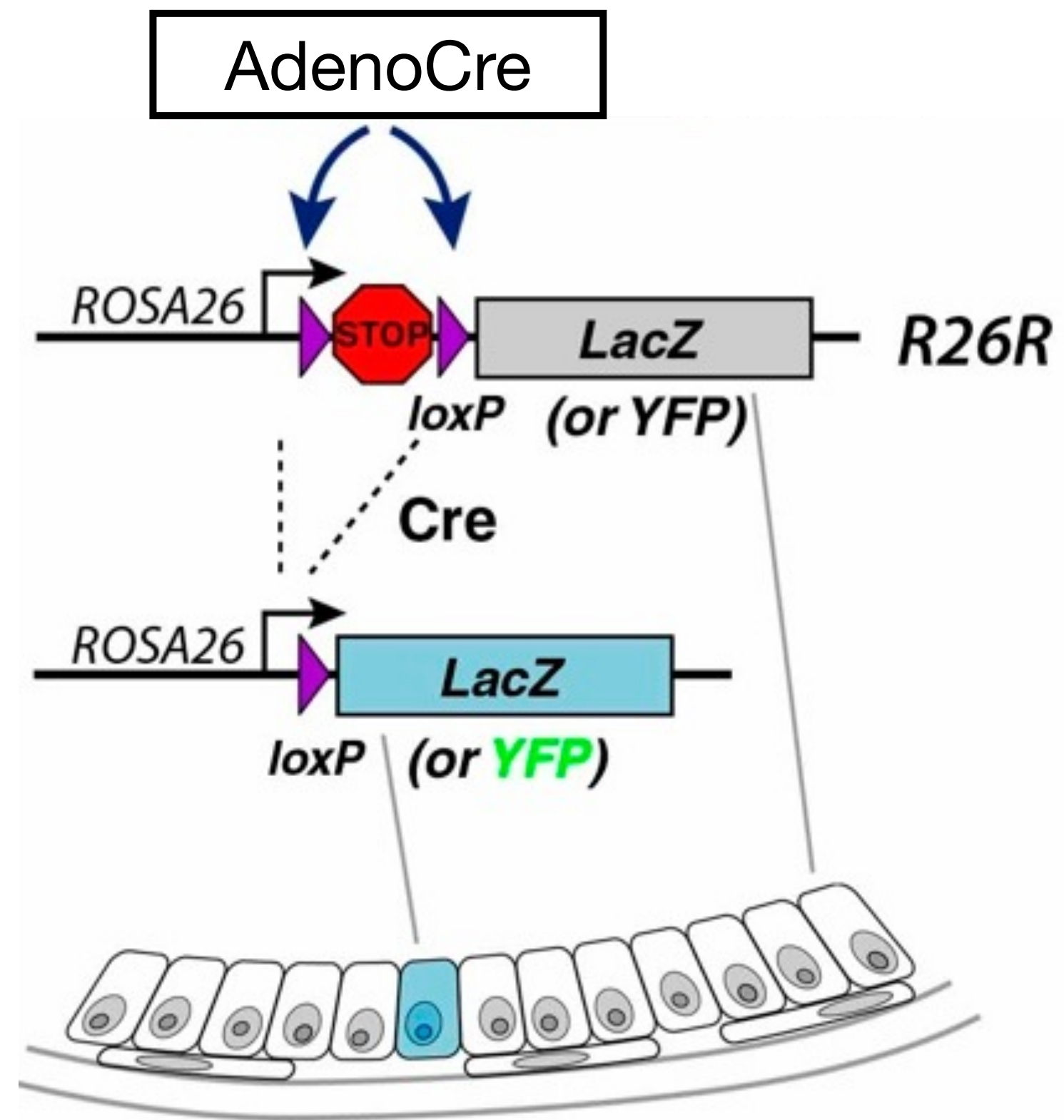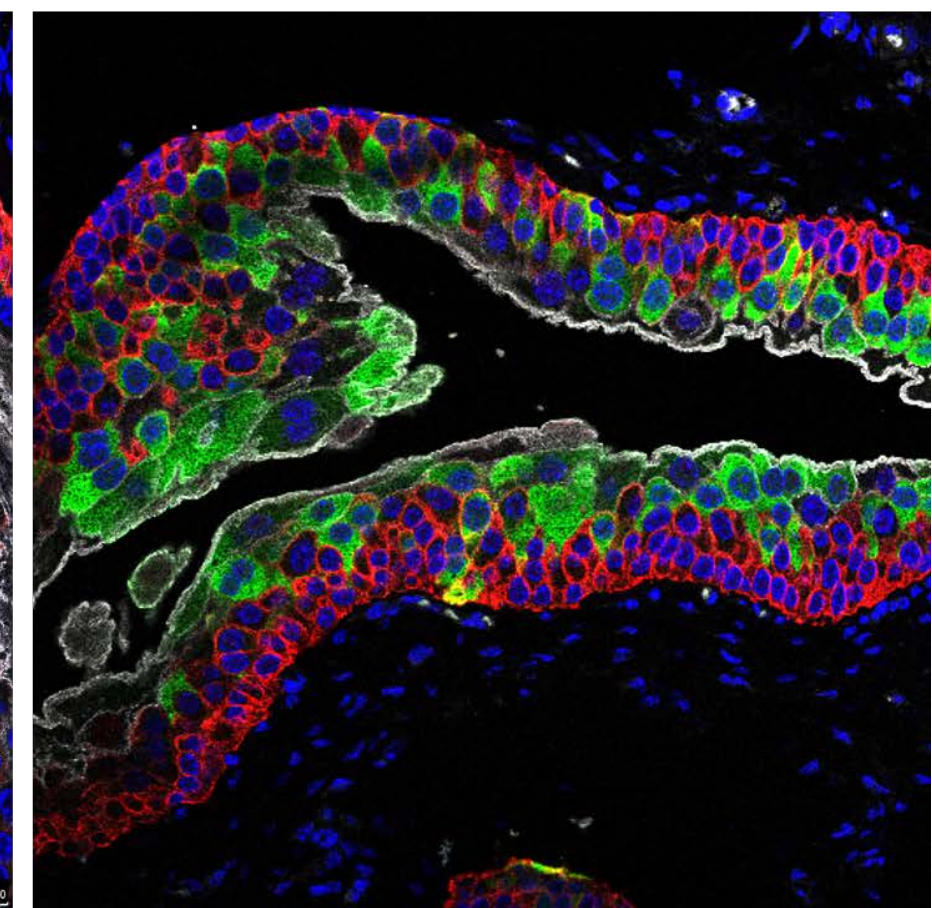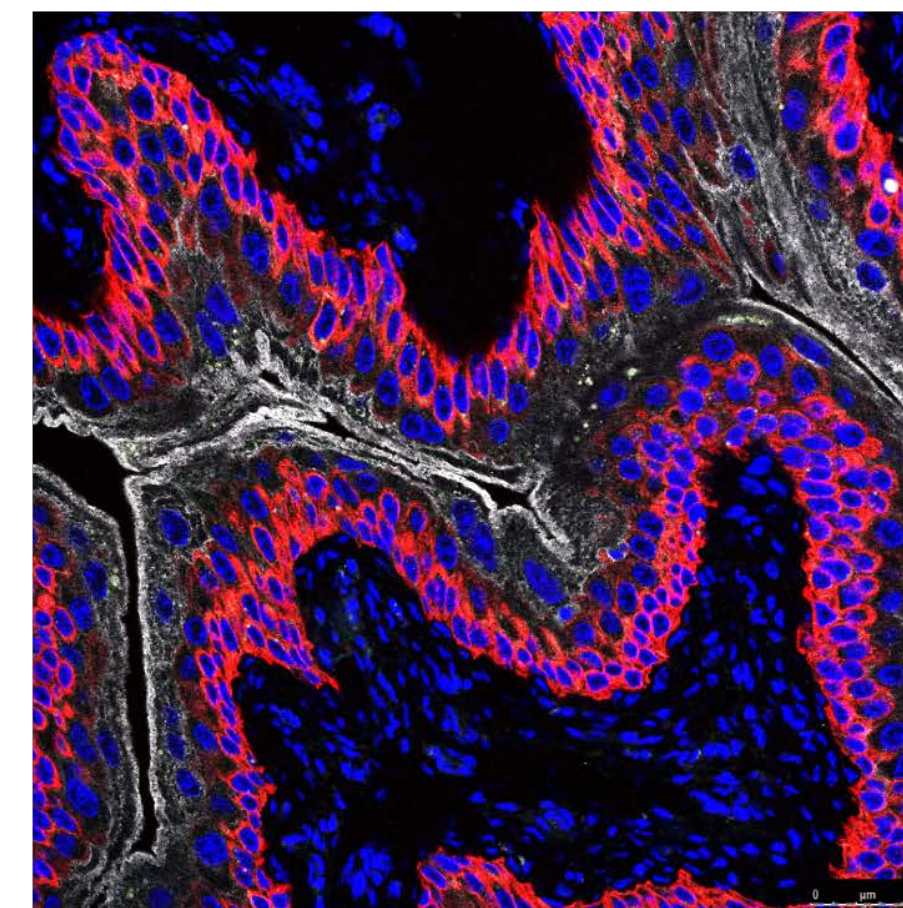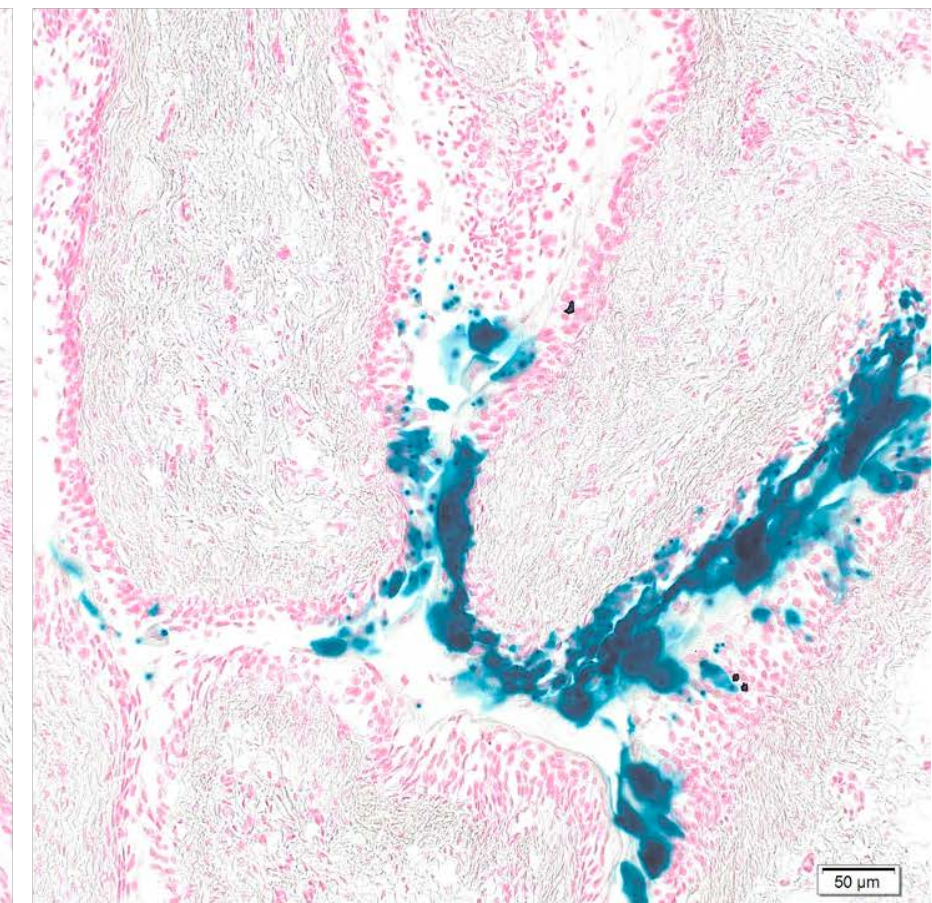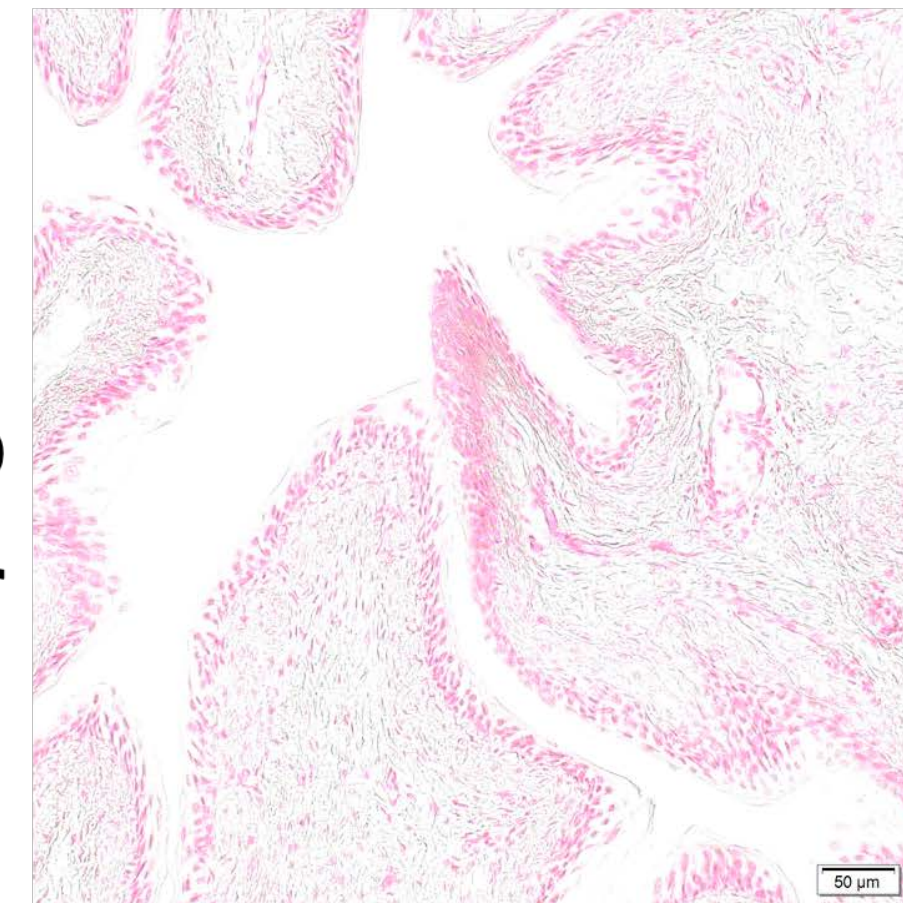
Modeling Bladder Cancer in Mice

$p53^{+/+}$; $Pten^{+/+}$ (N=10)
$p53^{flox/flox}$; $Pten^{+/+}$ (N=15)
$p53^{+/+}$; $Pten^{flox/flox}$ (N=12)

$p53^{flox/flox}$; $Pten^{flox/flox}$ (N=32)
P<0.001
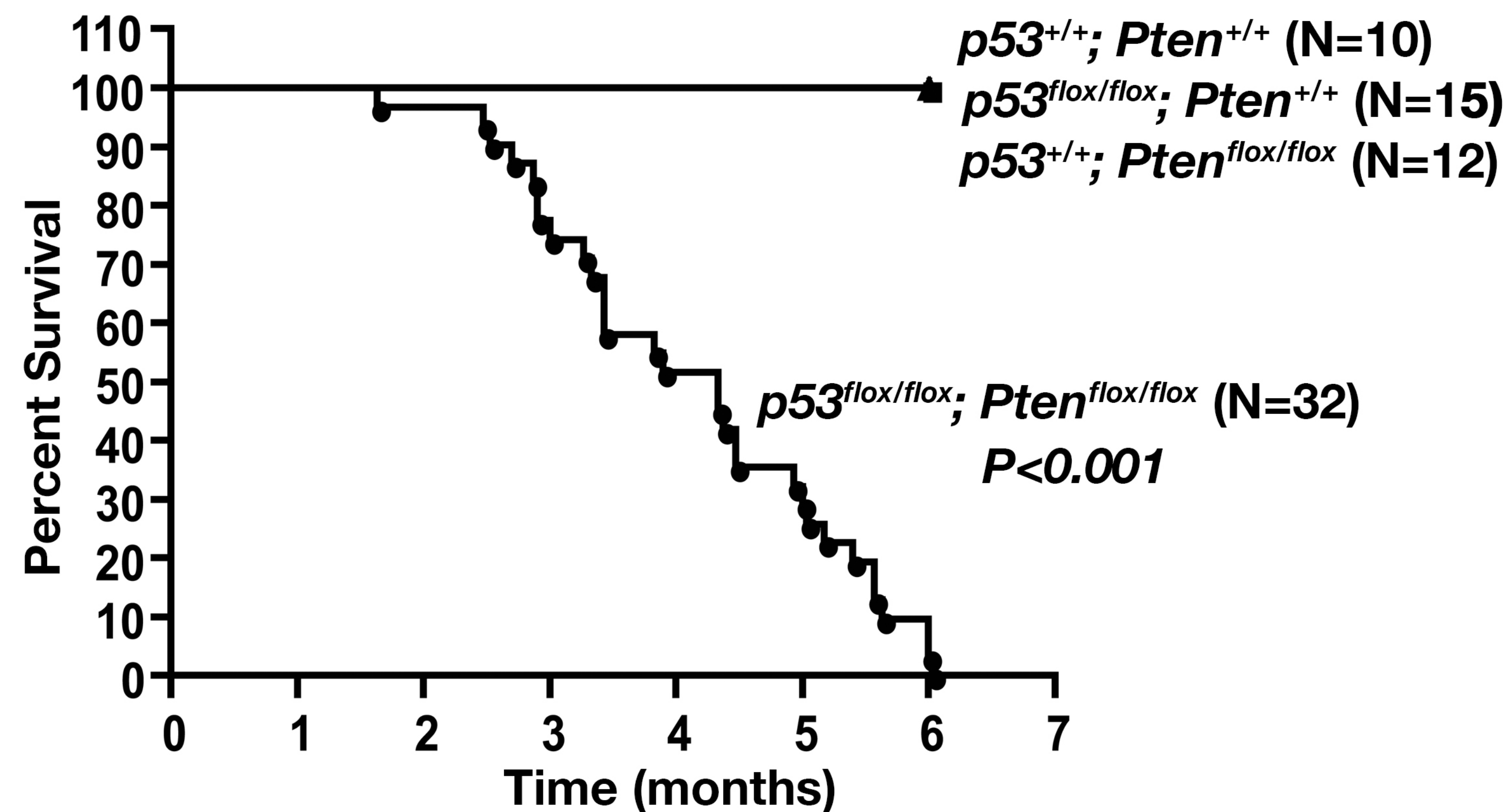
$p53^{+/+}$; $Pten^{+/+}$

$p53^{flox/flox}$; $Pten^{flox/flox}$

Puzio-Kuter et al., 2009
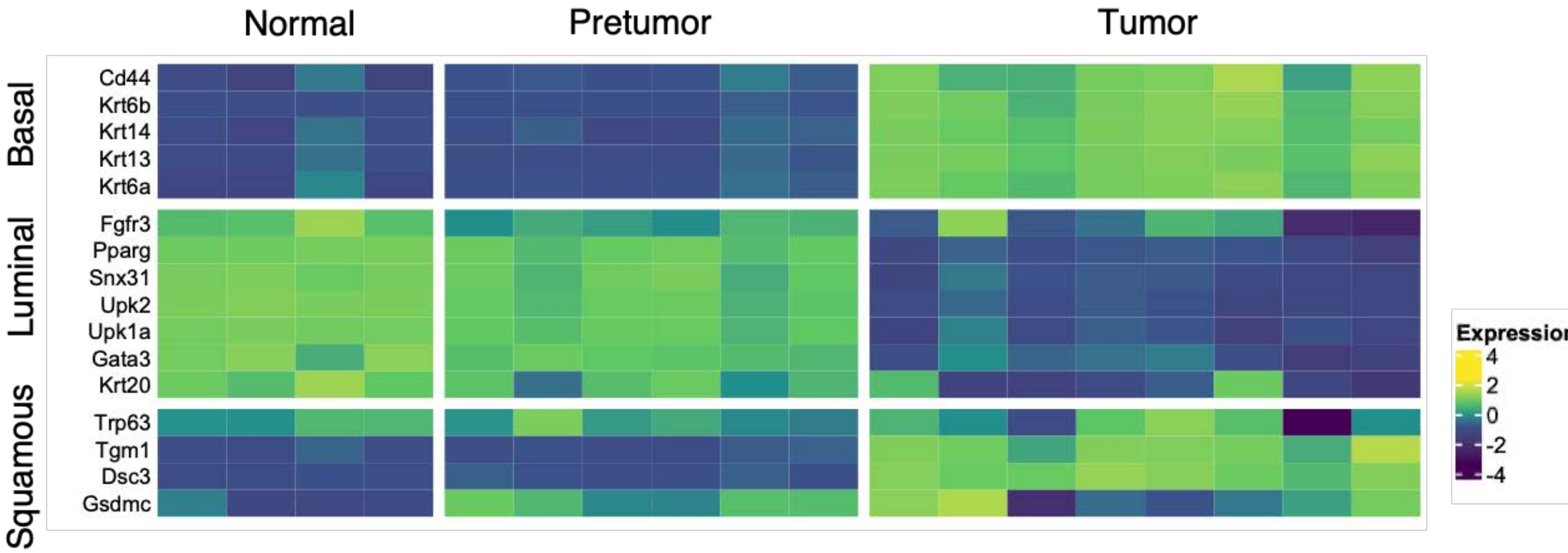*Park et al., 2021*
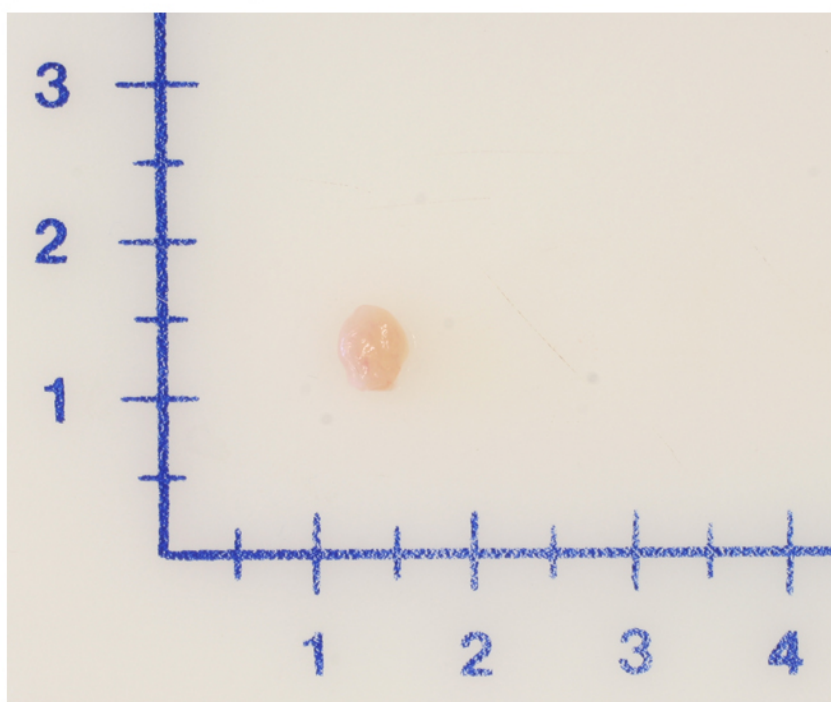
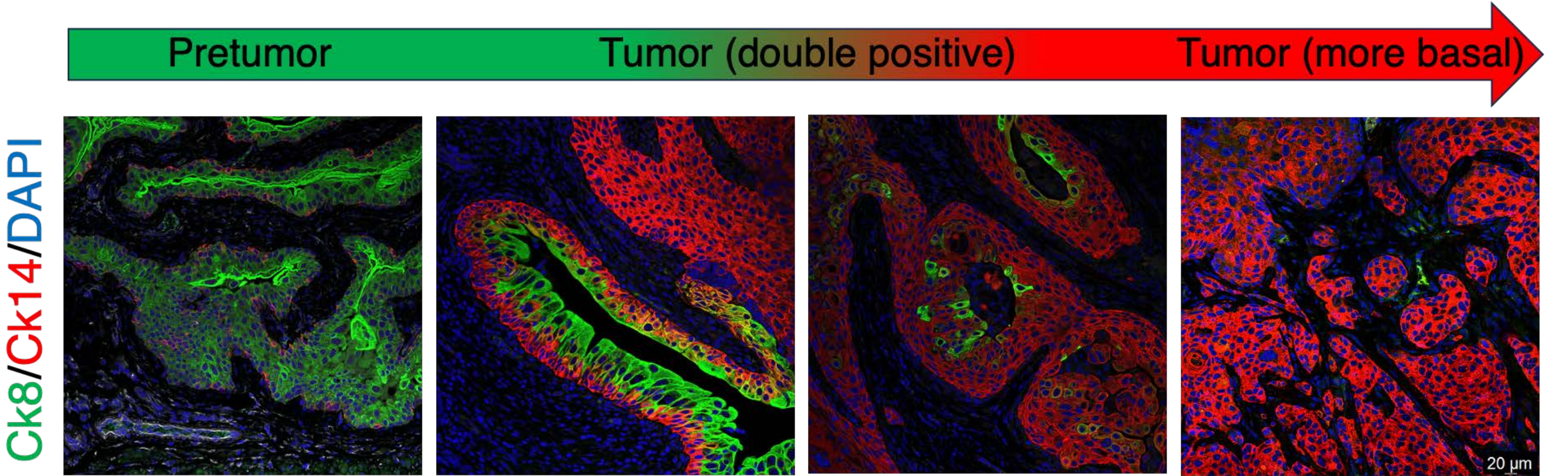# Refined Approaches to Model Bladder Cancer in Mice
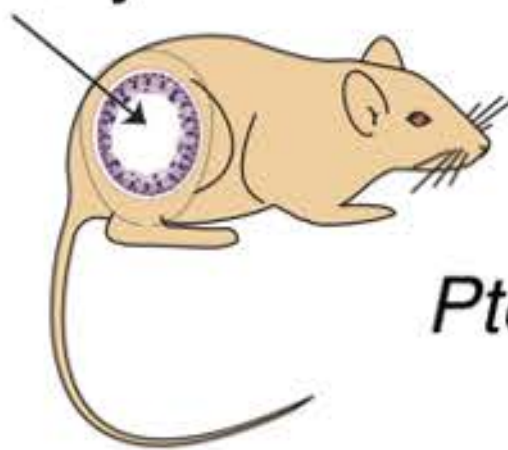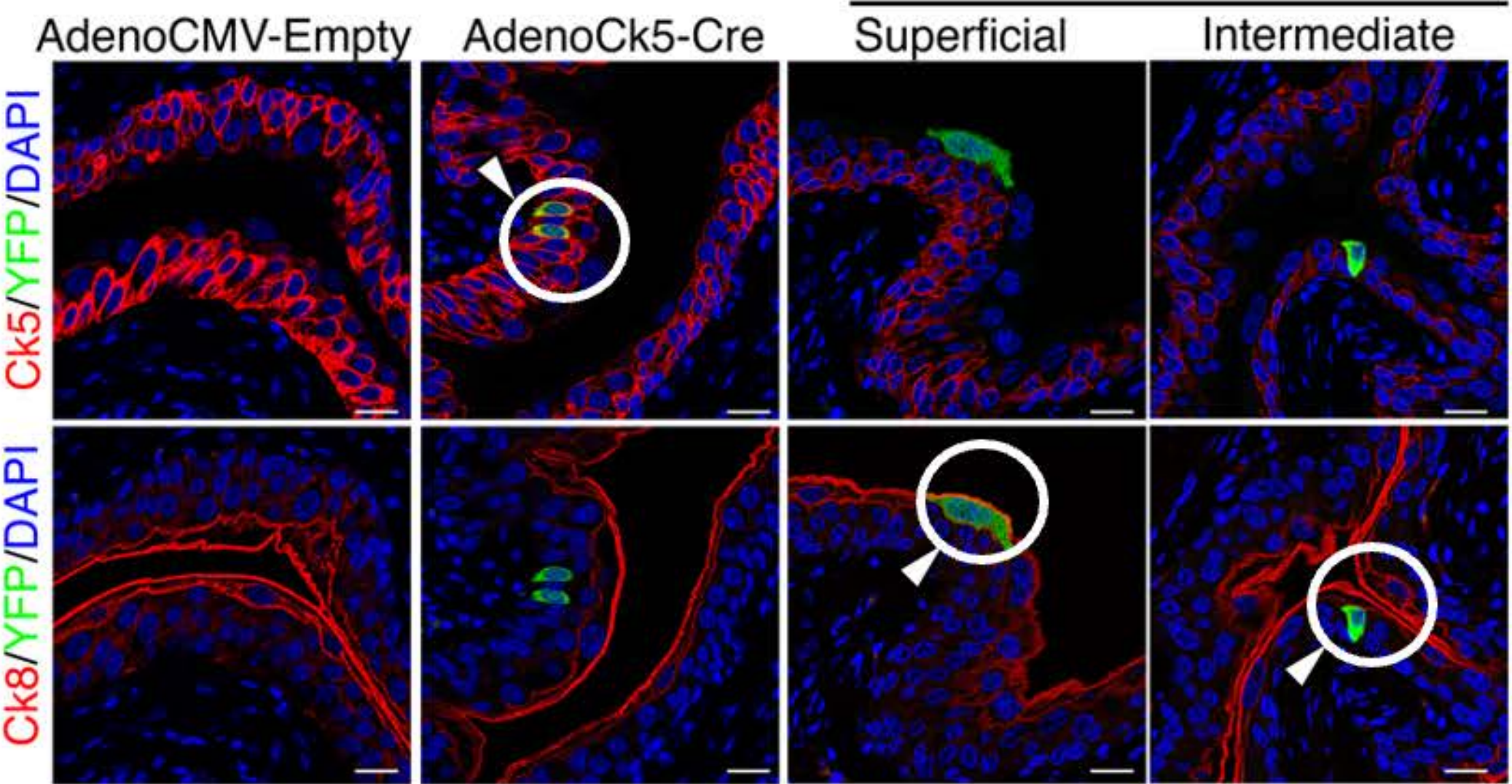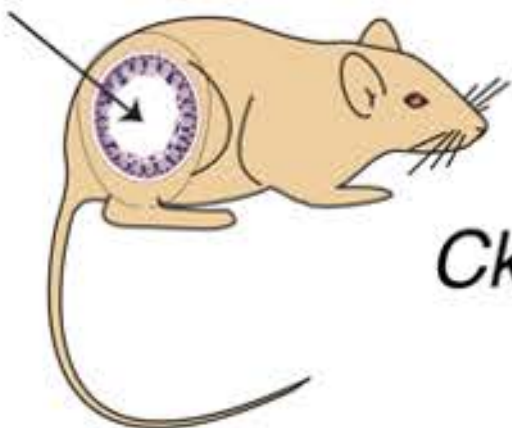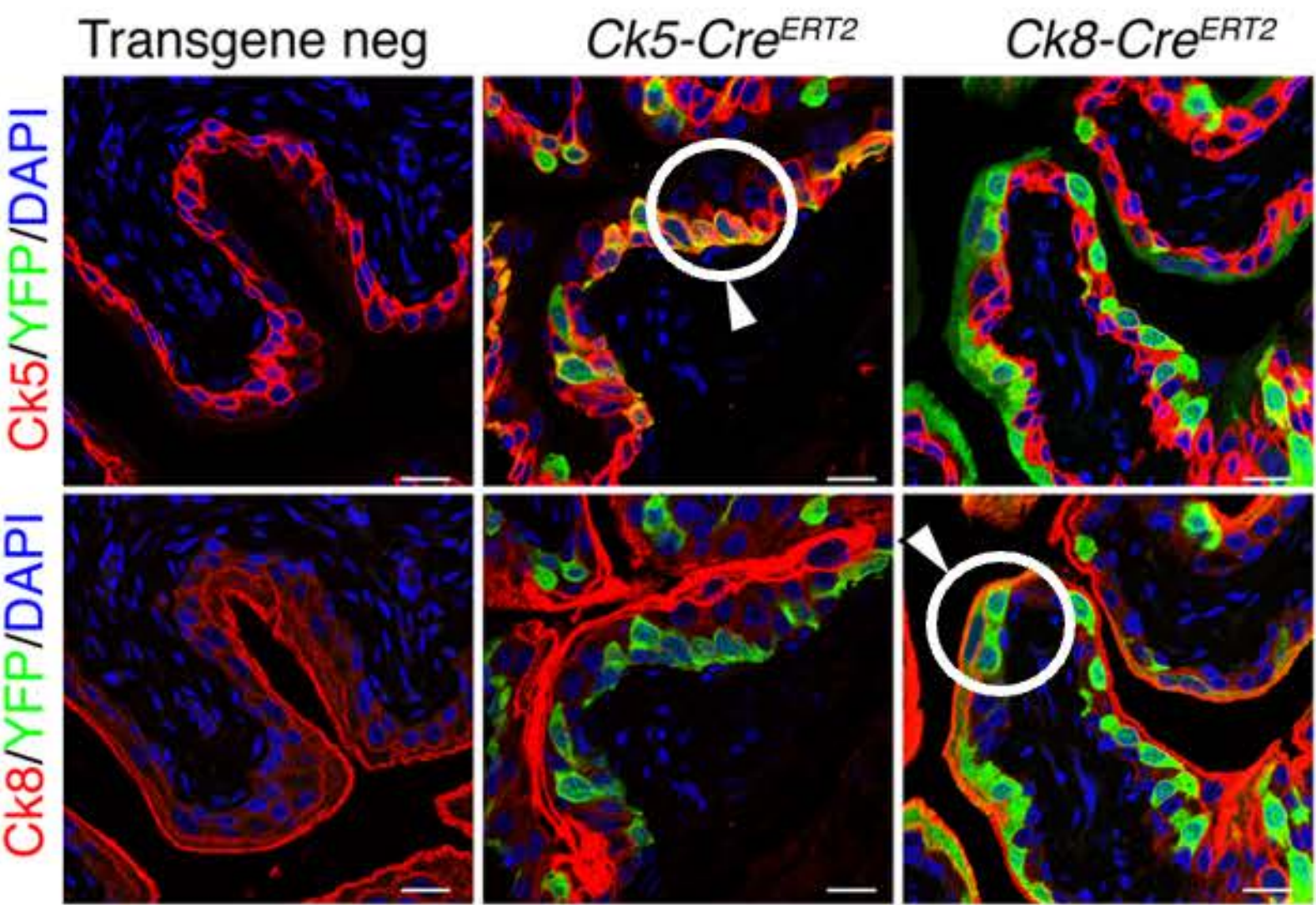
Frequently Mutated Genes in MIBC
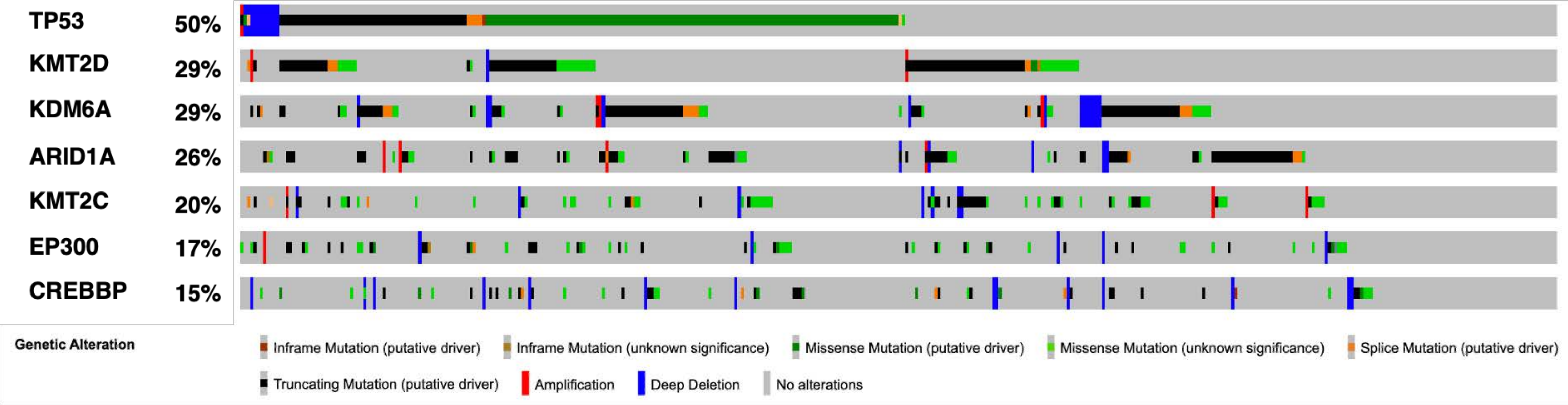
Modeling Bladder Cancer in Mice

Abbreviation	Full description	Phenotype	Mets	
DKO	*Pten$^{flox/flox}$; p53$^{flox/flox}$*	MIBC with sarcomatoid differentiation	~40%	
Kmt2d DKO	*Kmt2d$^{flox/flox}$; Pten$^{flox/flox}$; p53$^{flox/flox}$*	MIBC with squamous differentiation	~35%	→ Model of plasticity
Kdm6a DKO	*Kdm6a$^{flox/flox}$; Pten$^{flox/flox}$; p53$^{flox/flox}$*	MIBC with sarcomatoid differentiation	~40%	
Arid1a DKO	*Arid1a$^{flox/flox}$; Pten$^{flox/flox}$; p53$^{flox/flox}$*	MIBC with sarcomatoid differentiation	~90%	→ Model of metastasis
Ep300 DKO	*EP300$^{flox/flox}$; Pten$^{flox/flox}$; p53$^{flox/flox}$*	Under characterization		
Crebbp DKO	*Crebbp$^{flox/flox}$; Pten$^{flox/flox}$; p53$^{flox/flox}$*	Under characterization		
DKO inbred	*Pten$^{flox/flox}$; p53$^{flox/flox}$*	Under characterization		→ Model of TME

Modeling plasticity

Kmt2d DKO mouse
1.5 months after induction
Ck8/Ck14/DAPI

Overt basal/
squamous

Luminal

Luminal to basal
(Double-positive)

Ck8/Ck14/DAPI

Pretumor | Tumor (double positive) | Tumor (more basal)

20 µm

	Normal	Pretumor	Tumor

Basal: Cd44, Krt6b, Krt14, Krt13, Krt6a

Luminal: Fgfr3, Pparg, Snx31, Upk2, Upk1a, Gata3, Krt20

Squamous: Trp63, Tgm1, Dsc3, Gsdmc

Expression
4
2
0
-2
-4

Modeling metastasis

TKO

	Bright field	Fluorescence	Histology
Bladder			
Lymph node			
Liver			
Lung			

TKO: Arid1a DKO

Conserved Drivers of Metastasis

Top 25 VIPER regulators and their rank in expression

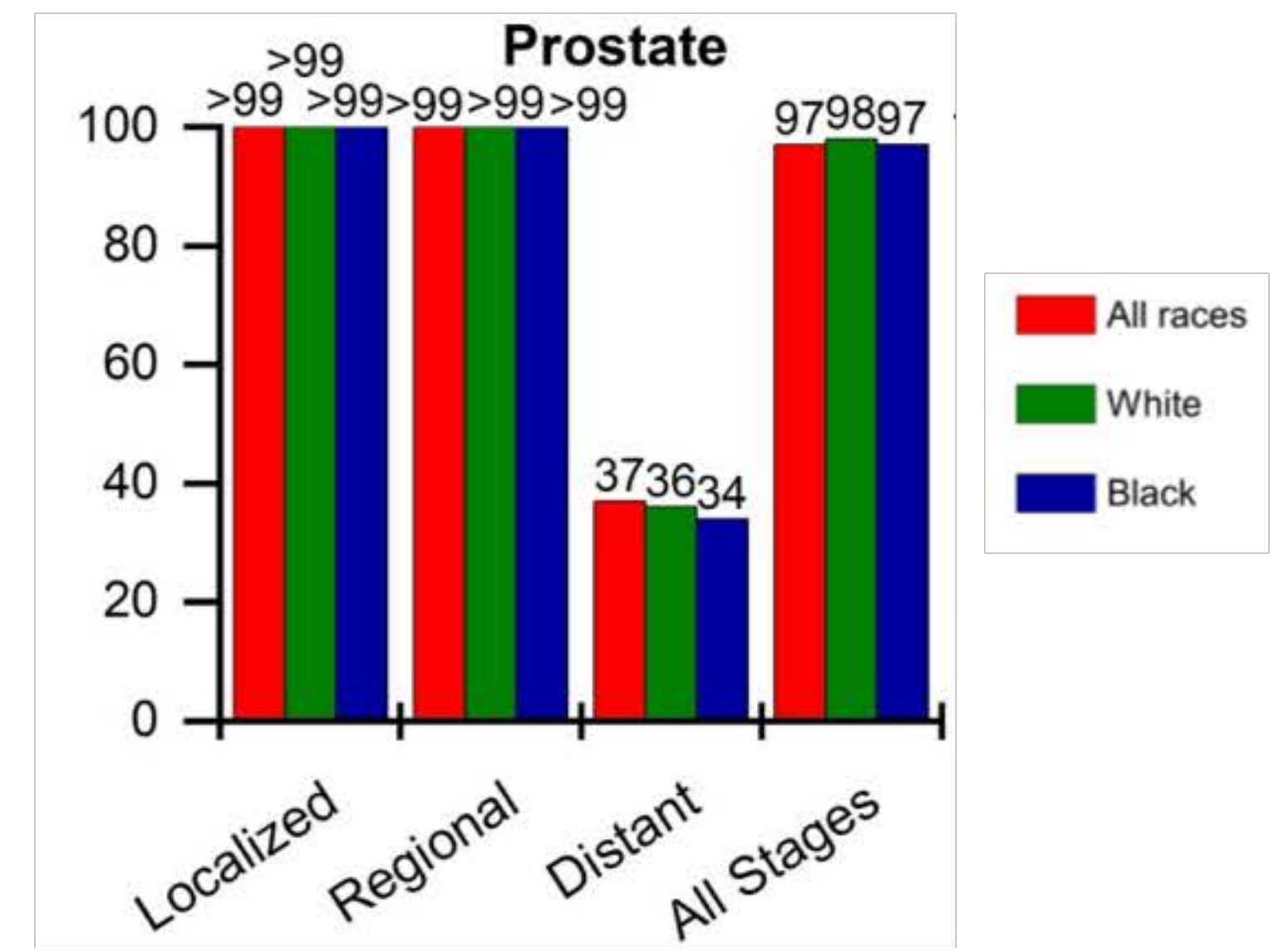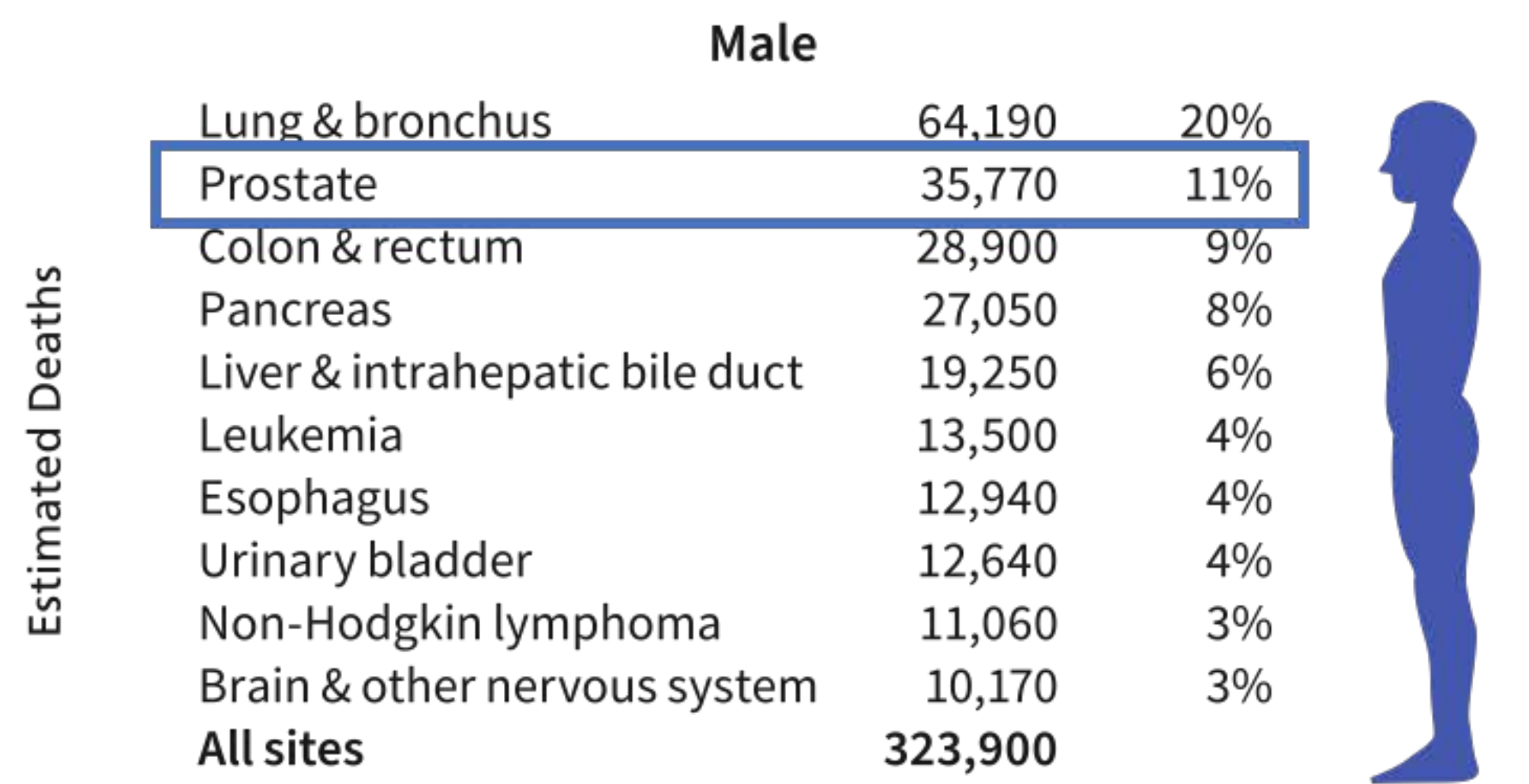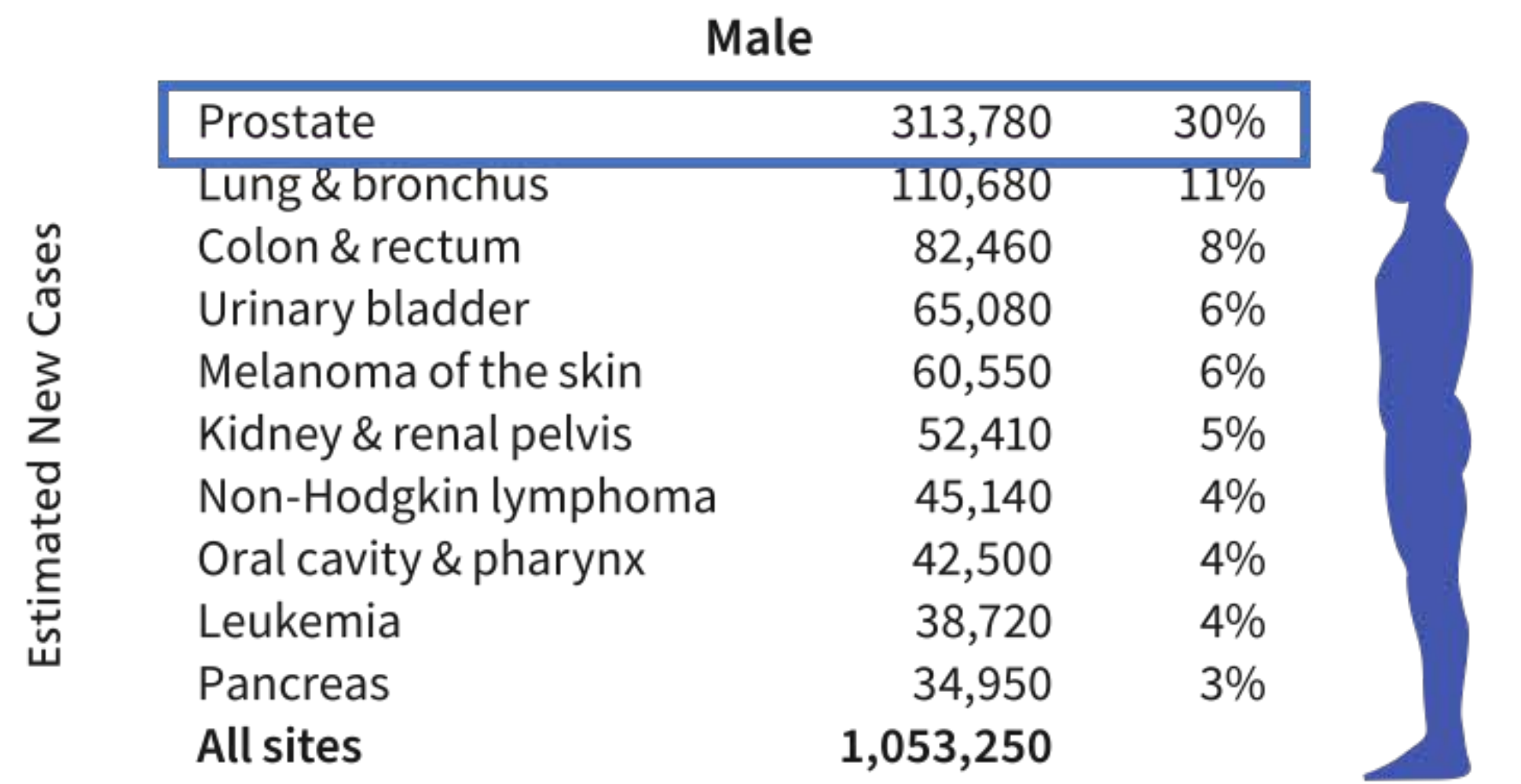*Maeve Humphery*
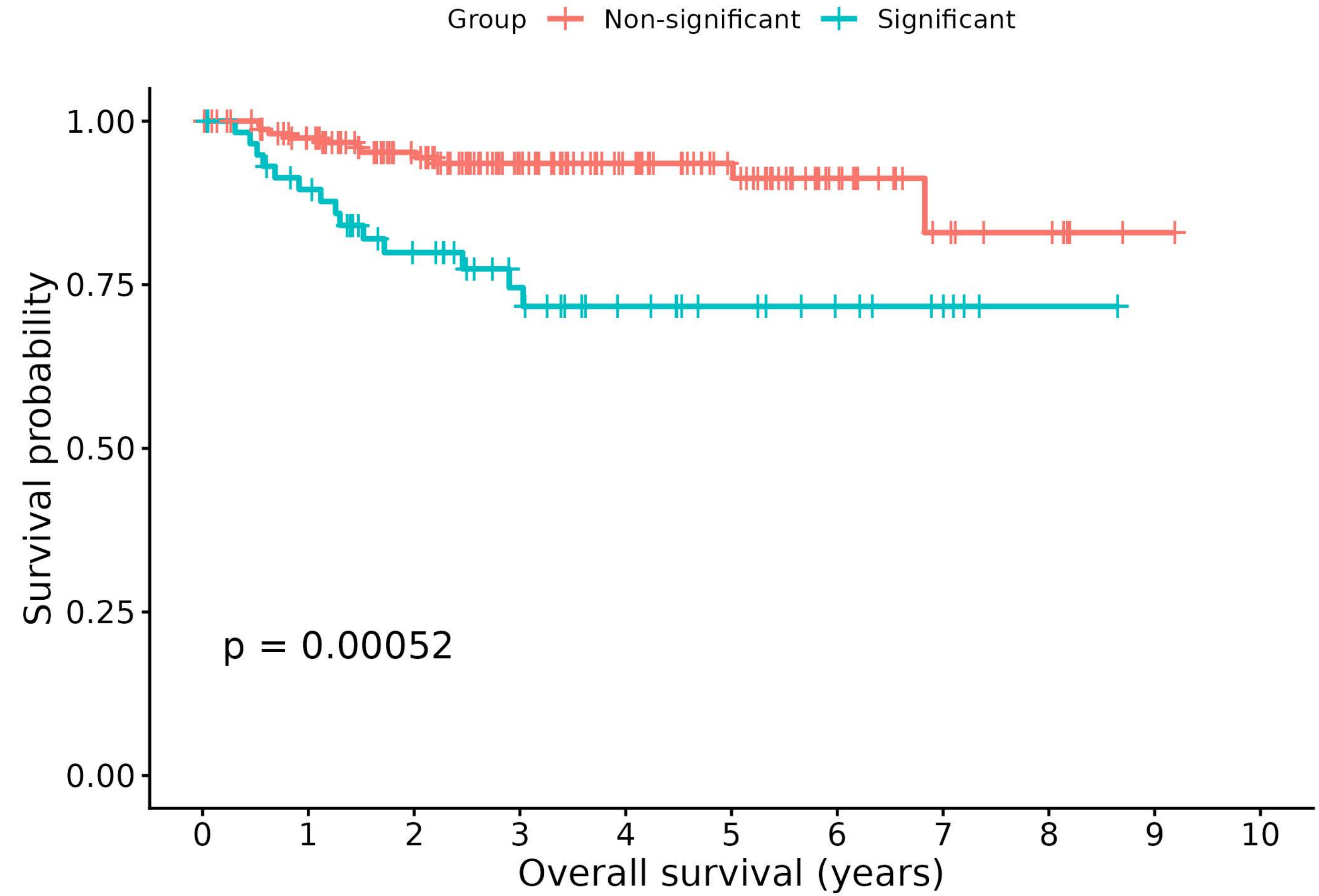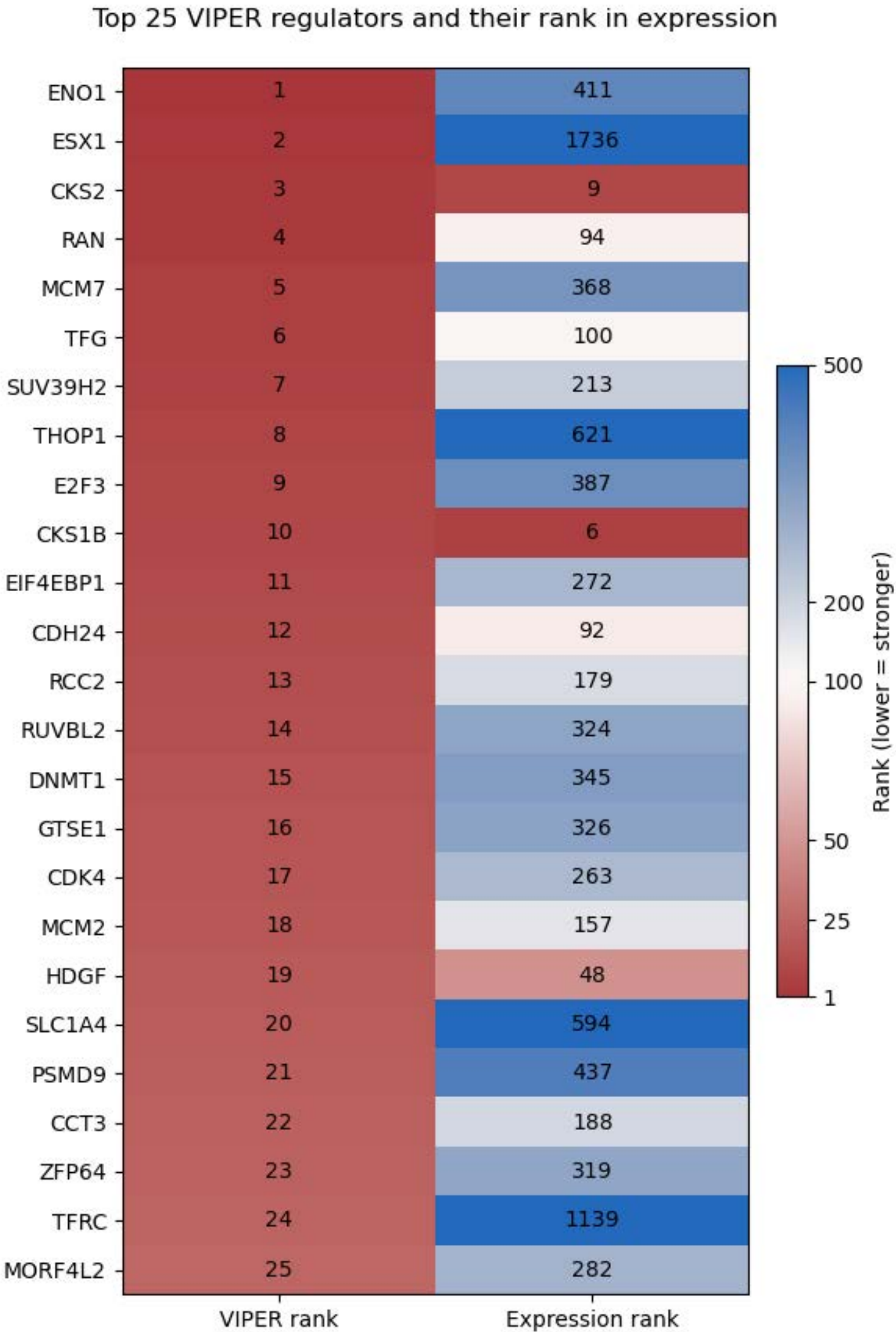
Summary: Bladder cancer

- Most people with bladder cancer do well, those with advanced disease have poor outcomes

- Bladder cancer is a genetically and phenotypically diverse disease with a range of outcomes

- Treatments depend on the stage and the genetics

- Can model bladder cancer in human organoids, PDX and GEMMs for preclinical investigation
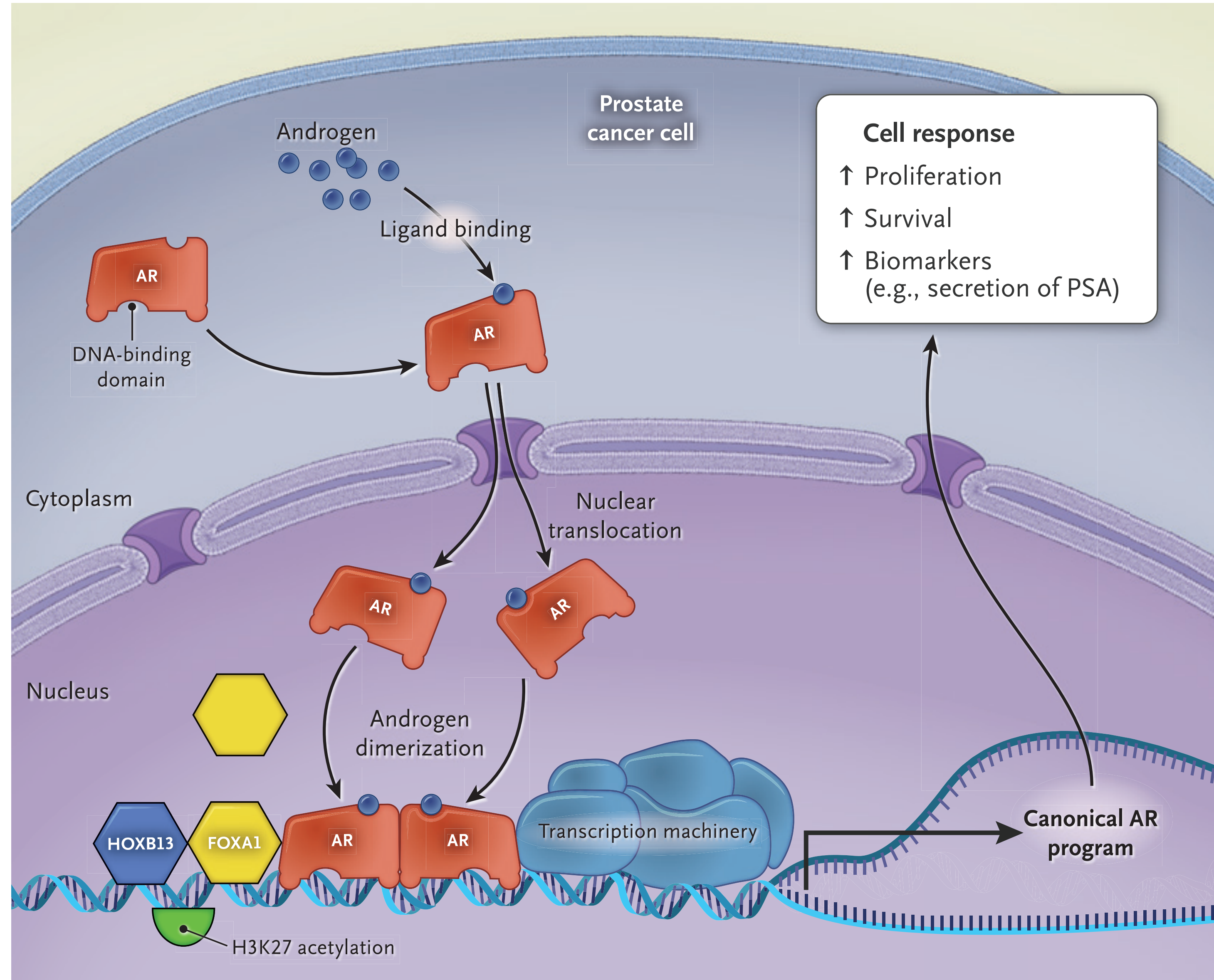
- Still no cure for metastatic disease

Prostate cancer progression

Normal epithelium → Prostatic intraepithelial neoplasia (PIN) → Invasive carcinoma → Metastasis
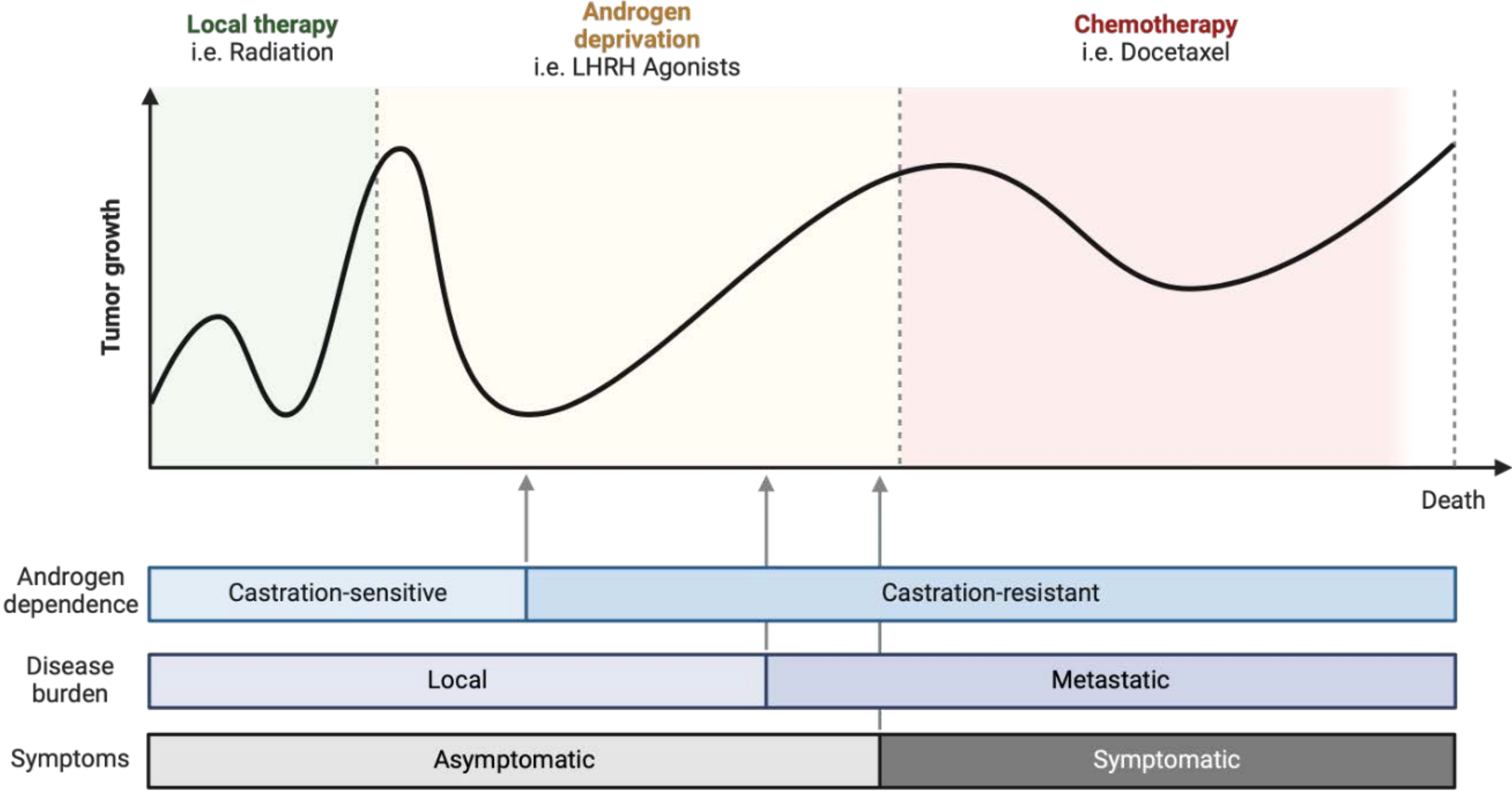
Castration Resistance
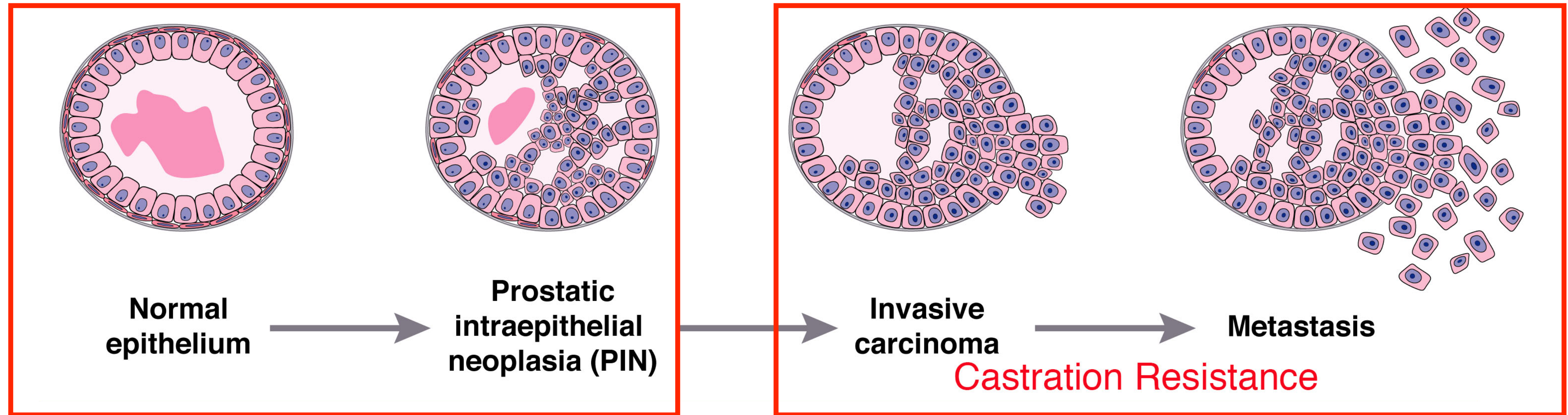
- Study developmental pathways to understand mechanisms of cancer initiation that can be targeted for prevention

- Mechanisms of castration resistance and metastasis that can be targeted for treatment
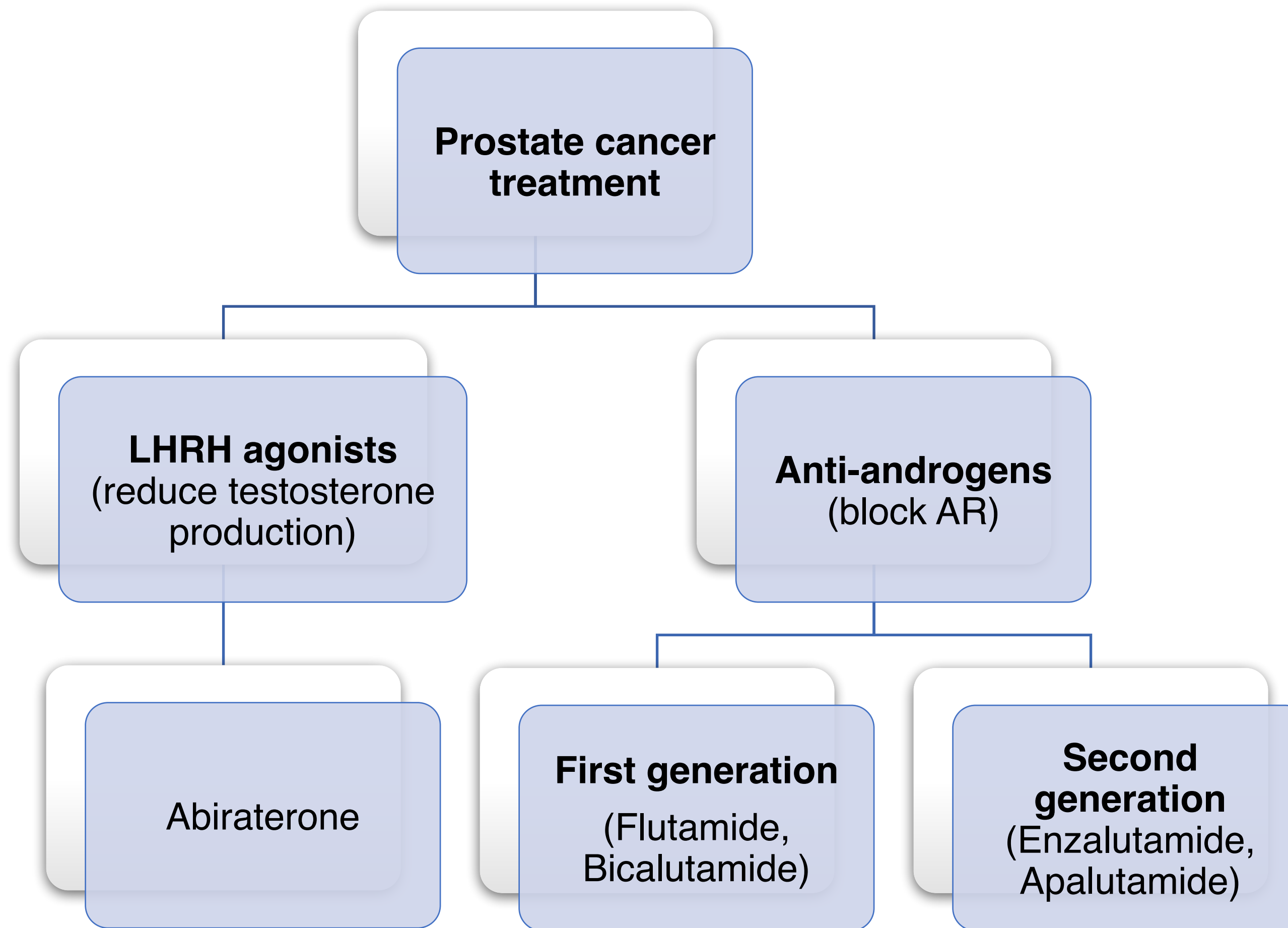
(Shen and Abate-Shen, 2010)
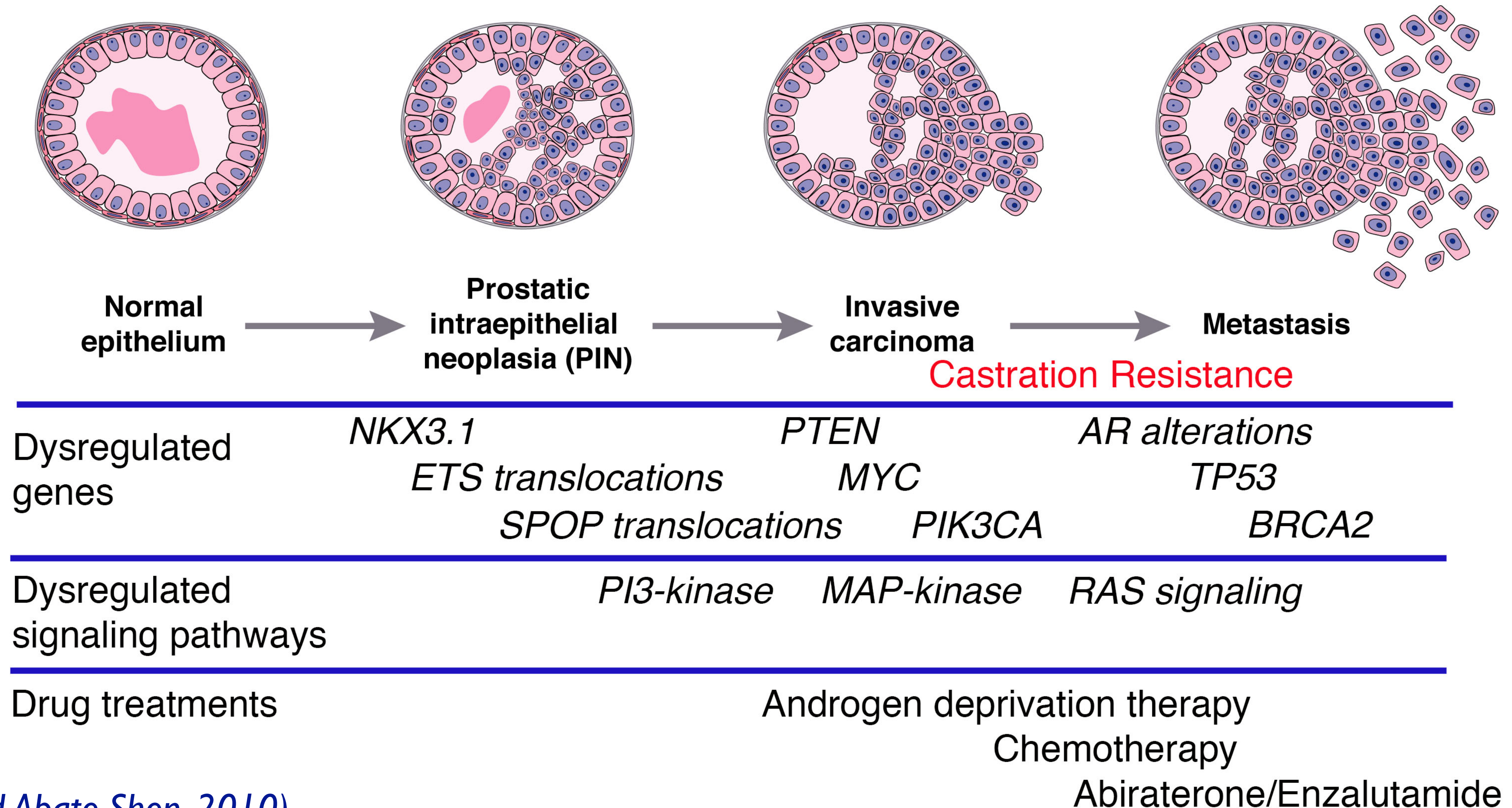
Male — Estimated New Cases

Cancer	New Cases	%
Prostate	313,780	30%
Lung & bronchus	110,680	11%
Colon & rectum	82,460	8%
Urinary bladder	65,080	6%
Melanoma of the skin	60,550	6%
Kidney & renal pelvis	52,410	5%
Non-Hodgkin lymphoma	45,140	4%
Oral cavity & pharynx	42,500	4%
Leukemia	38,720	4%
Pancreas	34,950	3%
All sites	**1,053,250**	

Male — Estimated Deaths

Cancer	Deaths	%
Lung & bronchus	64,190	20%
Prostate	35,770	11%
Colon & rectum	28,900	9%
Pancreas	27,050	8%
Liver & intrahepatic bile duct	19,250	6%
Leukemia	13,500	4%
Esophagus	12,940	4%
Urinary bladder	12,640	4%
Non-Hodgkin lymphoma	11,060	3%
Brain & other nervous system	10,170	3%
All sites	**323,900**	

Siegel et al., *CA Cancer J Clin* 2025

Androgen receptor signaling

Arap, Pasqualini, and Costello, *N Engl J Med.* 2020
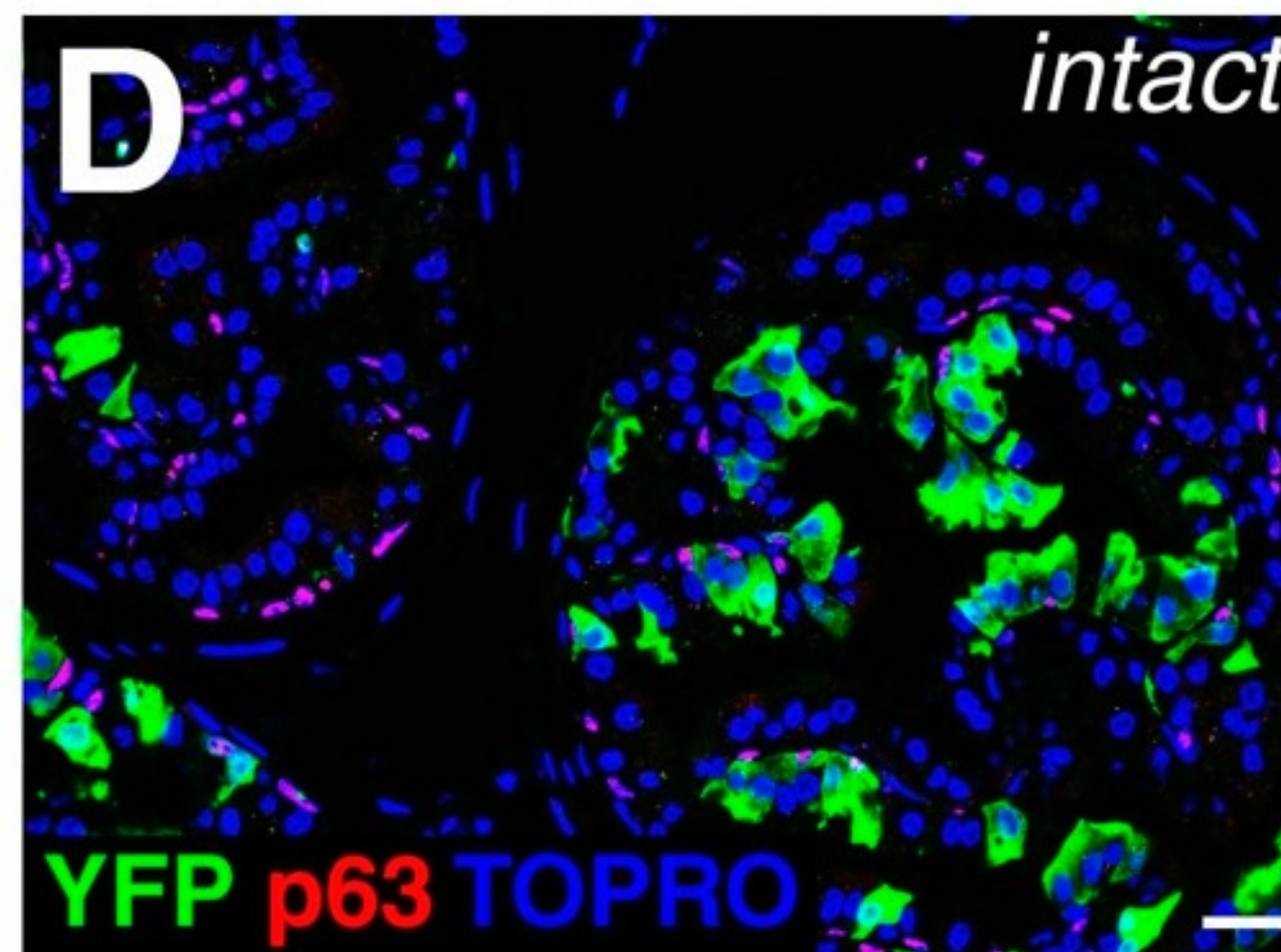
Prostate cancer stages and treatment options

Prostate cancer stages and treatment options

Modeling prostate cancer progression in mice

	Normal epithelium	Prostatic intraepithelial neoplasia (PIN)	Invasive carcinoma	Metastasis

Castration Resistance

Dysregulated genes		*NKX3.1* *ETS translocations* *SPOP translocations*	*PTEN* *MYC* *PIK3CA*	*AR alterations* *TP53* *BRCA2*
Dysregulated signaling pathways		*PI3-kinase*	*MAP-kinase*	*RAS signaling*
Drug treatments			Androgen deprivation therapy Chemotherapy Abiraterone/Enzalutamide	

(Shen and Abate-Shen, 2010)

Prostate-specific gene recombination in a luminal cell of origin
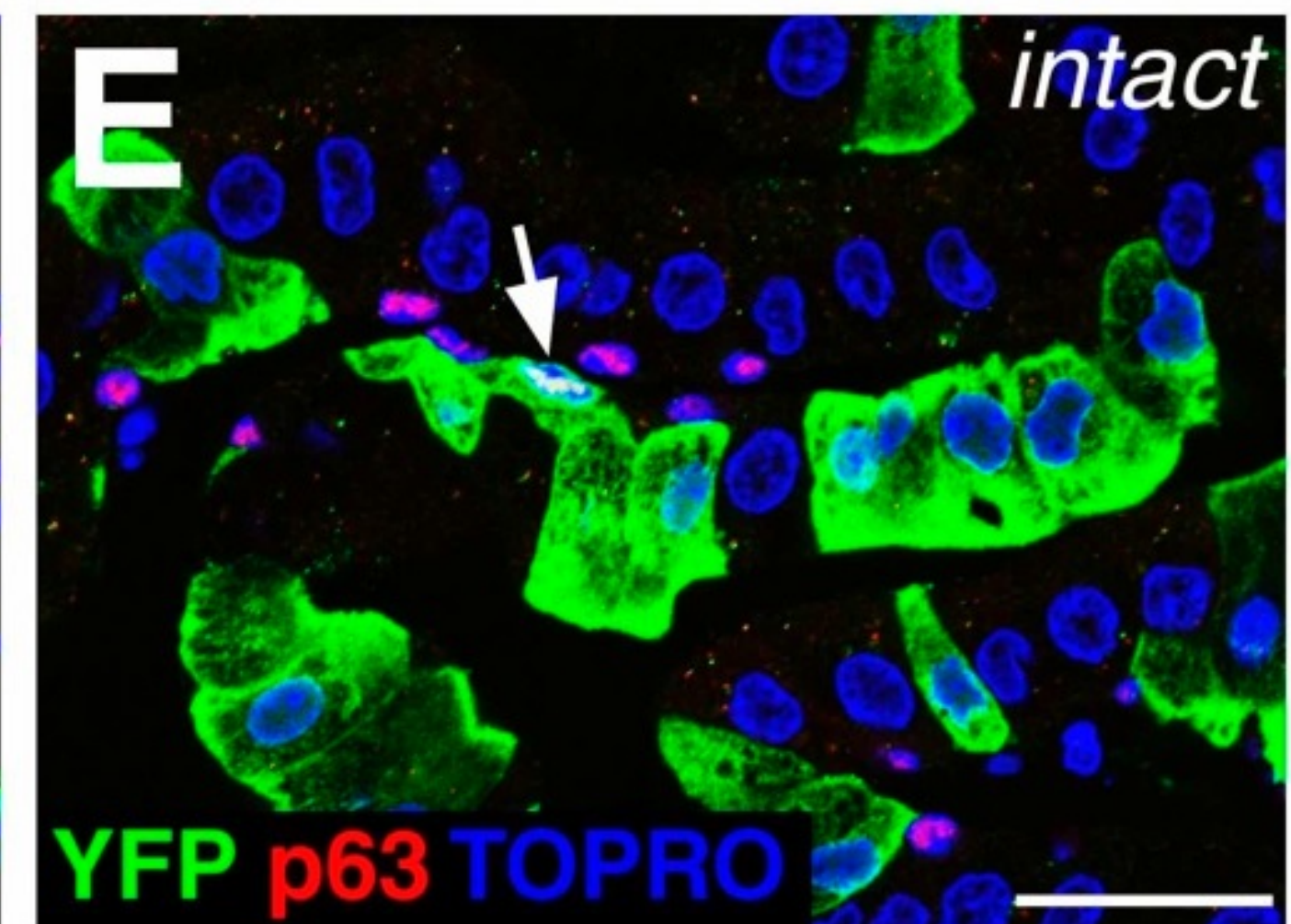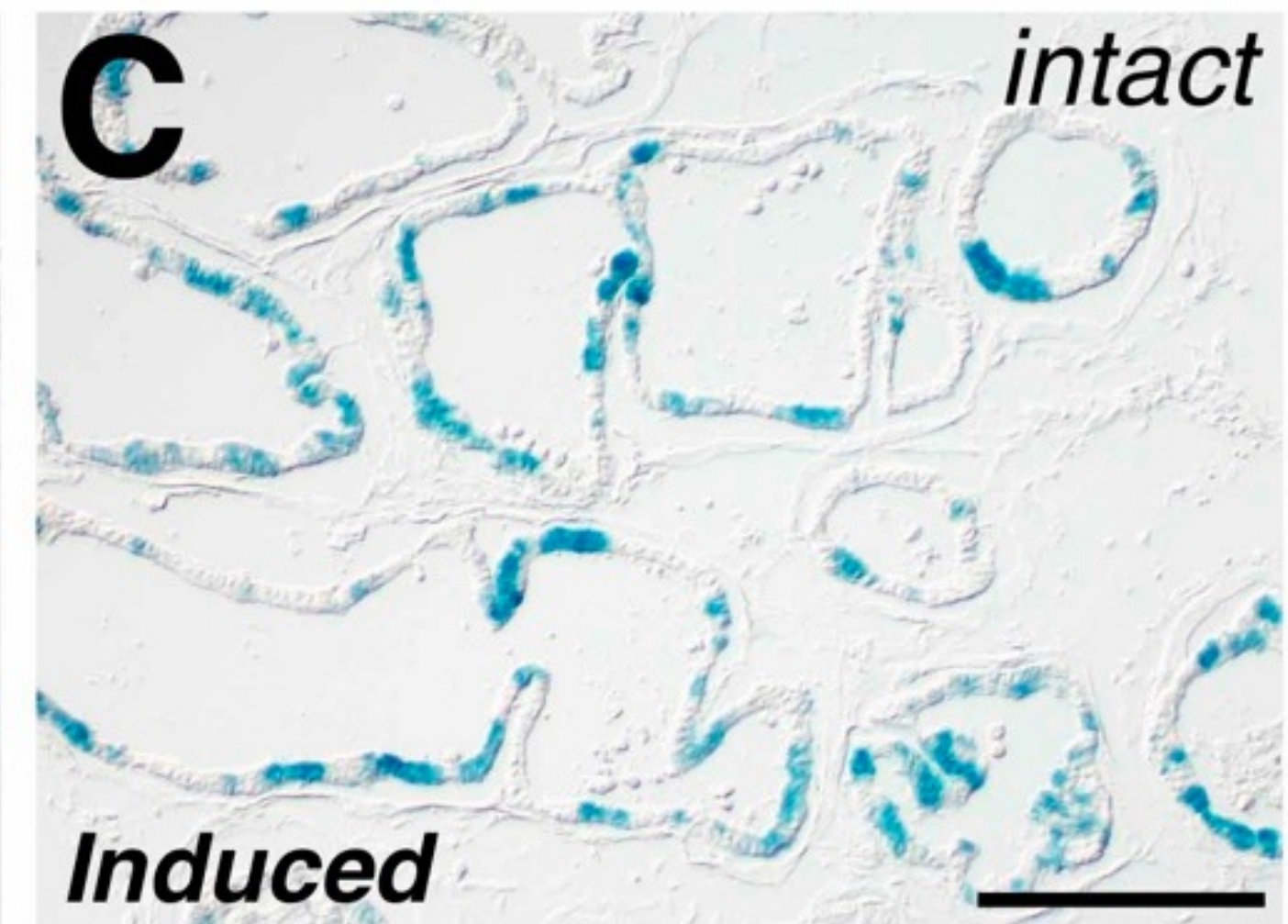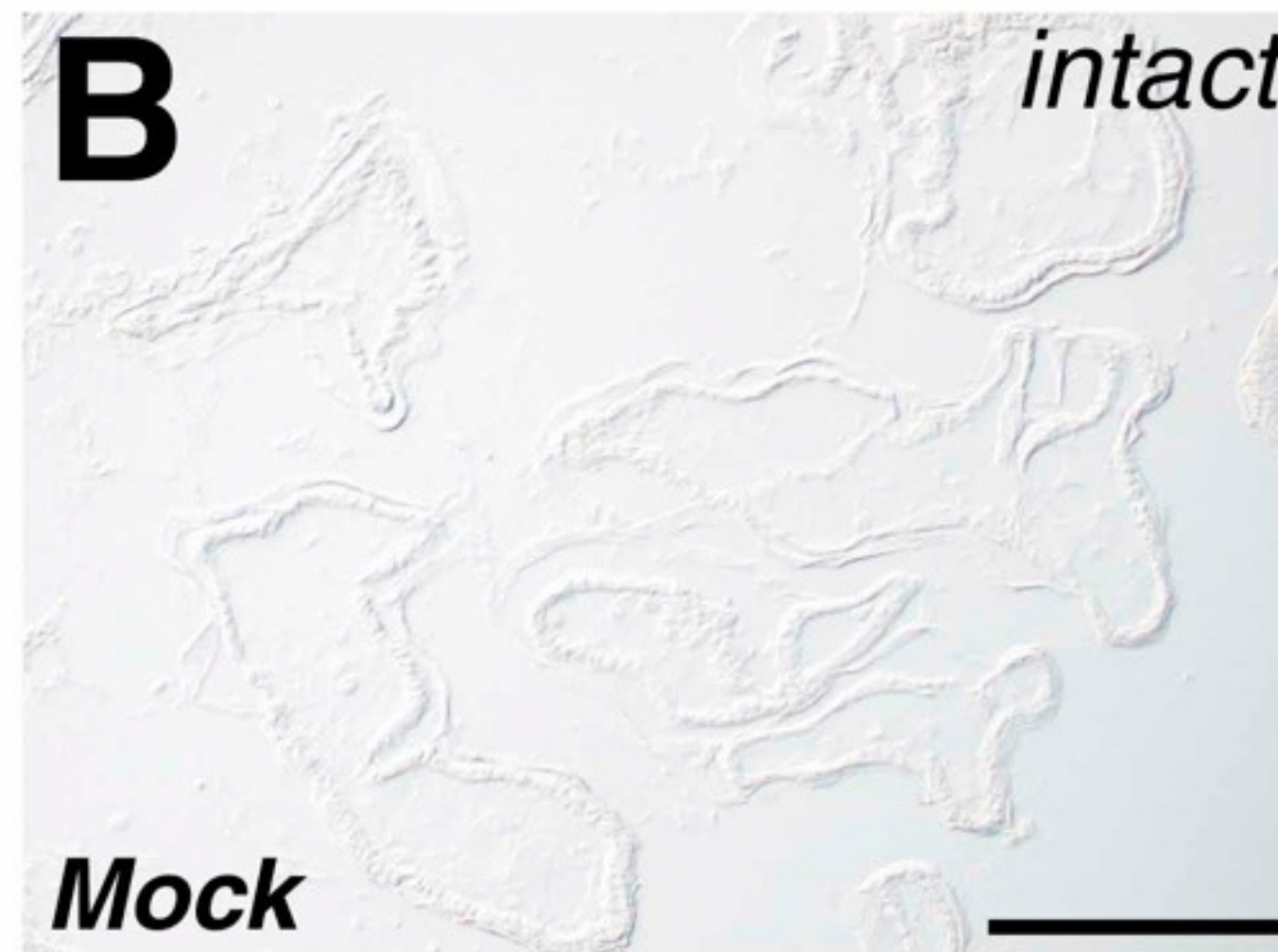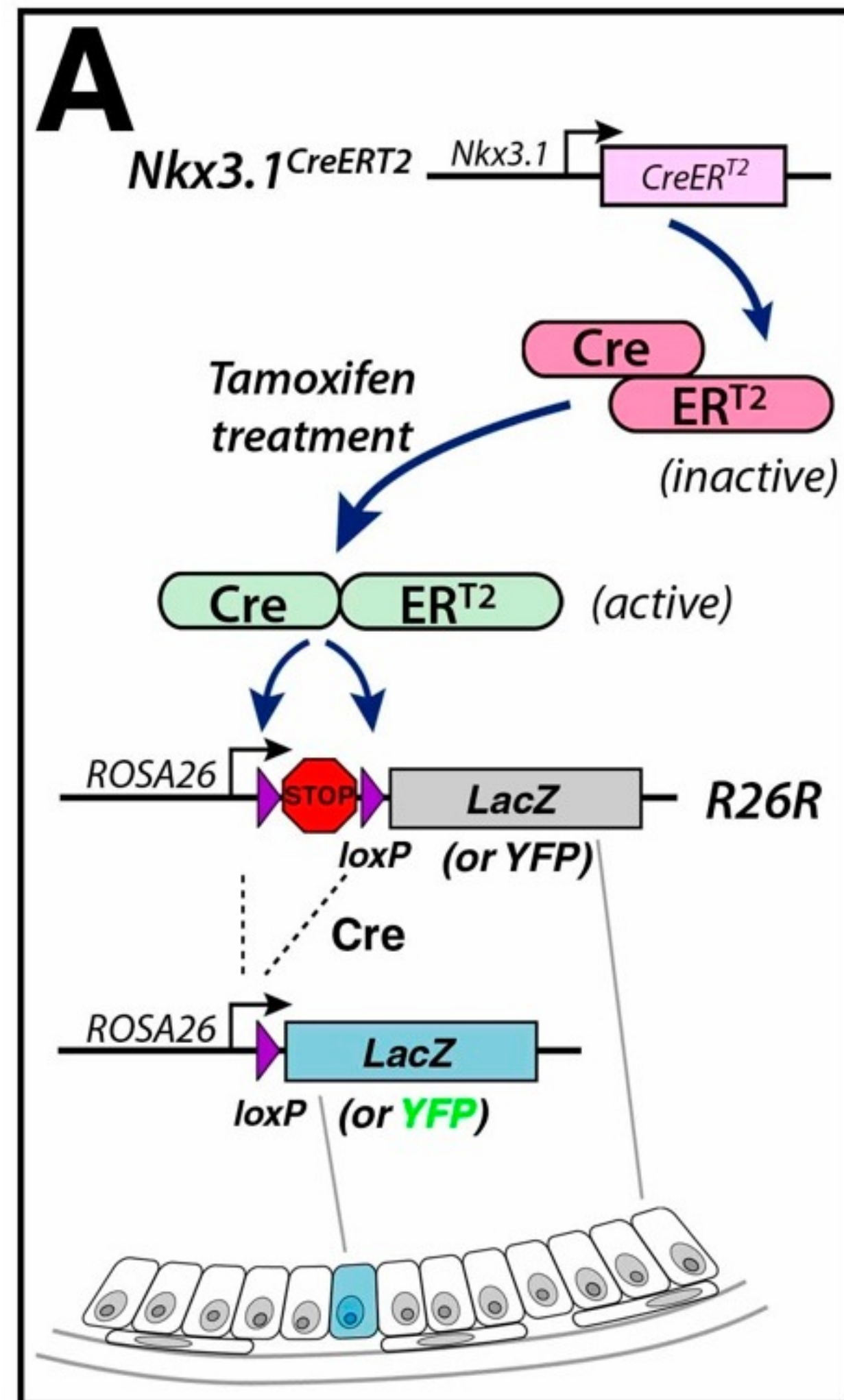
(Wang et al., Nature 2009)

A series of GEMMs that model all stages of prostate cancer

	Abbreviation	Full description	Phenotype	Mets
Outcome Group 1: Indolent	N	$Nkx3.1^{CreERT2/+}; Pten^{+/+}$	Low-grade PIN	0%
	NP	$Nkx3.1^{CreERT2/+}; Pten^{flox/flox}$	High-grade PIN/Adenocarcinoma	<5%
	NPE	$Nkx3.1^{CreERT2/+}; Pten^{flox/flox}; R26R-Erg$	High-grade PIN/Adenocarcinoma	<5%
Outcome Group 2: Adeno carcinoma	NPM	$Nkx3.1^{CreERT2/+}; Pten^{flox/flox}; Hi-Myc$	Adenocarcinoma	~40%
	NPp53	$Nkx3.1^{CreERT2/+}; Pten^{flox/flox}; p53^{flox/flox}$	Aggressive Adenocarcinoma/NEPC	~50%
	NPp53^{mut}	$Nkx3.1^{CreERT2/+}; Pten^{flox/flox}; p53^{R270H/flox}$	Aggressive Adenocarcinoma/NEPC	~50%
	NPp53Br1	$Nkx3.1^{CreERT2/+}; Pten^{flox/flox}; p53^{flox/flox}; Brca1^{flox/flox}$	Aggressive Adenocarcinoma/NEPC	~80%
	NPp53Br2	$Nkx3.1^{CreERT2/+}; Pten^{flox/flox}; p53^{flox/flox}; Brca2^{flox/flox}$	Aggressive Adenocarcinoma/NEPC	~80%
Outcome Group 3: Lethal	NPB	$Nkx3.1^{CreERT2/+}; Pten^{flox/flox}; B-Raf^{V600E}$	Poorly differentiated adenocarcinoma	100%
	NPK	$Nkx3.1^{CreERT2/+}; Pten^{flox/flox}; Kras^{G21D}$	Poorly differentiated adenocarcinoma	100%

GEMMs model the full range of prostate cancer phenotypes
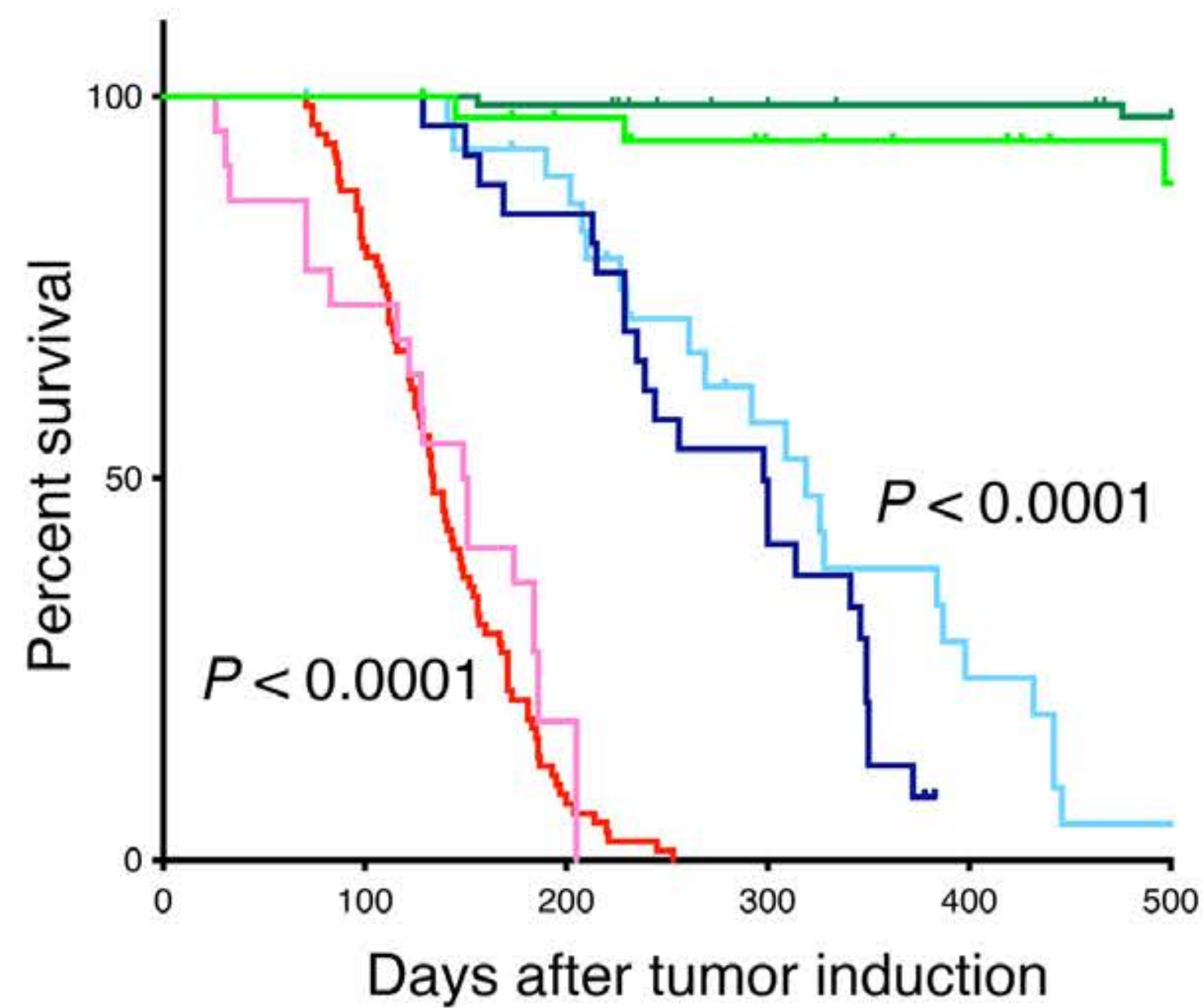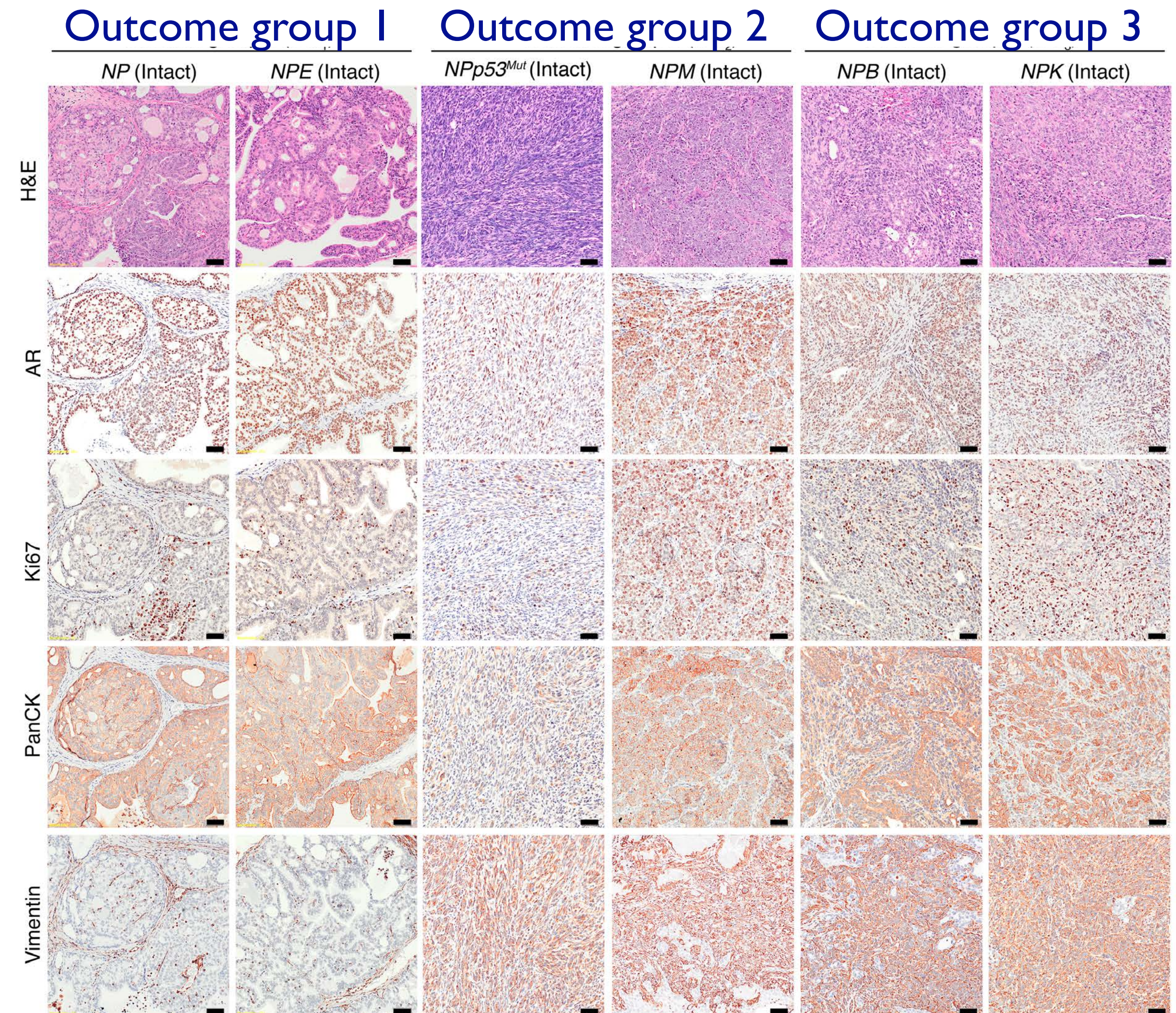
(*Vasciaveo, Arriaga, Nunes de Almeida et al, Cancer Discovery, 2023*)

Prostate cancer GEMMs available at the Jackson Laboratory

JAX#033750 STOCK Gt(ROSA)26Sor<tm3(CAG-EYFP)Hze> Nkx3-1<tm4(cre/ERT2)Mms>/AbshnJ
Common Name: N

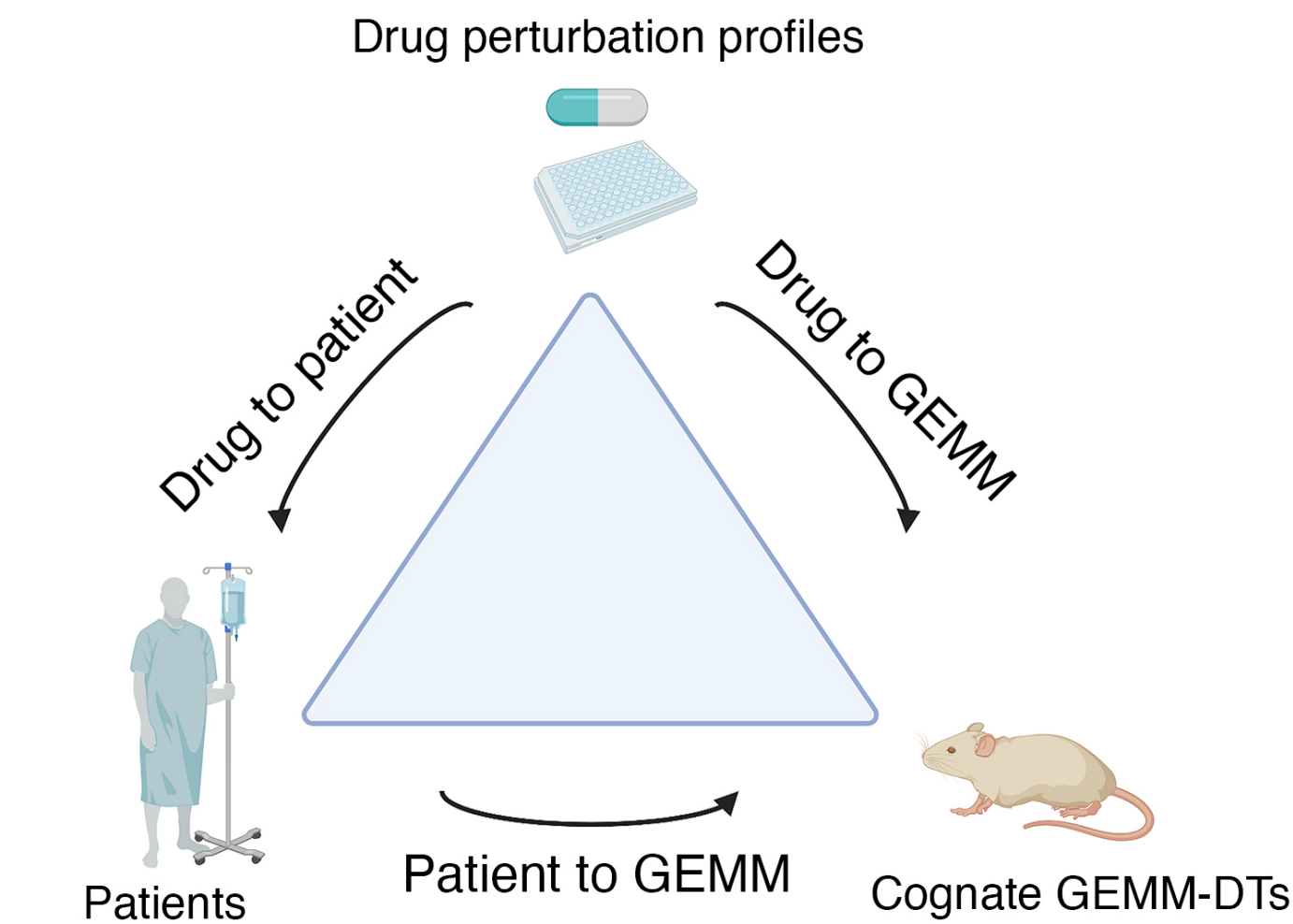JAX#033751 STOCK Gt(ROSA)26Sor<tm3(CAG-EYFP)Hze> Nkx3-1<tm4(cre/ERT2)Mms> Pten<tm1Hwu>/AbshnJ
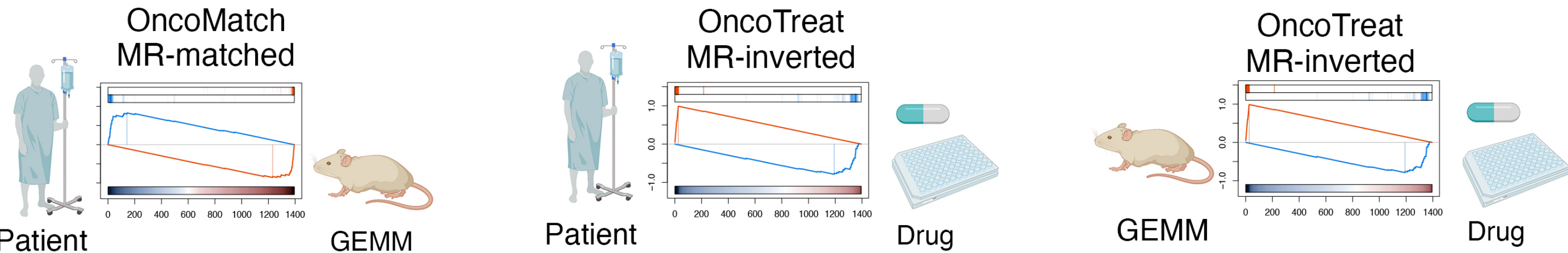Common Name: NP

JAX#033752 STOCK Gt(ROSA)26Sor<tm1(TMPRSS2/ERG)Key> Nkx3-1<tm4(cre/ERT2)Mms> Pten<tm1Hwu>/AbshnJ
Common Name: NPE

JAX#033753 STOCK Gt(ROSA)26Sor<tm3(CAG-EYFP)Hze> Brca1<tm2Cxd> Nkx3-1<tm4(cre/ERT2)Mms> Pten<tm1Hwu>/AbshnJ
Common Name: NPBR1

JAX#033754 STOCK Brca2<tm1Brn> Gt(ROSA)26Sor<tm3(CAG-EYFP)Hze> Trp53<tm1Brn> Nkx3-1<tm4(cre/ERT2)Mms> Pten<tm1Hwu>/AbshnJ
Common Name: NPp53BR2

JAX#033755 STOCK Gt(ROSA)26Sor<tm3(CAG-EYFP)Hze> Trp53<tm1Brn> Nkx3-1<tm4(cre/ERT2)Mms> Pten<tm1Hwu>/AbshnJ
Common Name: NPp53

JAX#033756 STOCK Gt(ROSA)26Sor<tm3(CAG-EYFP)Hze> Trp53<tm1Brn> Trp53<tm3Tyj> Nkx3-1<tm4(cre/ERT2)Mms> Pten<tm1Hwu>/AbshnJ
Common Name: NPp53MUT

JAX#033757 STOCK Gt(ROSA)26Sor<tm3(CAG-EYFP)Hze> Nkx3-1<tm4(cre/ERT2)Mms> Pten<tm1Hwu> Tg(ARR2/Pbsn-MYC)7Key/AbshnJ
Common Name: NPM

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Common Name: NPS

JAX#033760 STOCK Braf<tm1Mmcm> Gt(ROSA)26Sor<tm3(CAG-EYFP)Hze> Nkx3-1<tm4(cre/ERT2)Mms> Pten<tm1Hwu>/AbshnJ
Common Name: NPB

JAX#033761 STOCK Gt(ROSA)26Sor<tm3(CAG-EYFP)Hze> Kras<tm4Tyj> Nkx3-1<tm4(cre/ERT2)Mms> Pten<tm1Hwu>/AbshnJ
Common Name: NPK

JAX#033763 STOCK Gt(ROSA)26Sor<tm2(myc*T58A)Rcse> Nkx3-1<tm4(cre/ERT2)Mms> Pten<tm1Hwu>/AbshnJ
Common Name: NPMycTA

https://www.jax.org/

JAX Strain Datasheet

The Jackson Laboratory
Leading the search for tomorrow's cures

OncoLoop: A network-based precision cancer medicine framework

Conceptual Framework

Drug perturbation profiles

Drug to patient

Drug to GEMM

Patients

Patient to GEMM

Cognate GEMM-DTs

Network Analysis

GEMM data

Patient data

Drug perturbation data

PDX data

Gene expression profiling

Reverse engineer regulatory networks

Protein activity signatures

Regulatory proteins

Expression signature

Oncoloop Analysis

OncoMatch MR-matched

Patient

GEMM

OncoTreat MR-inverted

Patient

Drug

OncoTreat MR-inverted

GEMM

Drug

Drug prediction and validation

OncoLoop

P

D

G

Candidate drugs

In vivo validation

Allograft

Syngeneic

PDX
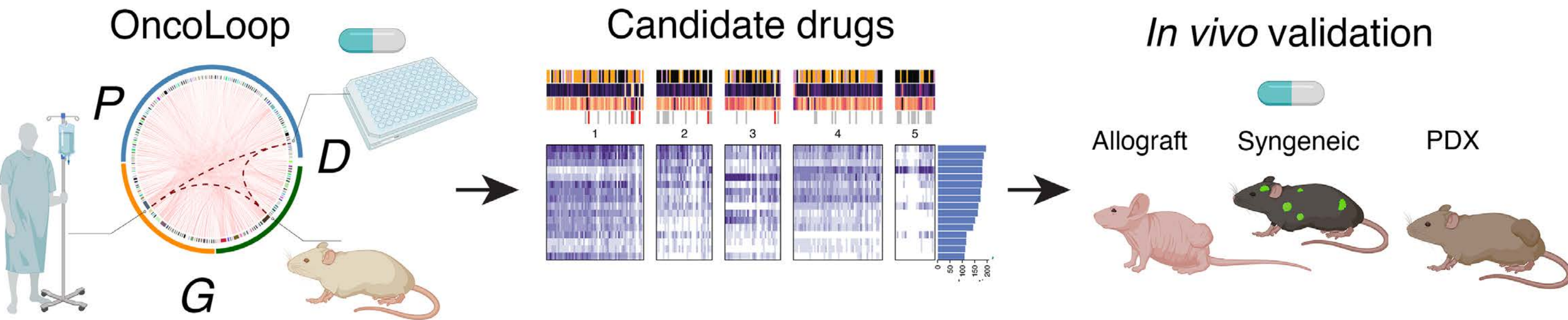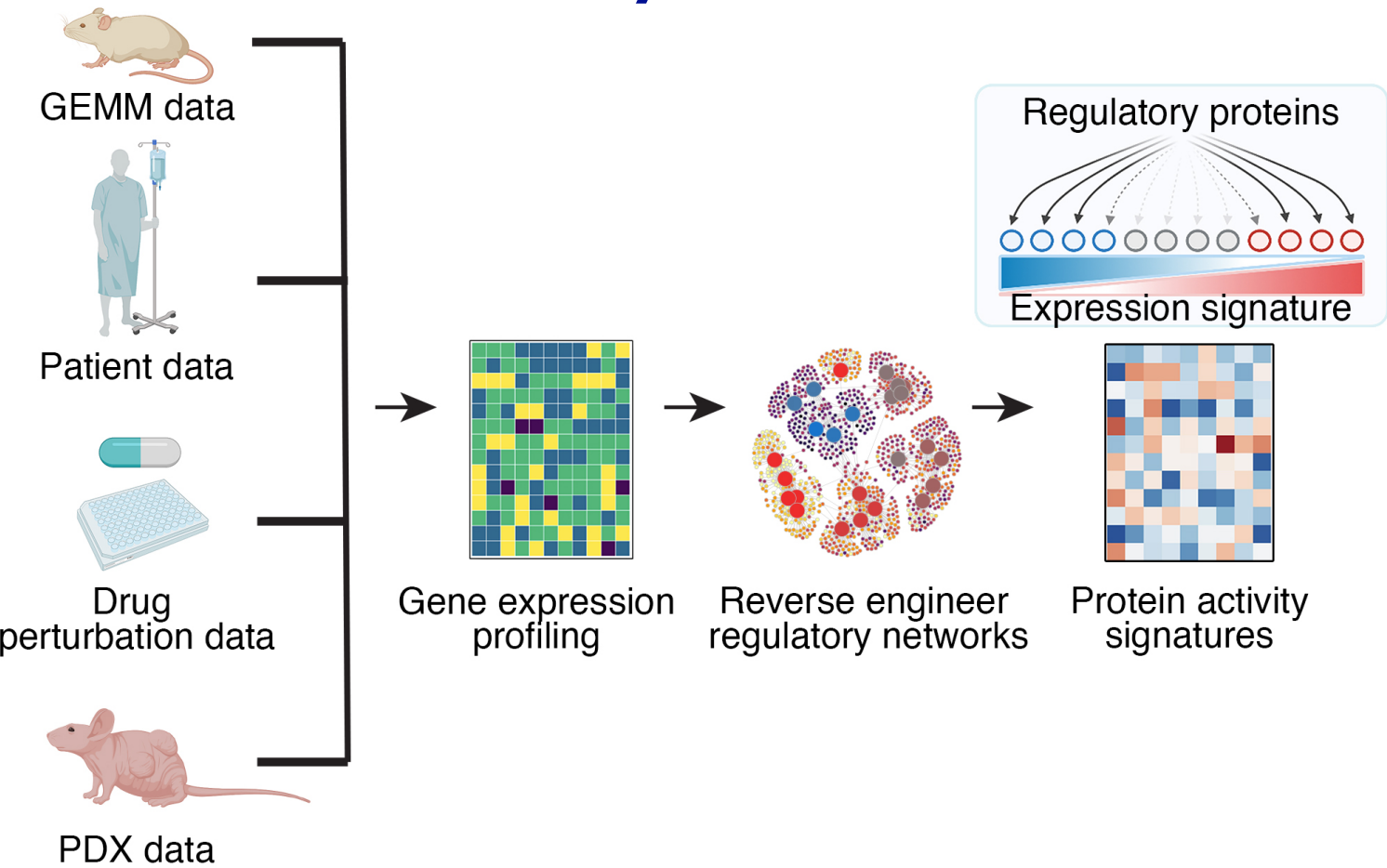
(Vasciaveo, Arriaga, Nunes de Almeida et al, Cancer Discovery, 2023)

Lineage plasticity in development and cancer

"ability of a cell to change from one identity to another"
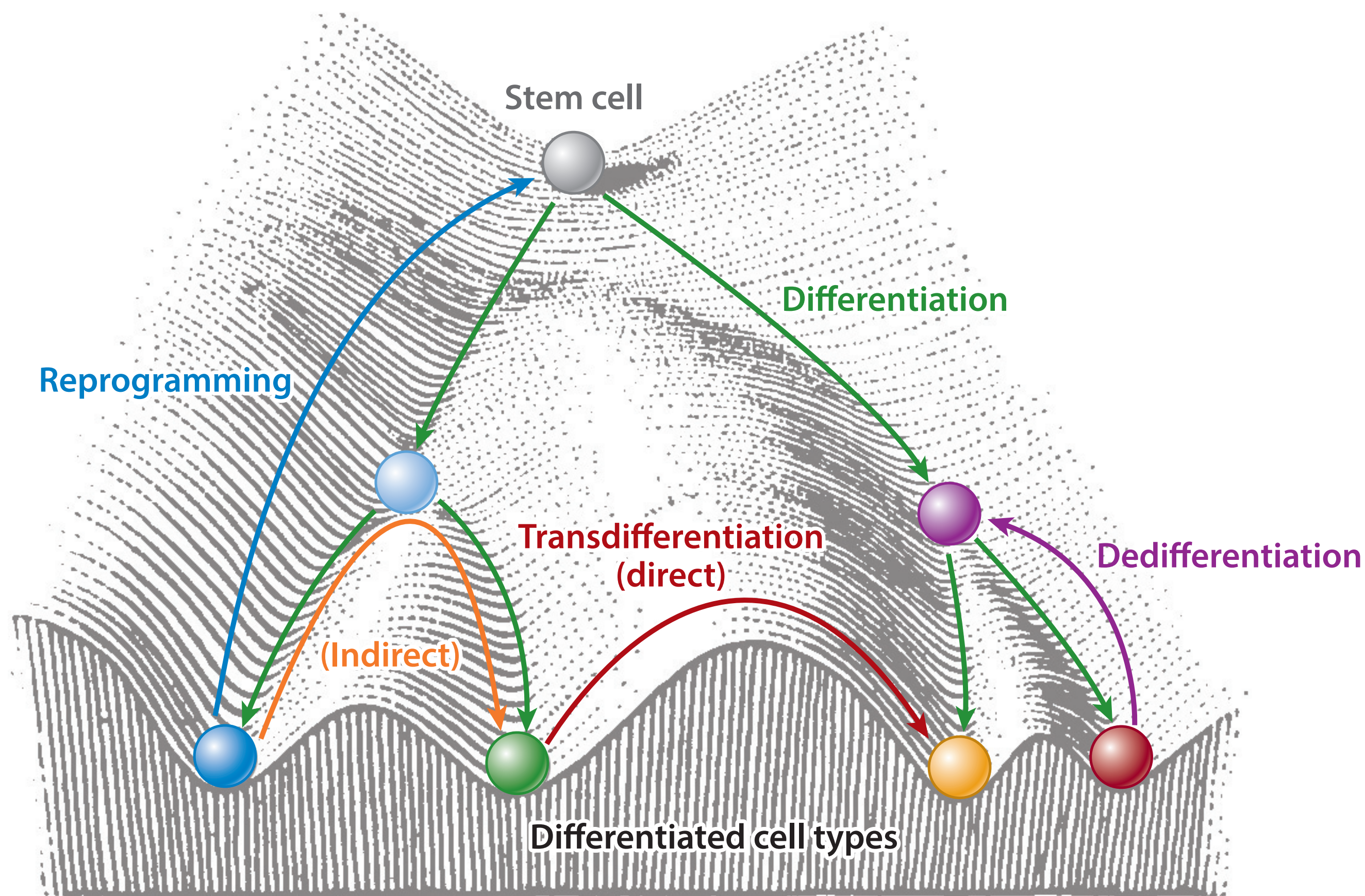
- A phenotypic change in cellular state at the single-cell level, often in response to microenvironmental signals or drug treatment

- Can occur through alterations at the genomic, epigenetic, transcriptional, or post-transcriptional level

- Can be reversible or irreversible

- Can be difficult to distinguish from clonal selection at the population level

Le Magnen *et al.* (2018) *Annu. Rev. Cancer Biol.* 2: 271-289

A series of GEMMs that model all stages of prostate cancer
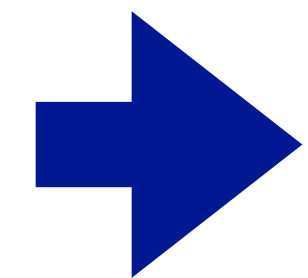
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NPp53Br1	$Nkx3.1^{CreERT2/+}; Pten^{flox/flox}; p53^{flox/flox}; Brca1^{flox/flox}$	Aggressive Adenocarcinoma/NEPC	~80%
NPp53Br2	$Nkx3.1^{CreERT2/+}; Pten^{flox/flox}; p53^{flox/flox}; Brca2^{flox/flox}$	Aggressive Adenocarcinoma/NEPC	~80%
NPB	$Nkx3.1^{CreERT2/+}; Pten^{flox/flox}; B-Raf^{V600E}$	Poorly differentiated adenocarcinoma	100%
NPK	$Nkx3.1^{CreERT2/+}; Pten^{flox/flox}; Kras^{G21D}$	Poorly differentiated adenocarcinoma	100%

PTEN and *TP53* up-regulated in castration-resistant prostate cancer (CRPC)

PTEN
TP53

| | Deep Deletion | ▪ Missense Mutation | ▪ Inframe Mutation | ▪ Truncating Mutation | ❭ Fusion |

TCGA % cases w/ alterations

| | 0 | 20 | 40 | 60 | 80 | 100 |

PTEN — 17%
TP53 — 8%
PTEN + TP53 — 1.5%

SU2C % cases w/alterations

| | 0 | 20 | 40 | 60 | 80 | 100 |

PTEN — 40%
TP53 — 50%
PTEN + TP53 — 23%
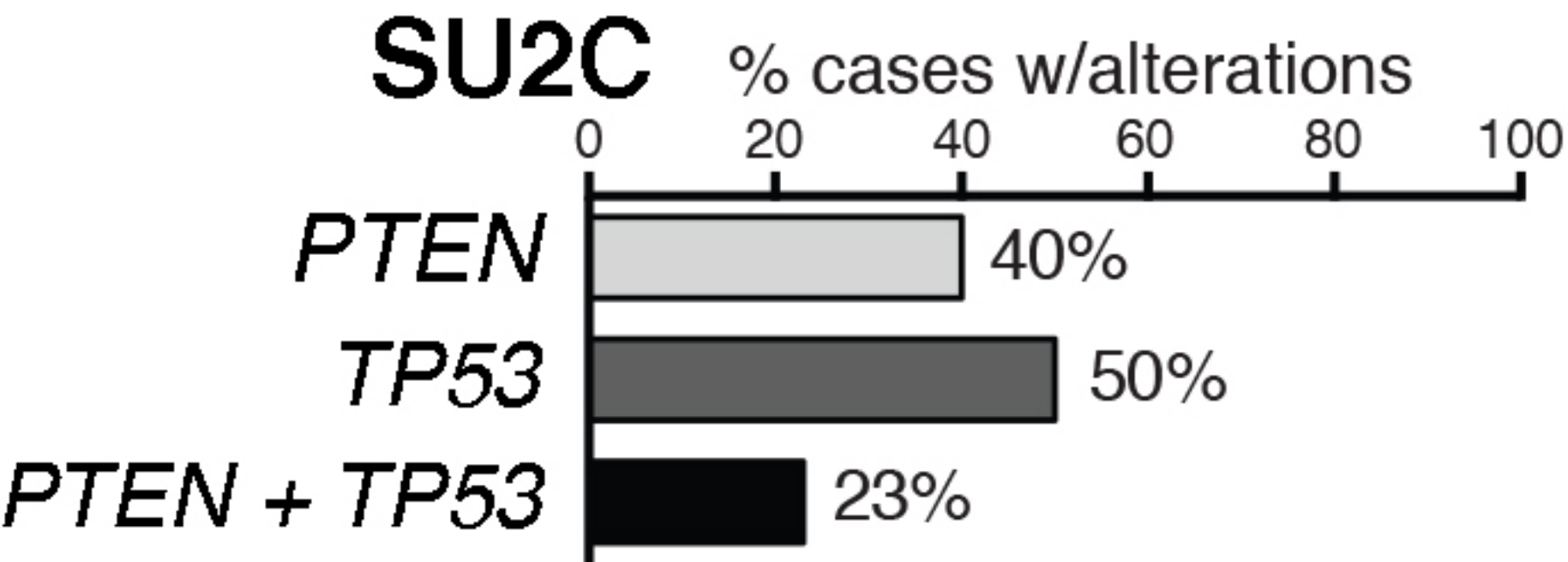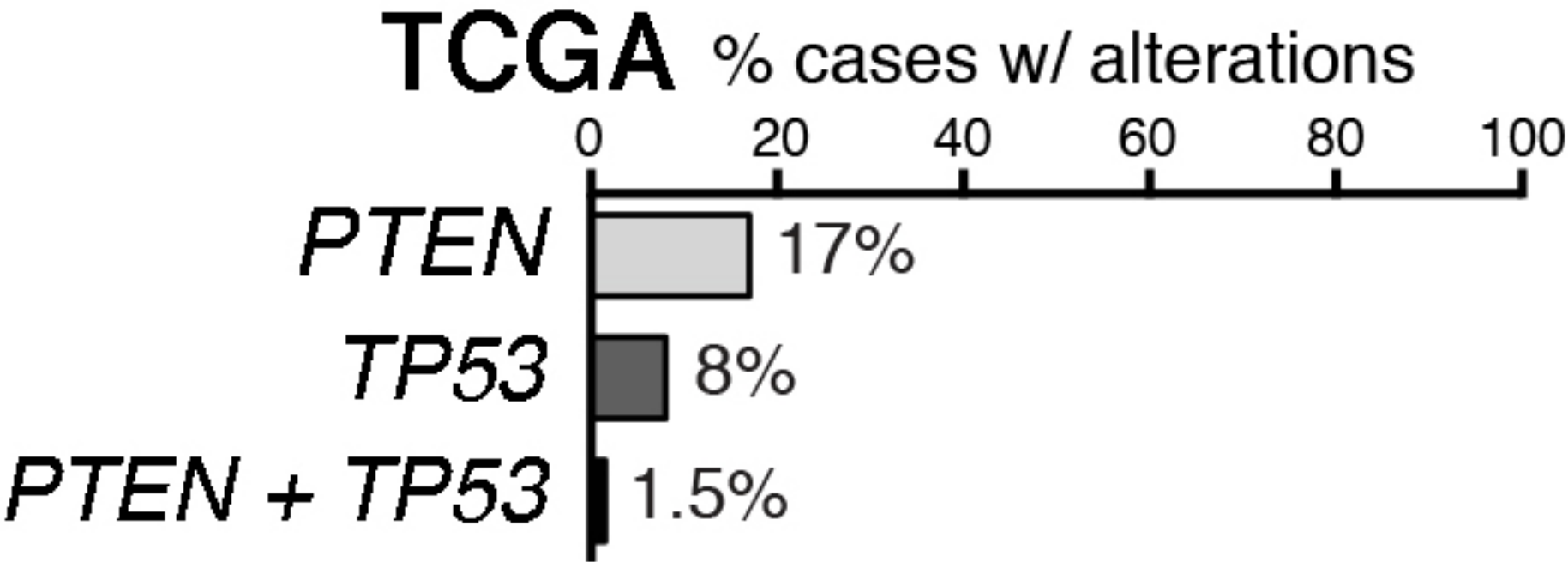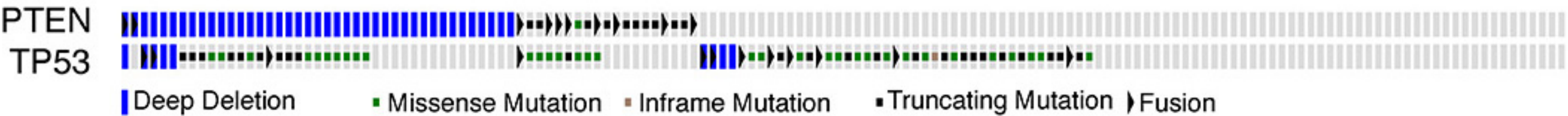
(Zou, …. Califano, Shen, Abate-Shen Cancer Discovery, 2017)

NPp53 mice share molecular features with human CRPC
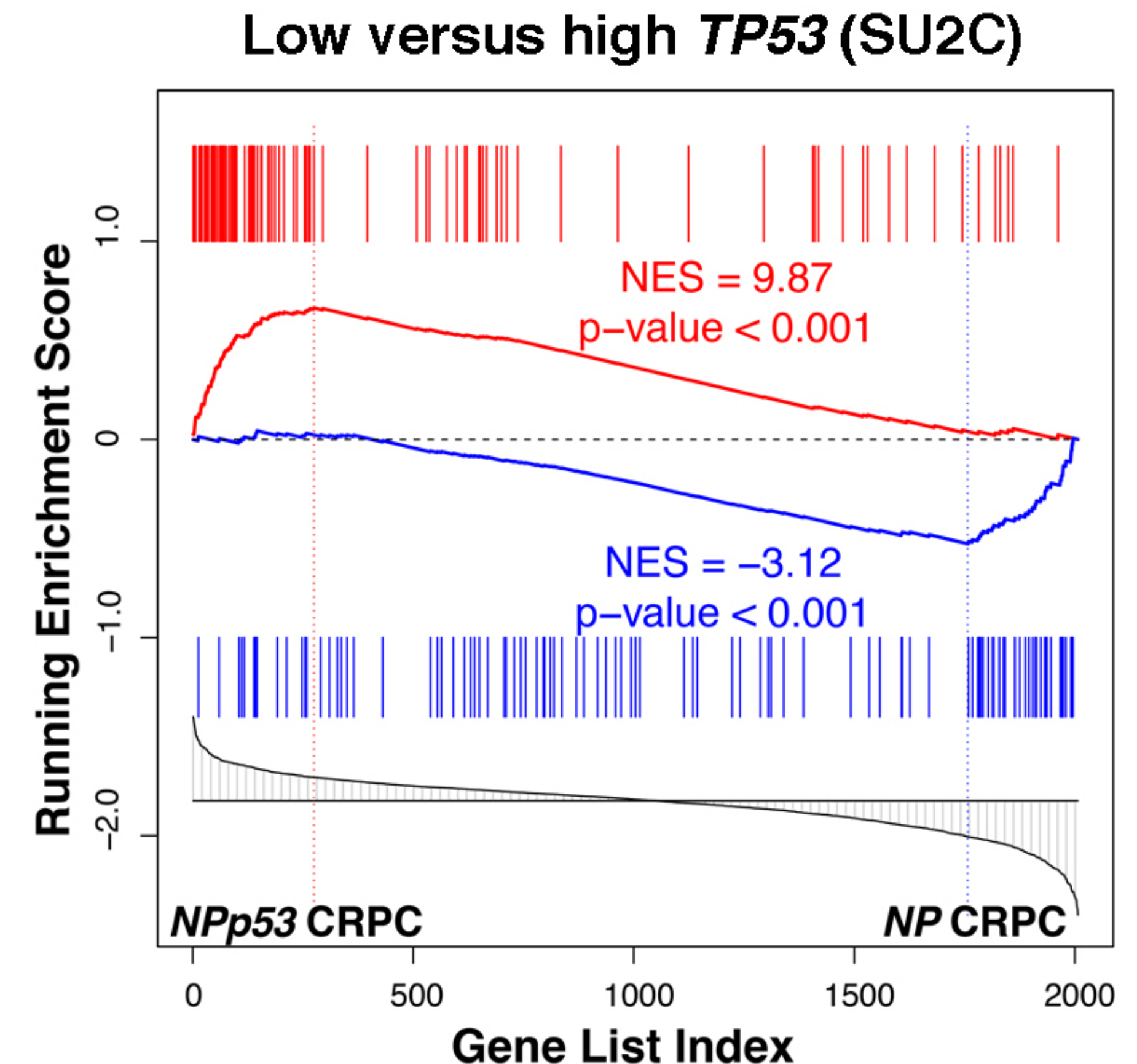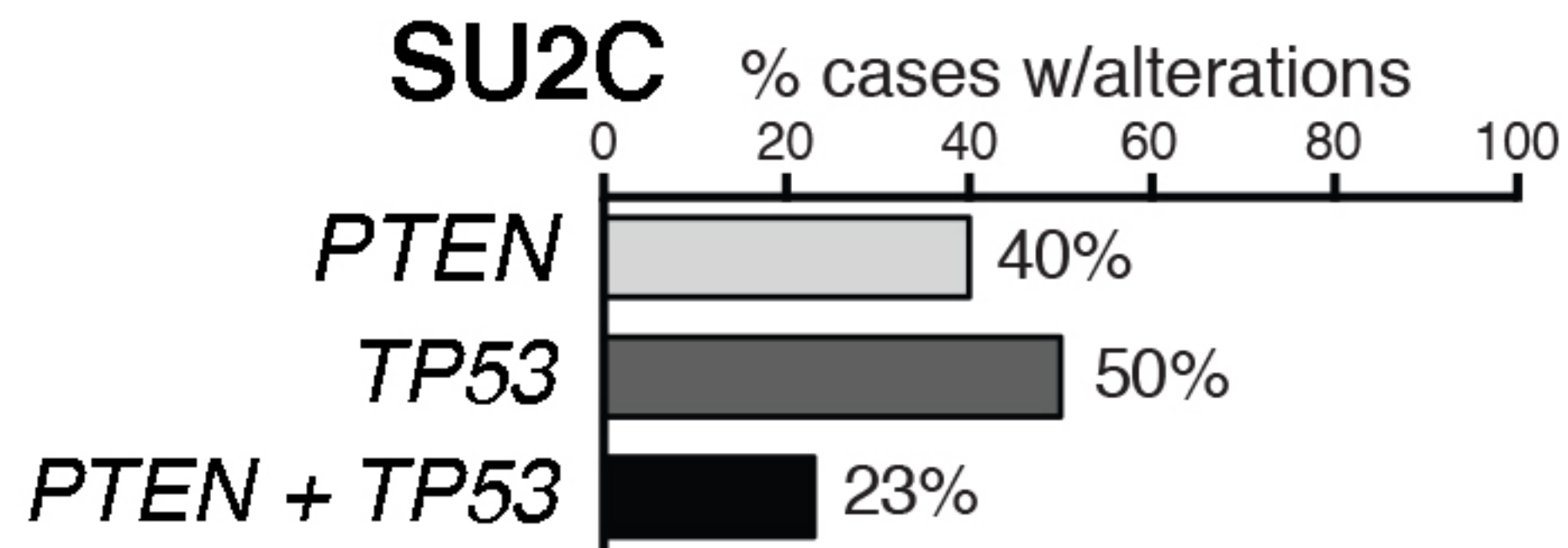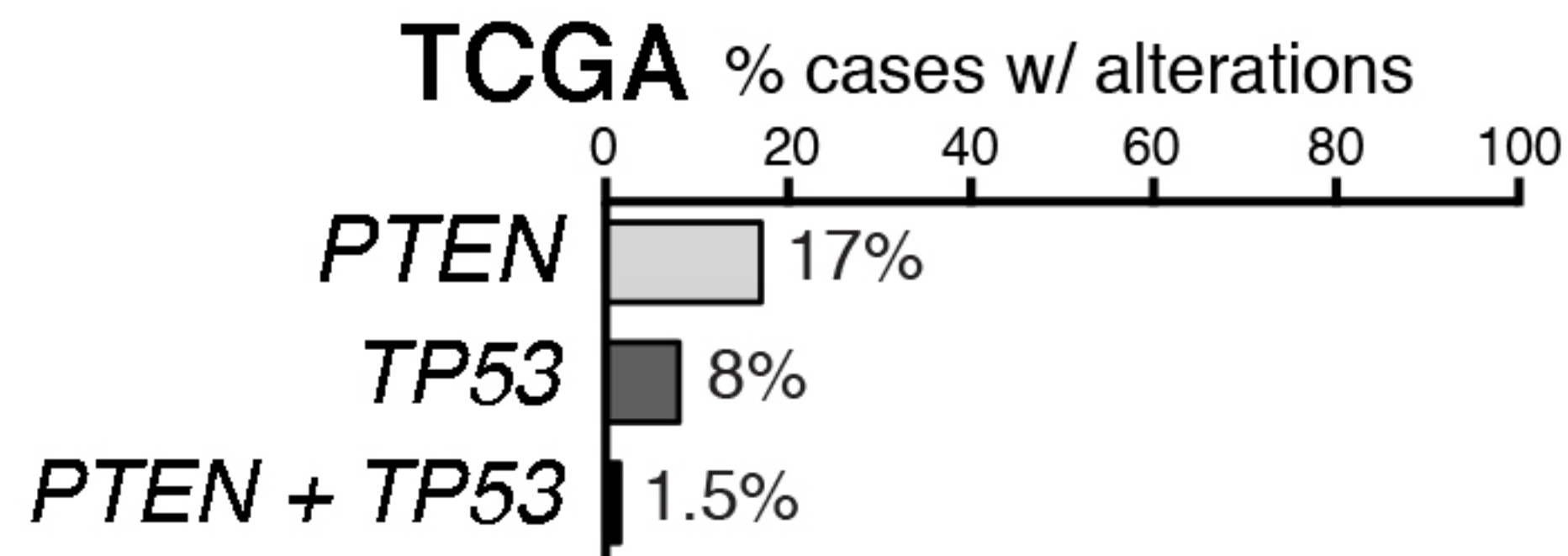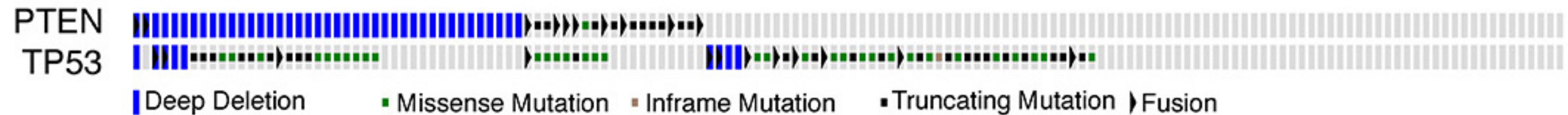
(Zou, …. Califano, Shen, Abate-Shen Cancer Discovery, 2017)

Abiraterone accelerates CRPC in *NPp53*
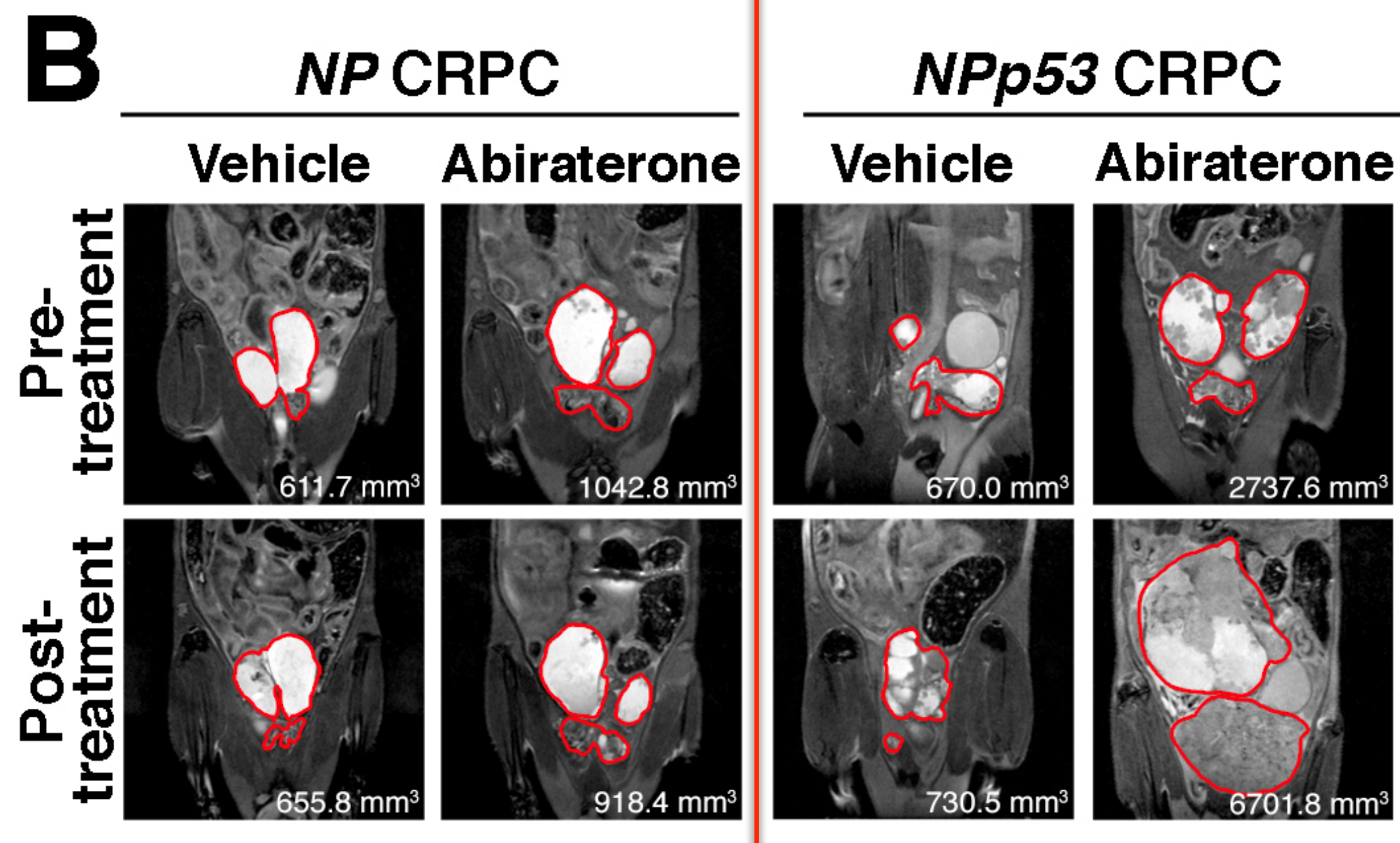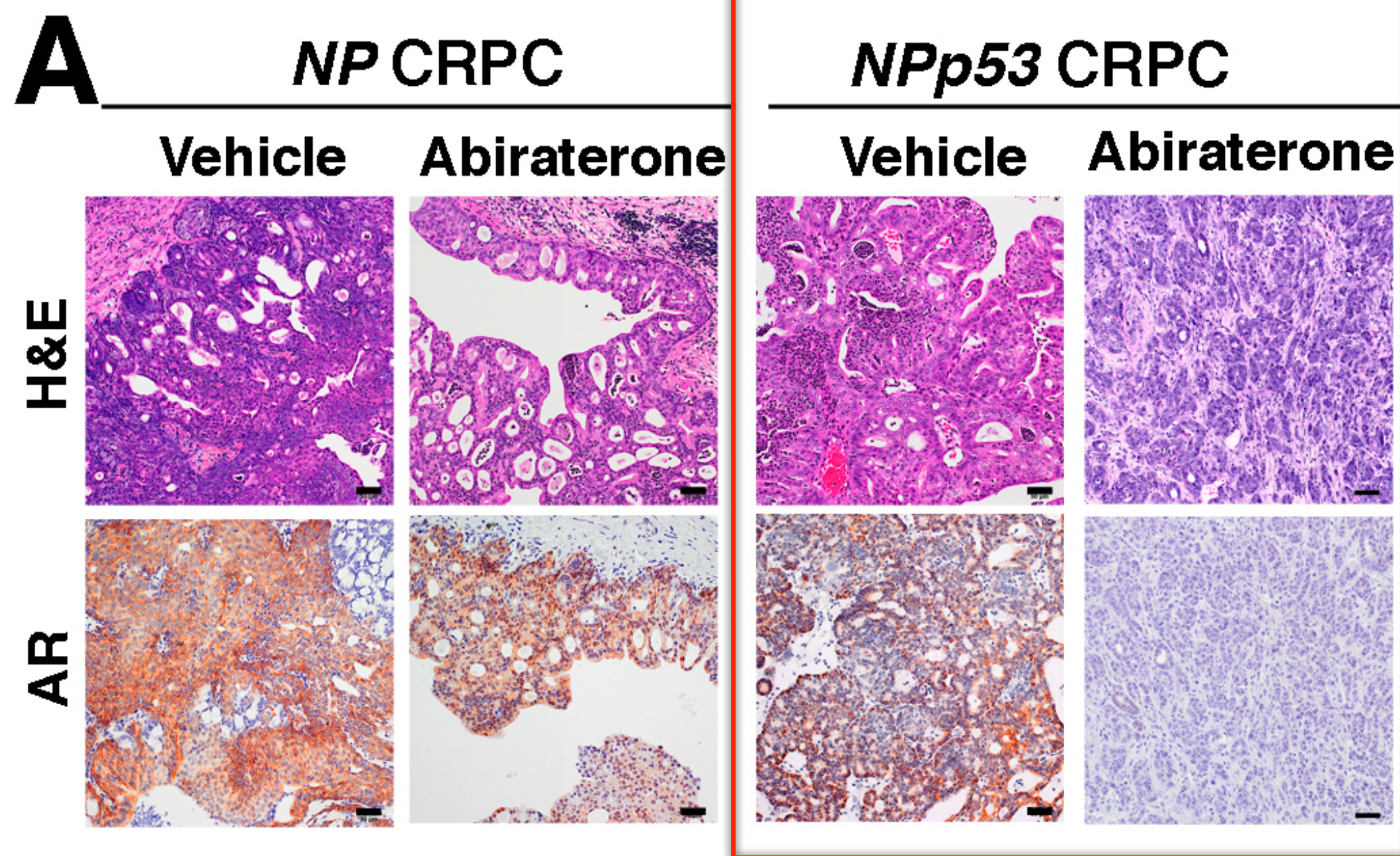
Neuroendocrine differentiation (NEPC) arises via transdifferentiation of adenocarcinoma cells
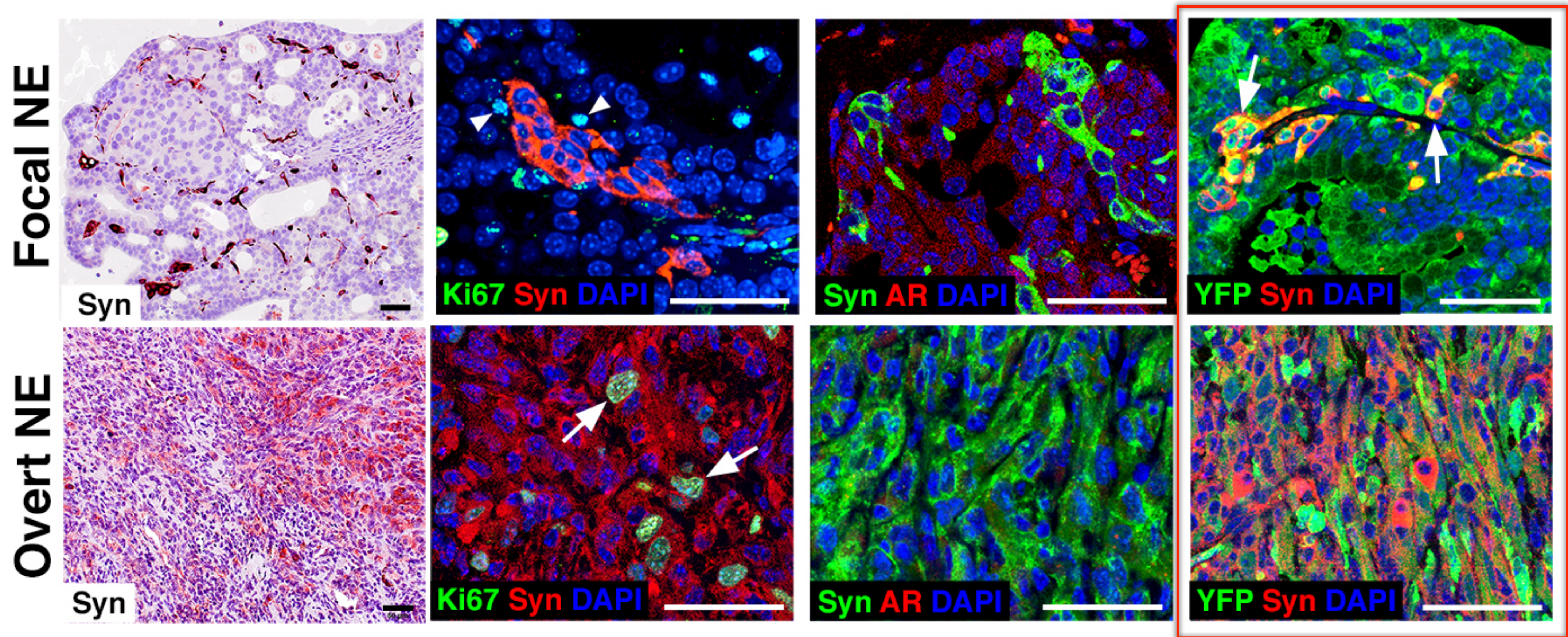
Treatment resistance leads to NEPC via transdifferentiation
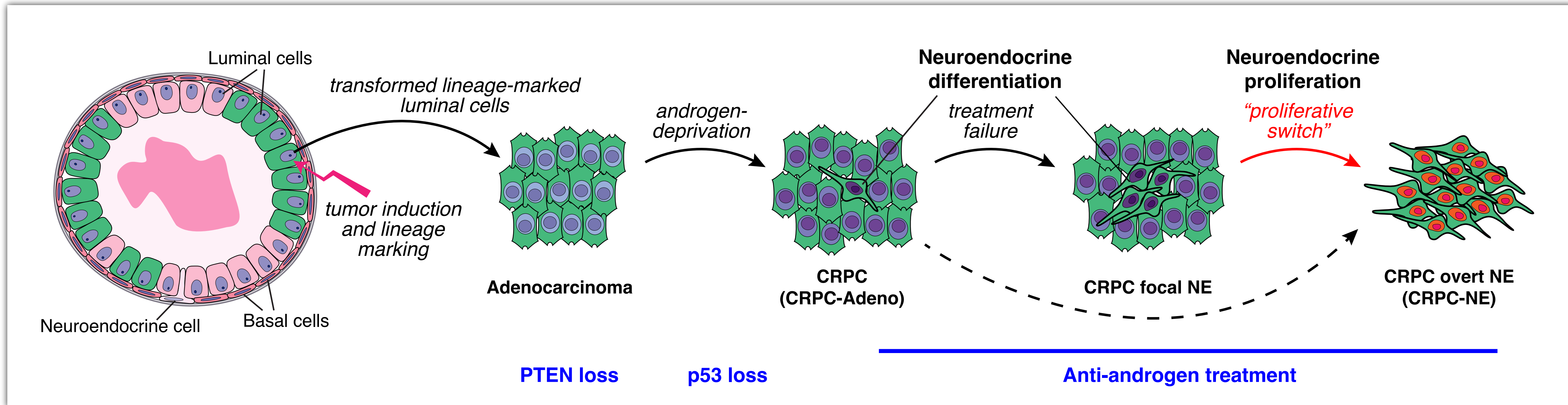
Sleeping beauty forward genetic screening

Adapted from Copeland and Jenkins (2010) Nat Rev Cancer
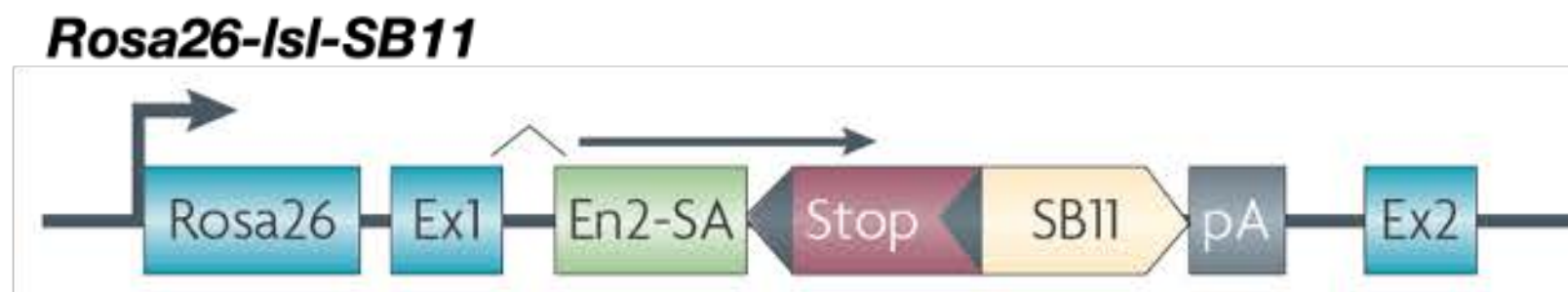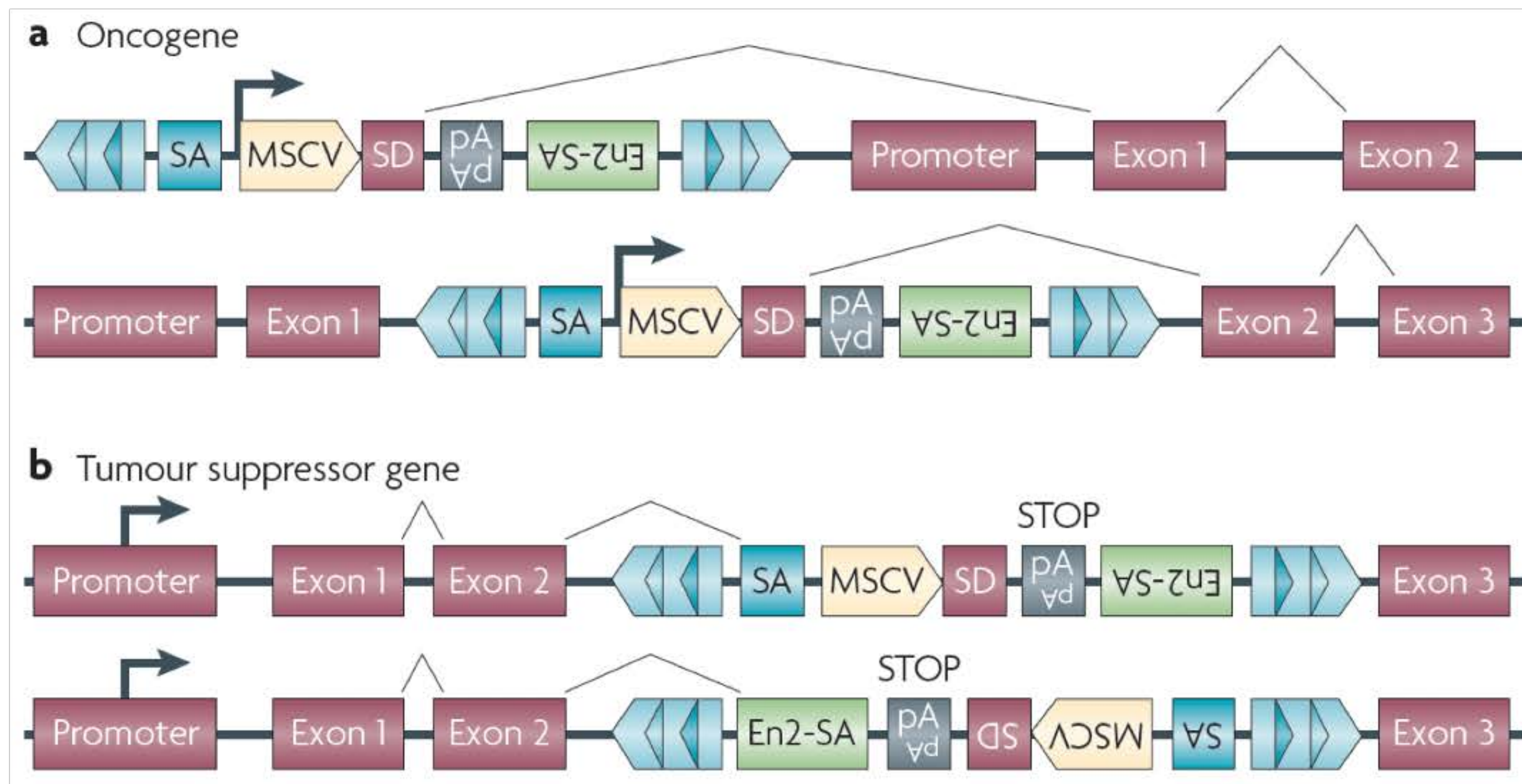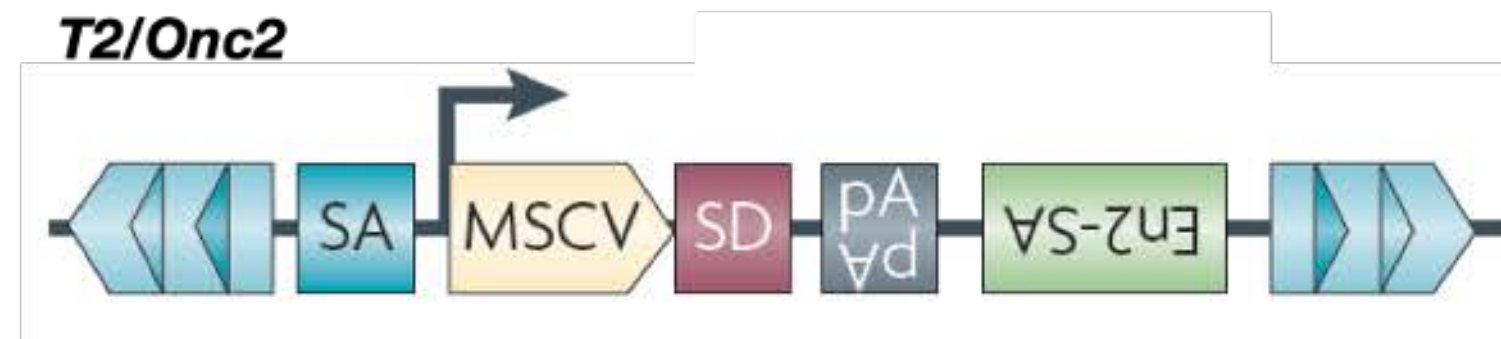
Francisca Nunes de Almeida

Forward genetic screen to identify drivers of NEPC

NPp53-SB(−)

Nkx3.1CreER$^{T2/+}$
Pten$^{flox/flox}$; p53$^{flox/flox}$
R26-LSL-SB$^{flox/flox}$
T2/Onc (−)

NPp53-SB(+)

Nkx3.1CreER$^{T2/+}$
Pten$^{flox/flox}$; p53$^{flox/flox}$
R26-LSL-SB$^{flox/flox}$
T2/Onc (+)

Birth

Tumor Induction

Monitoring

Endpoint

Months 2-3

9-15

Analysis

Phenotypic

Transcriptomic

Genomic sequencing (CIS)

$-\mathsf{l}-$ NPp53-SB(−) n=31
$+$ NPp53-SB(+) n=93

Log–rank
$P < 0.0001$

Survival probability (%)

Days after TAM

$P = 0.0001$

NEPC frequency (%)

NPp53-SB(−)   NPp53-SB(+)

AR   Syp   Sox2   Vim

NPp53-SB(−) Non-NEPC

NPp53-SB(+) Non-NEPC

NEPC

$P < 0.0001$

ns

Metastasis frequency (%)

Non-NEPC   Non-NEPC   NEPC

NPp53-SB(−)   NPp53-SB(+)

(Nunes de Almeida, Vasciaveo, Giacobbe, Zou, … Califano, Abate-Shen, In revision)

Sleeping beauty tumors enriched for a molecular signature of NEPC

Labrecque et al., 2019
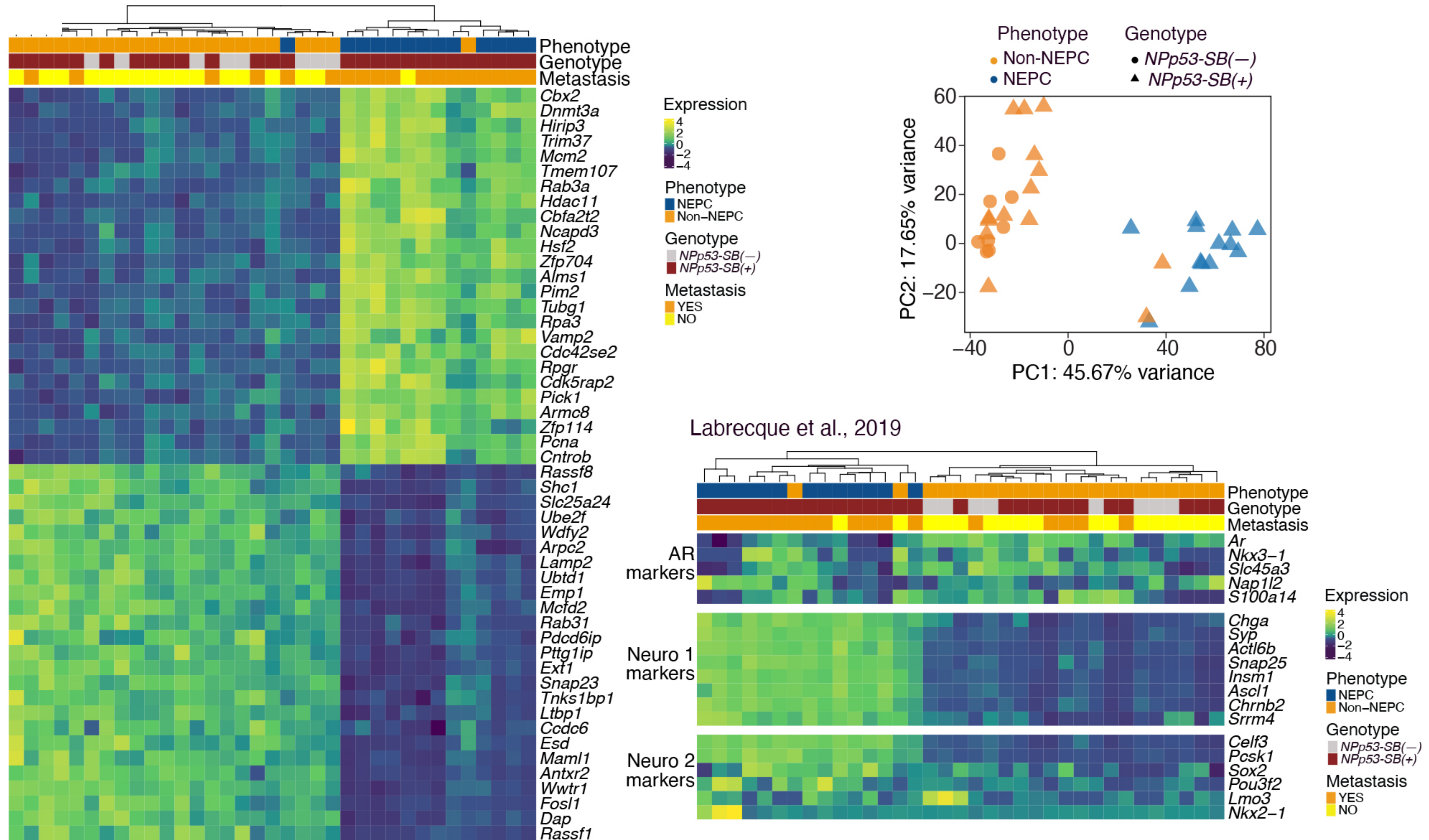
Sleeping beauty tumors enriched for master regulators of NEPC
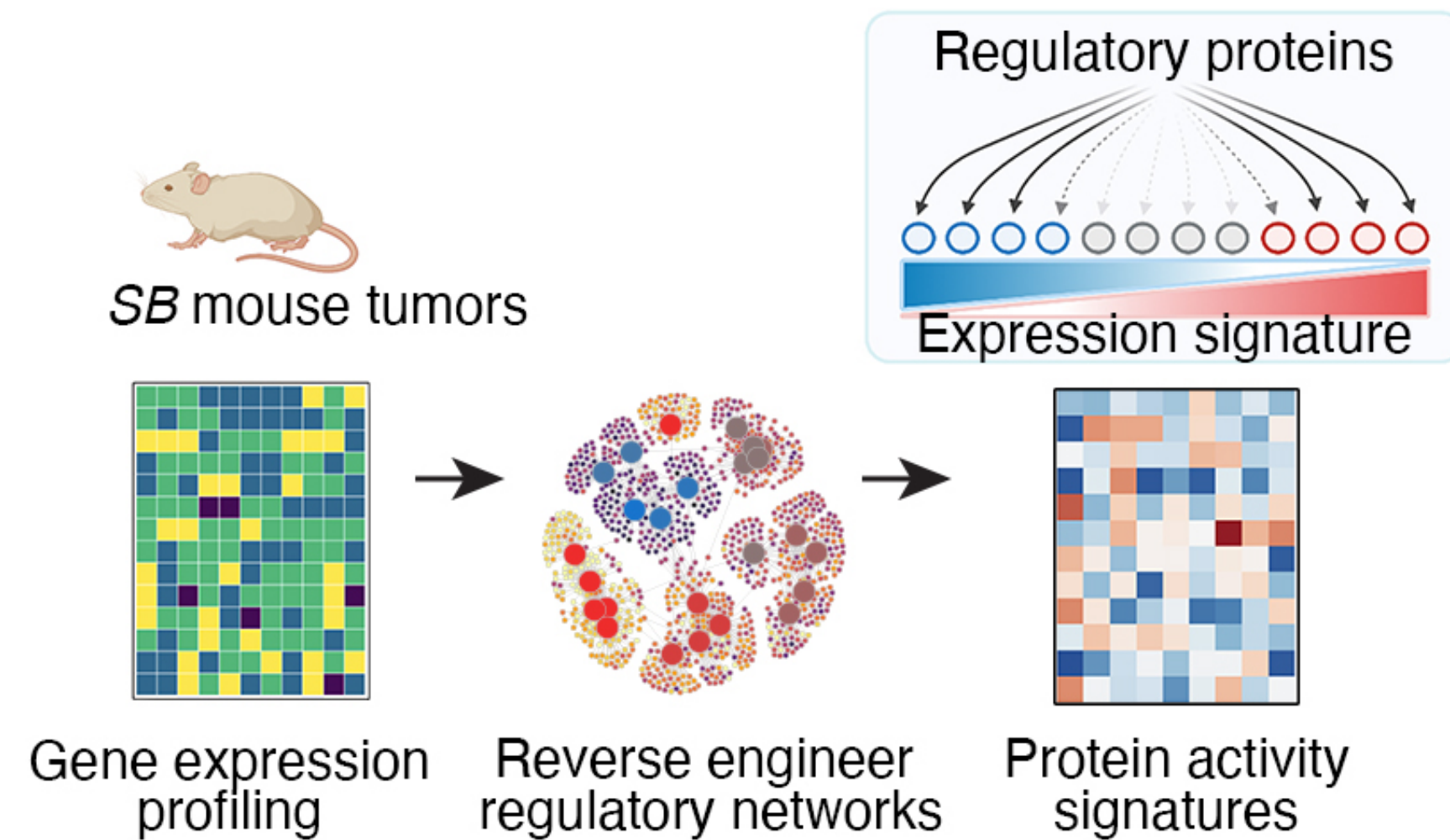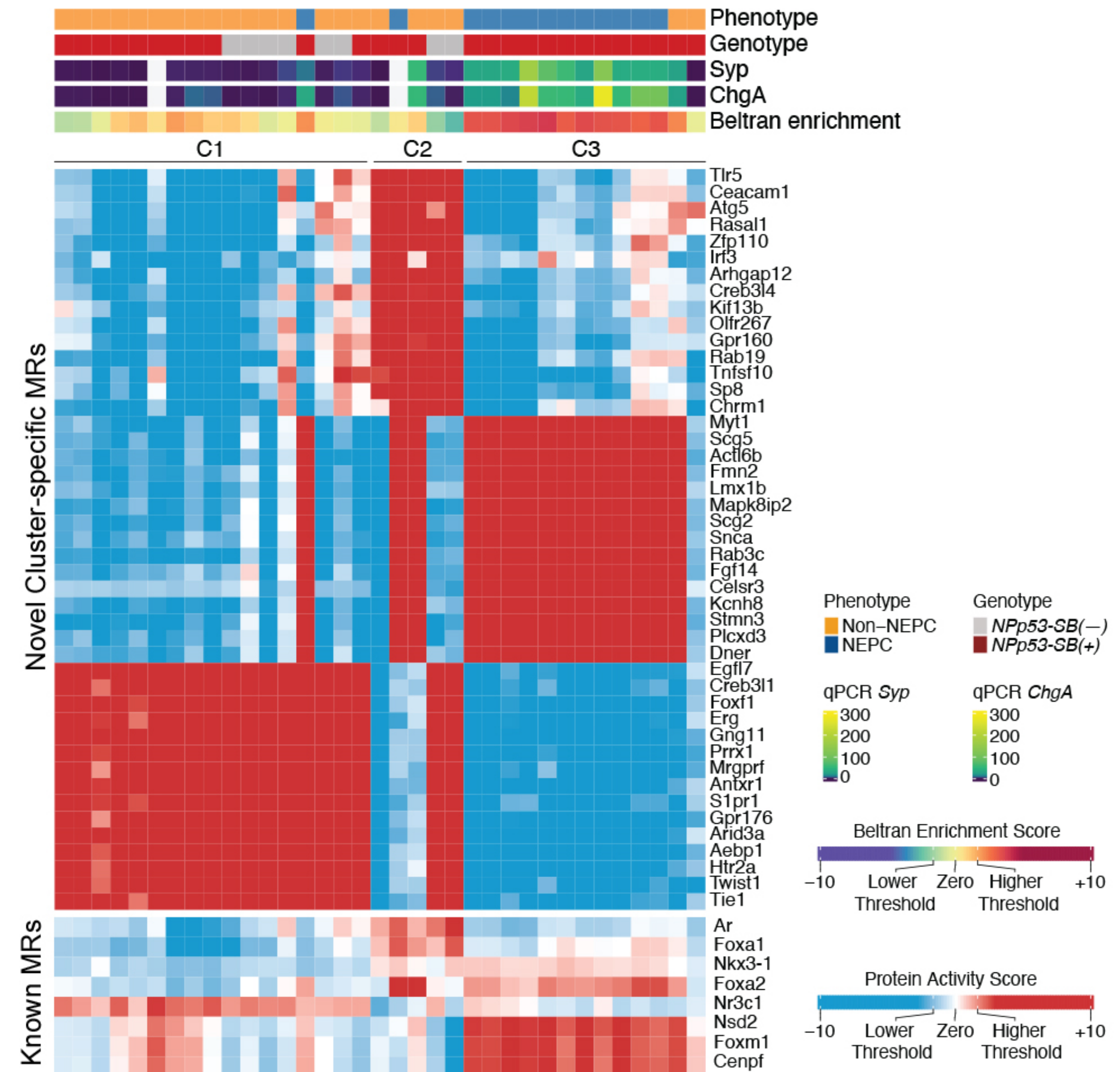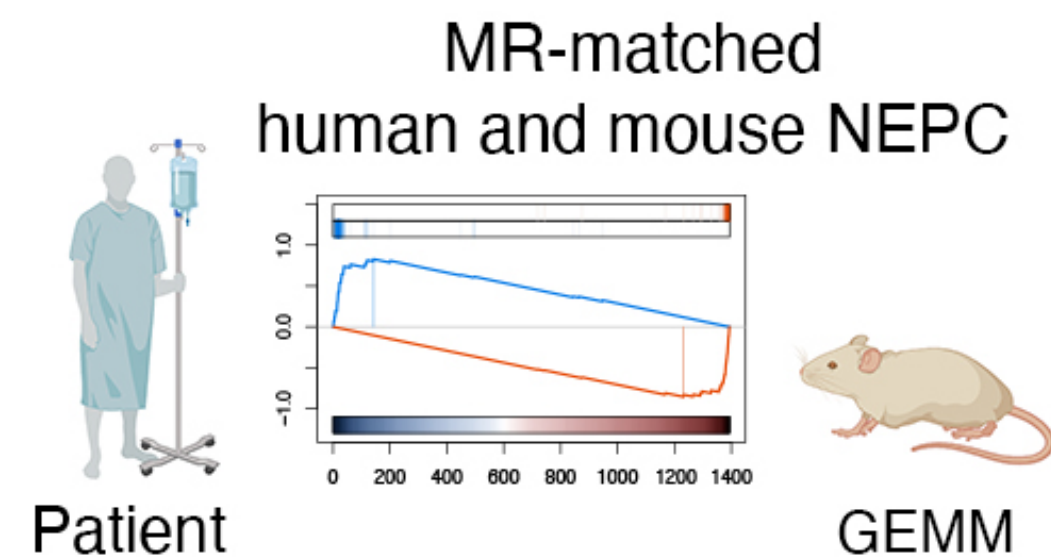
Sleeping beauty tumors "match" with NEPC patients
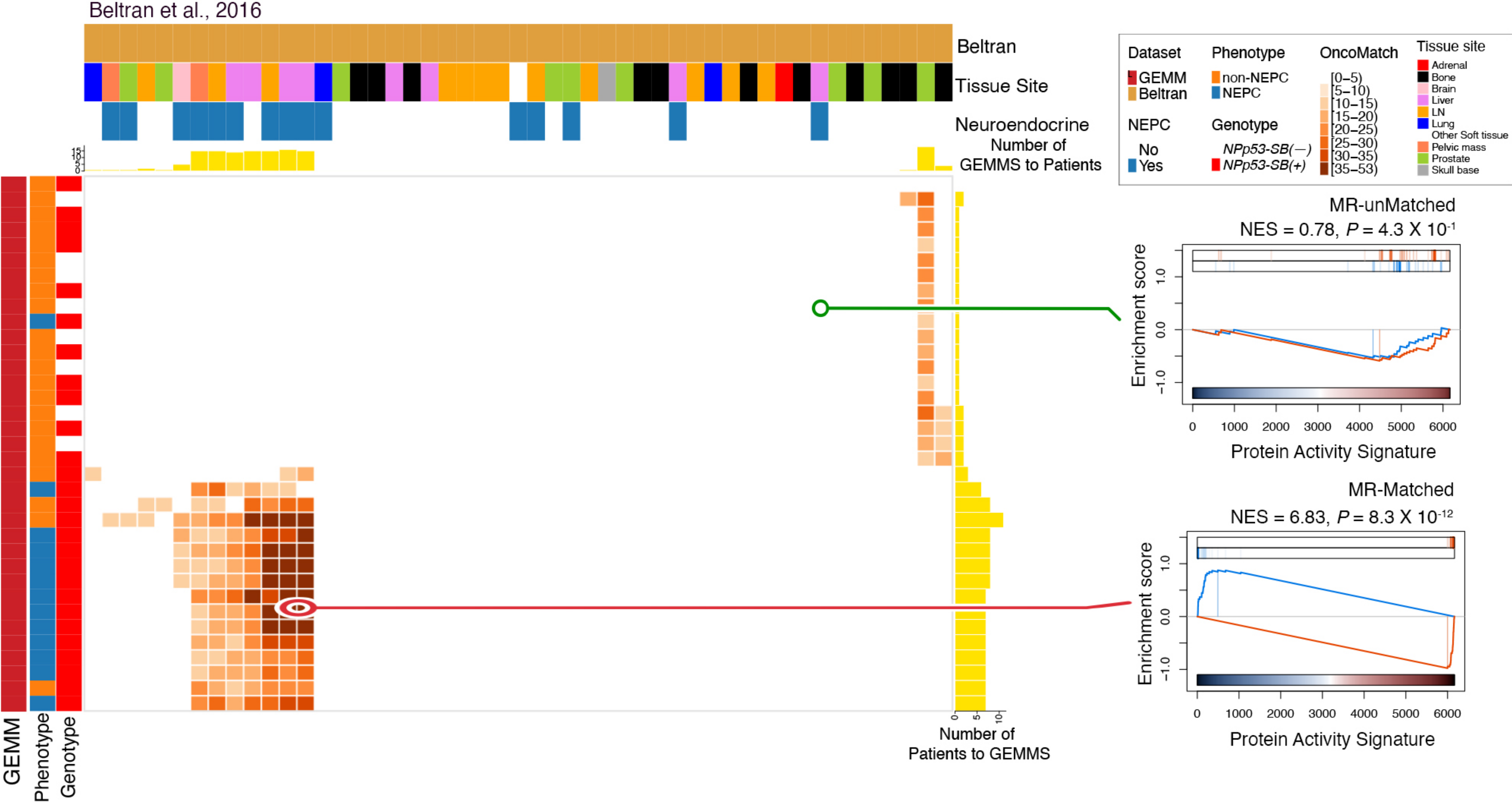
Common insertion sites (CIS) enriched for a molecular signature of NEPC
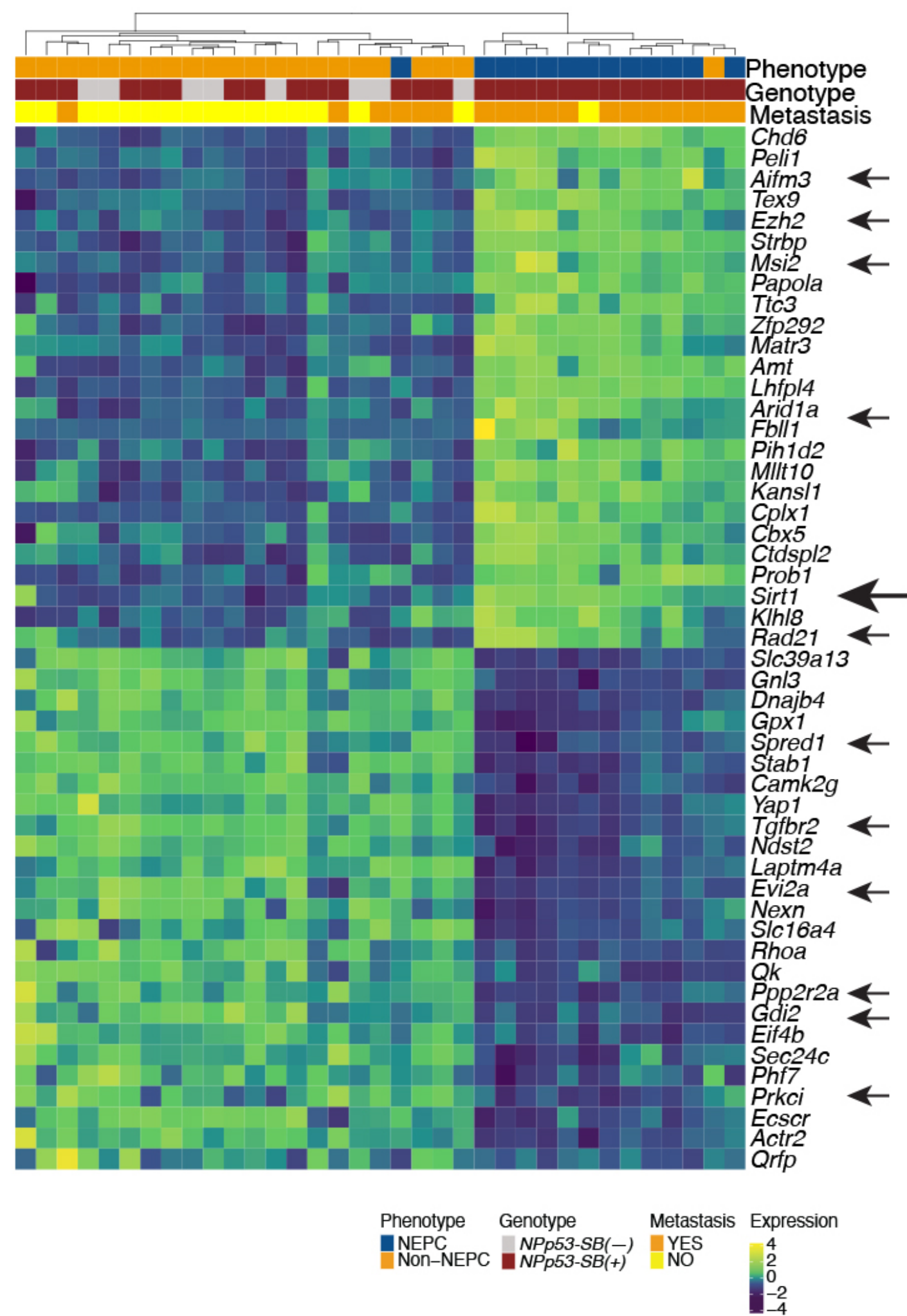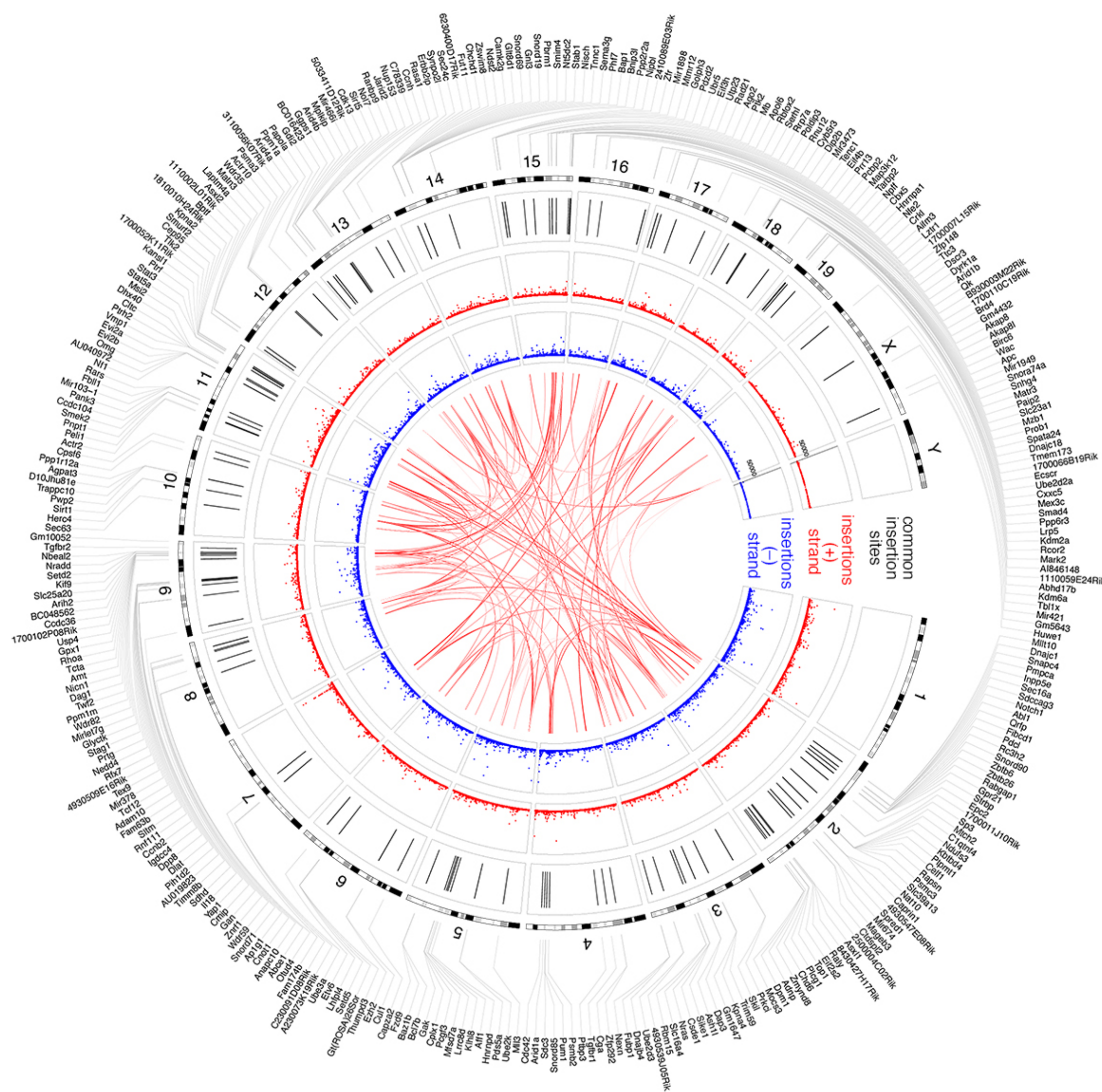
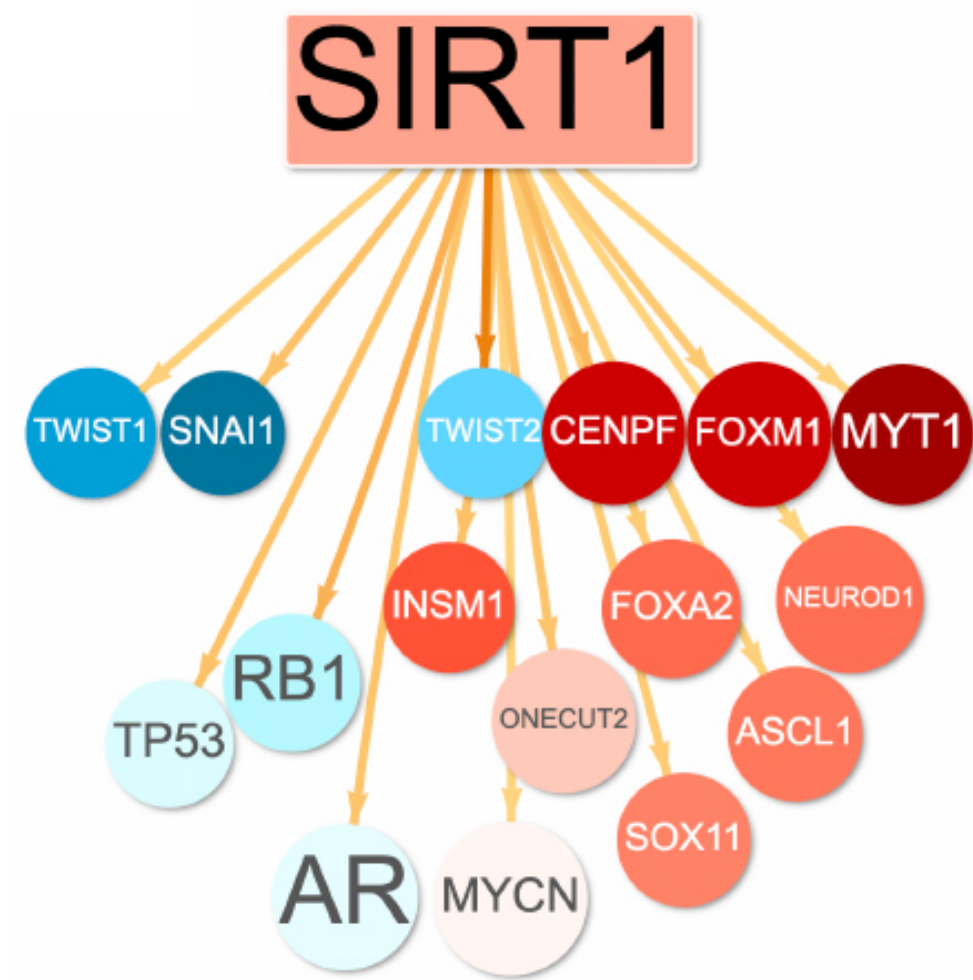# Integration of genomic (CIS) and transcriptomic data identifies modulators of NEPC
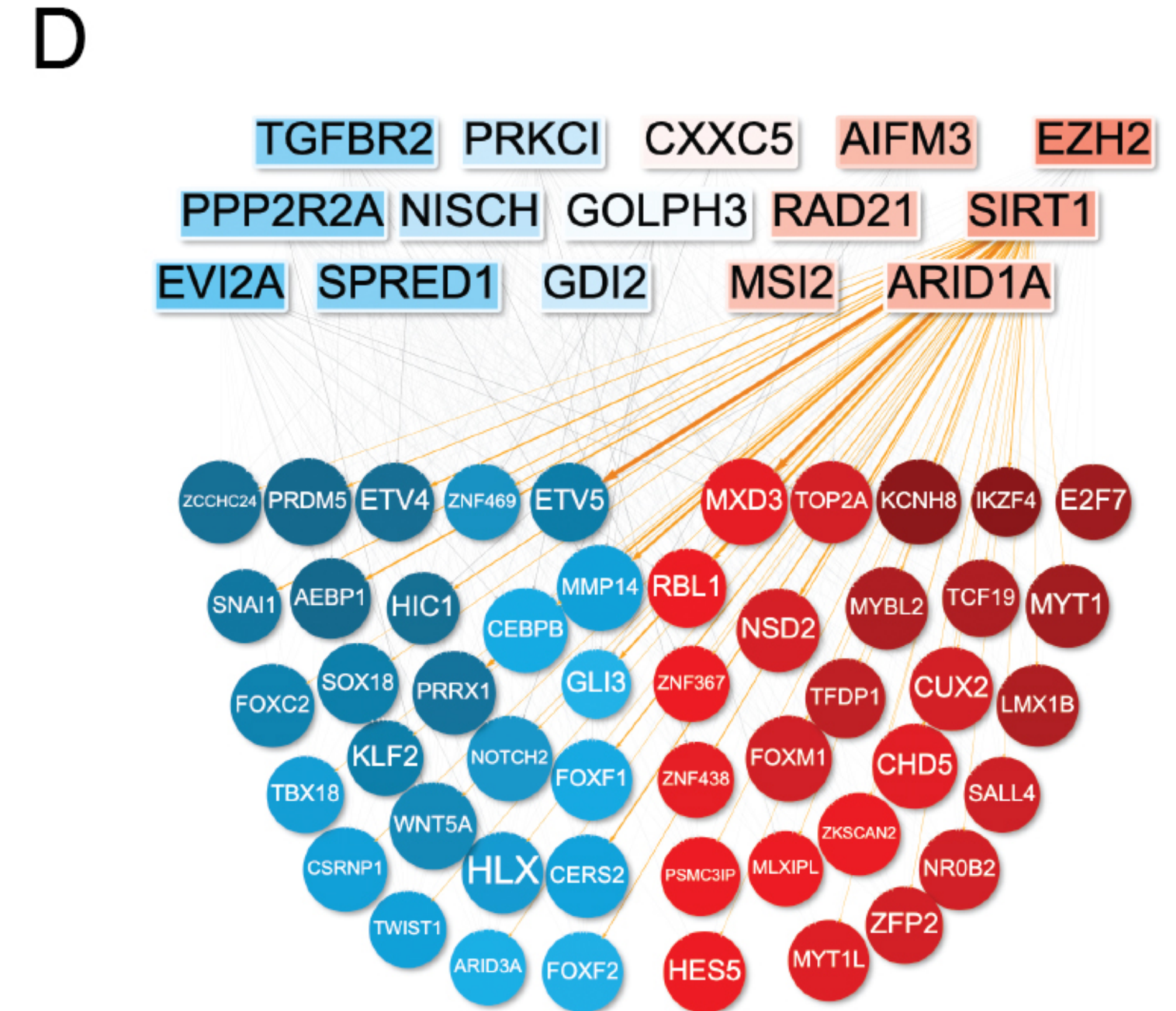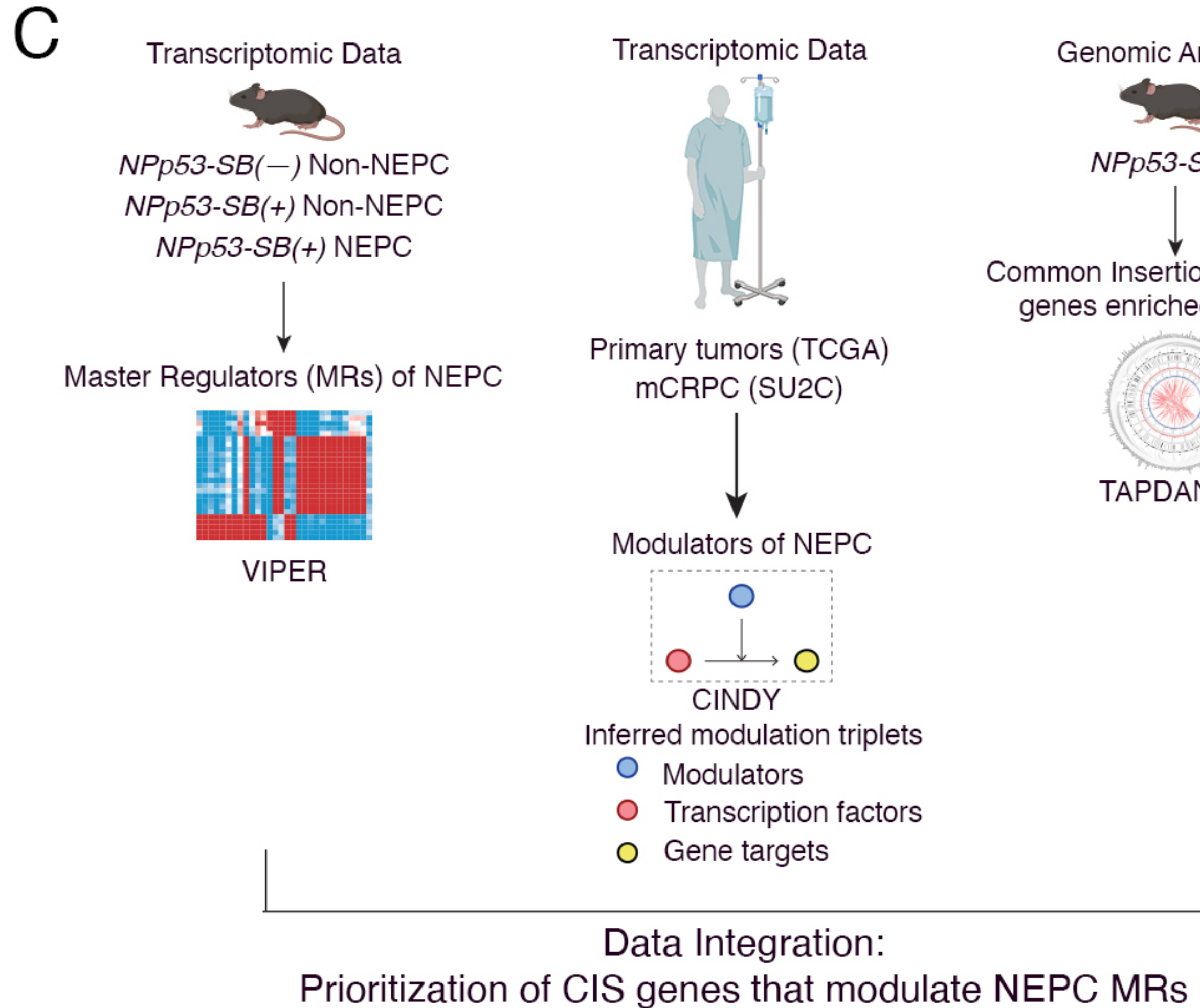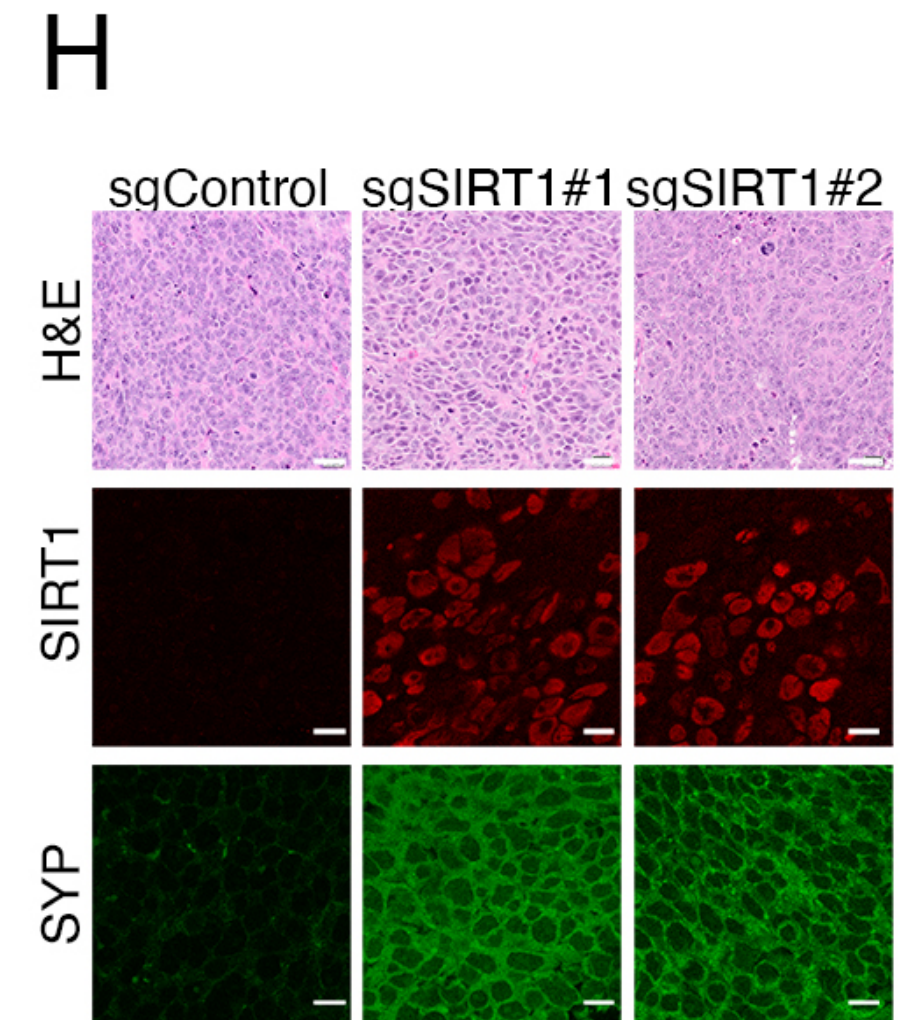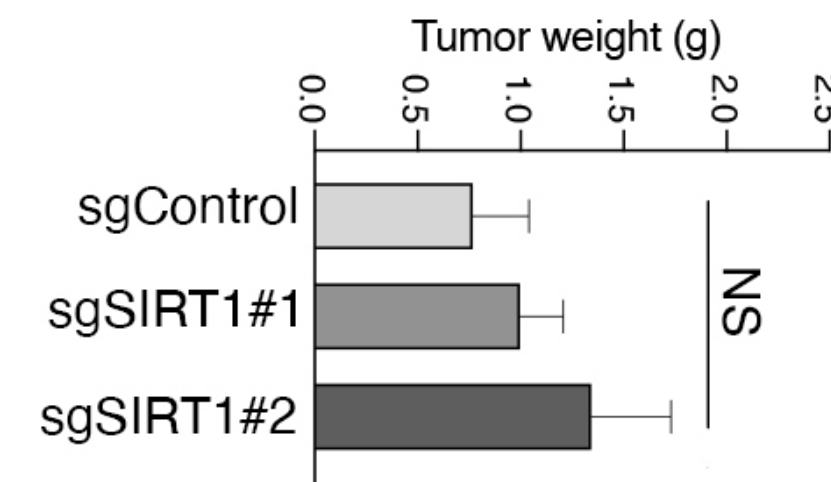
Lead candidate NEPC regulator is SIRT1
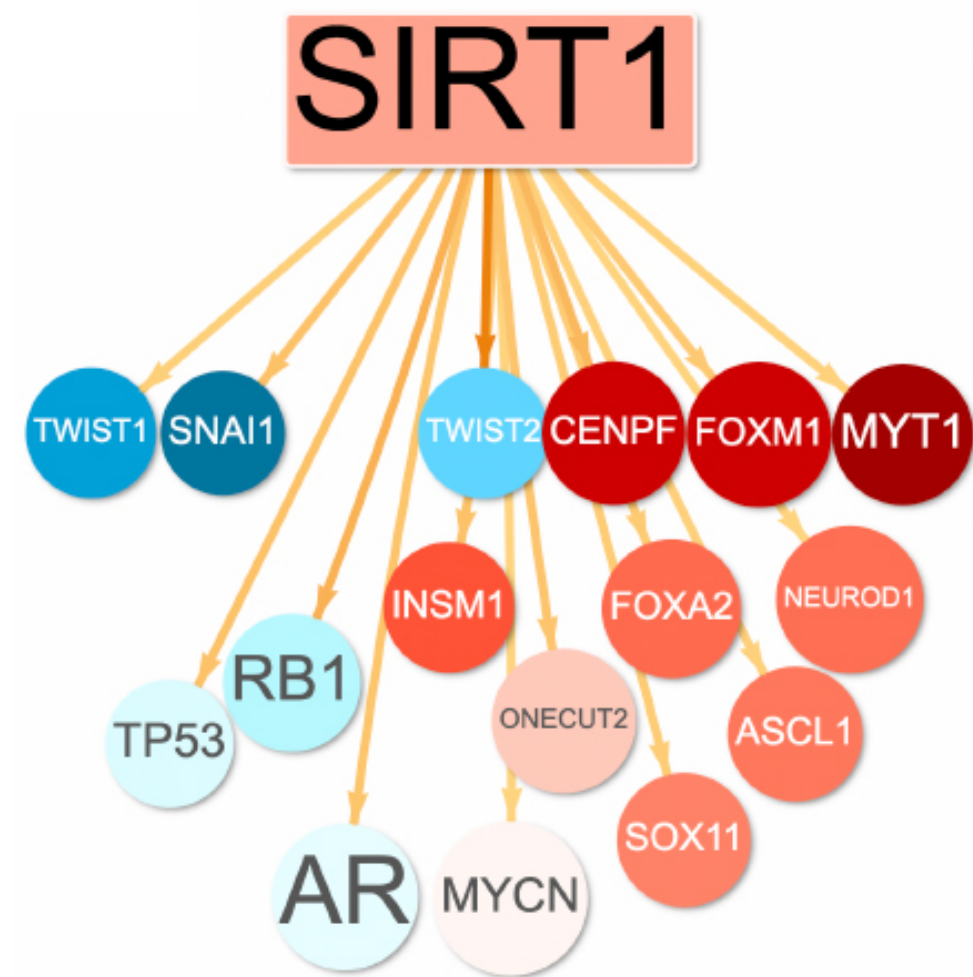
SIRT1 is an NAD-dependent deacetylase that plays a key role in regulating metabolism, cellular stress responses, and aging.
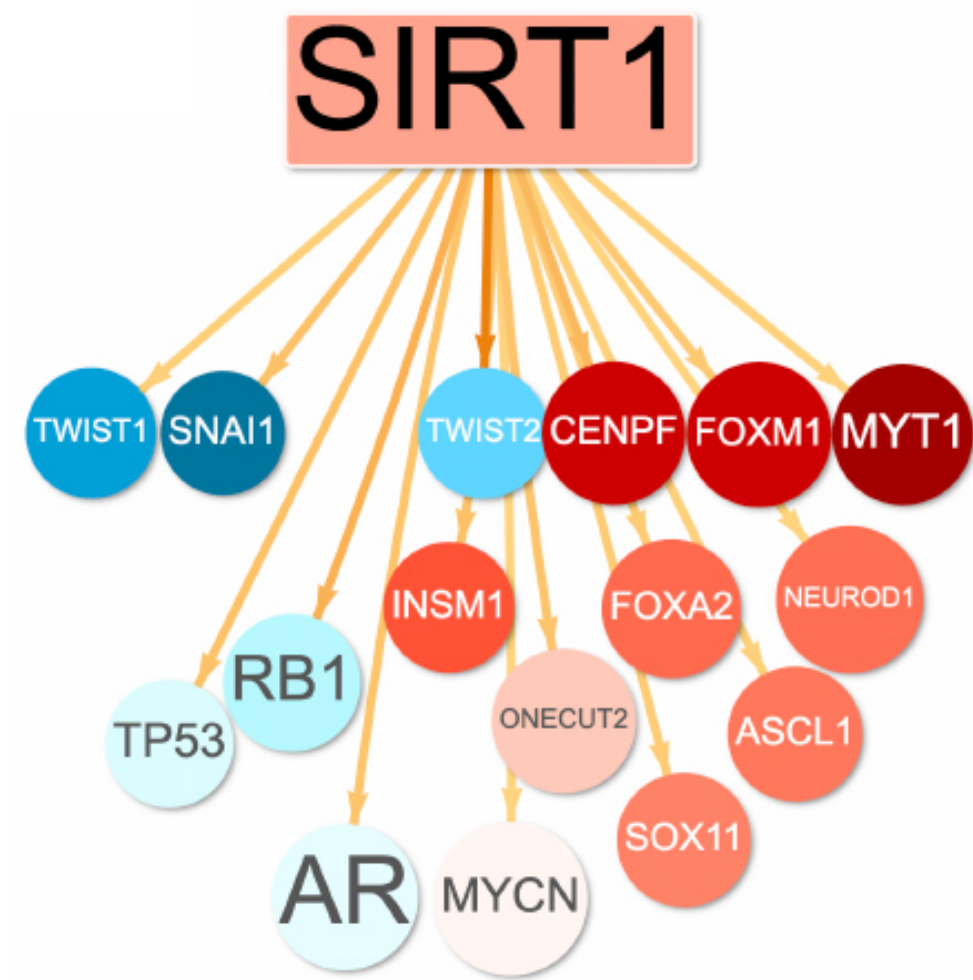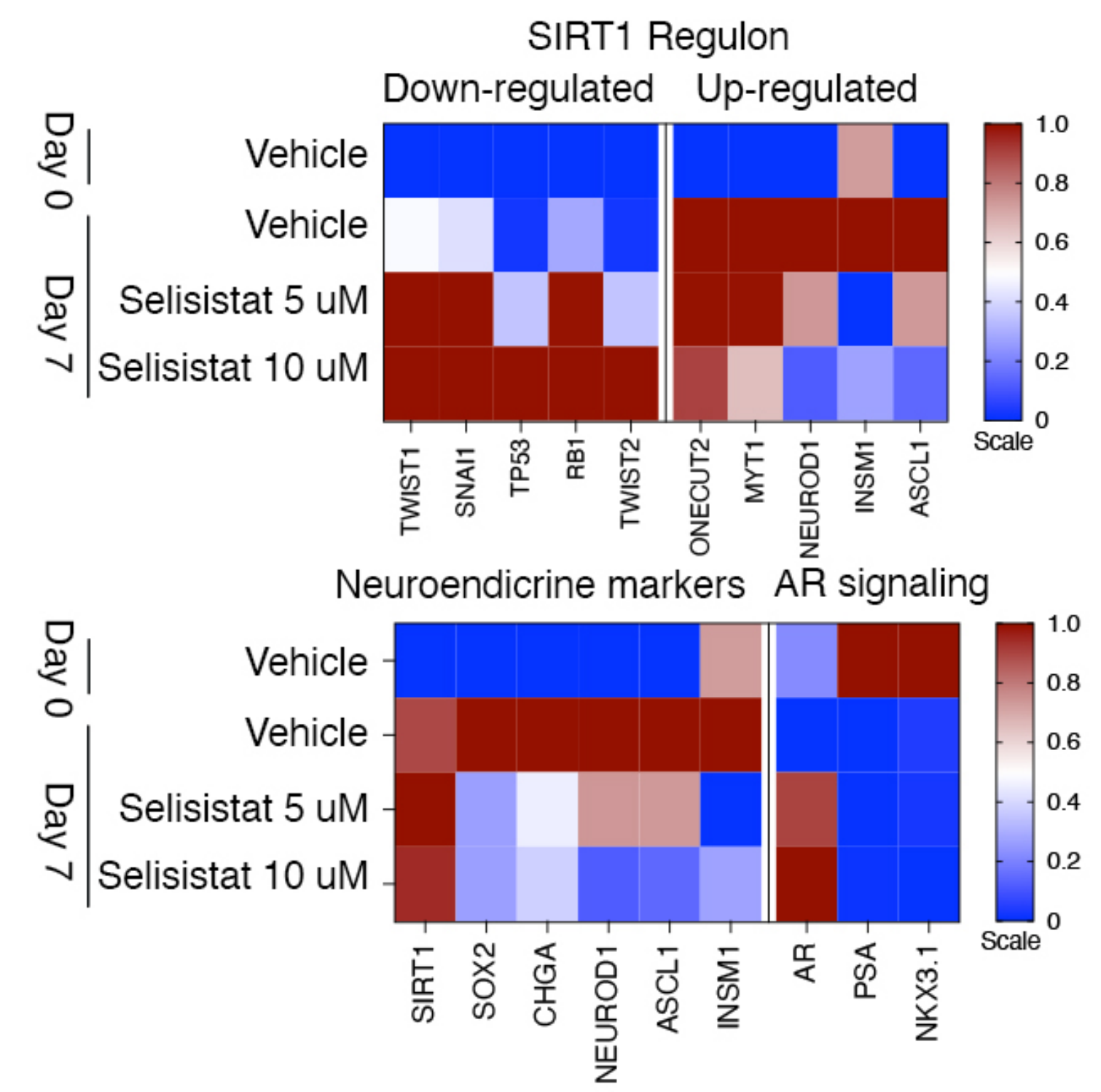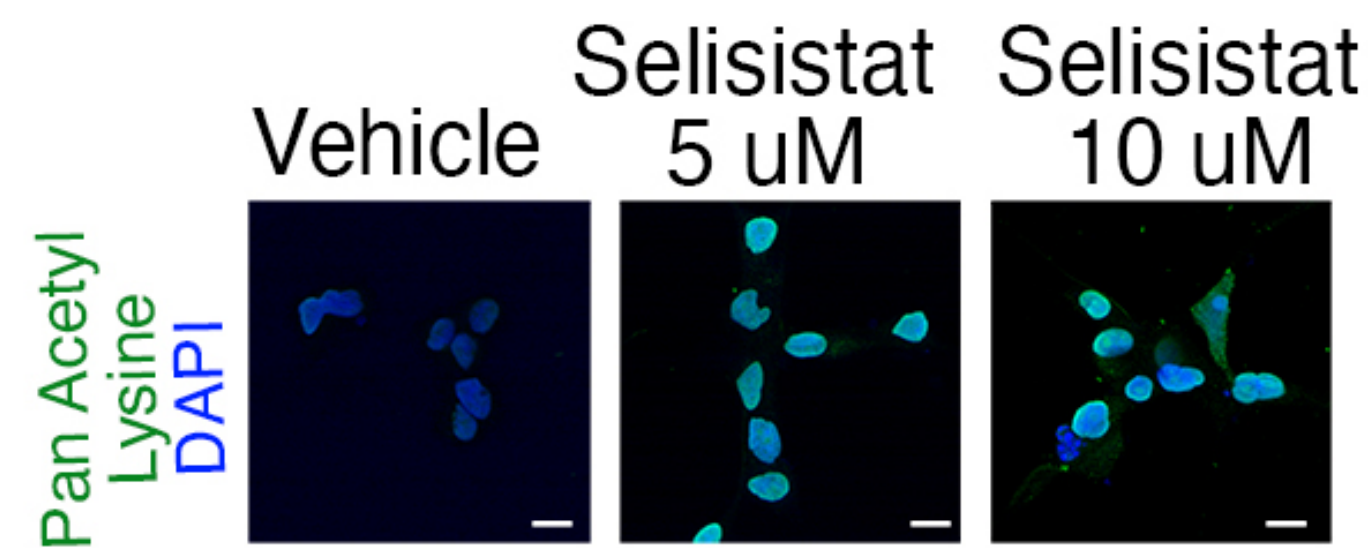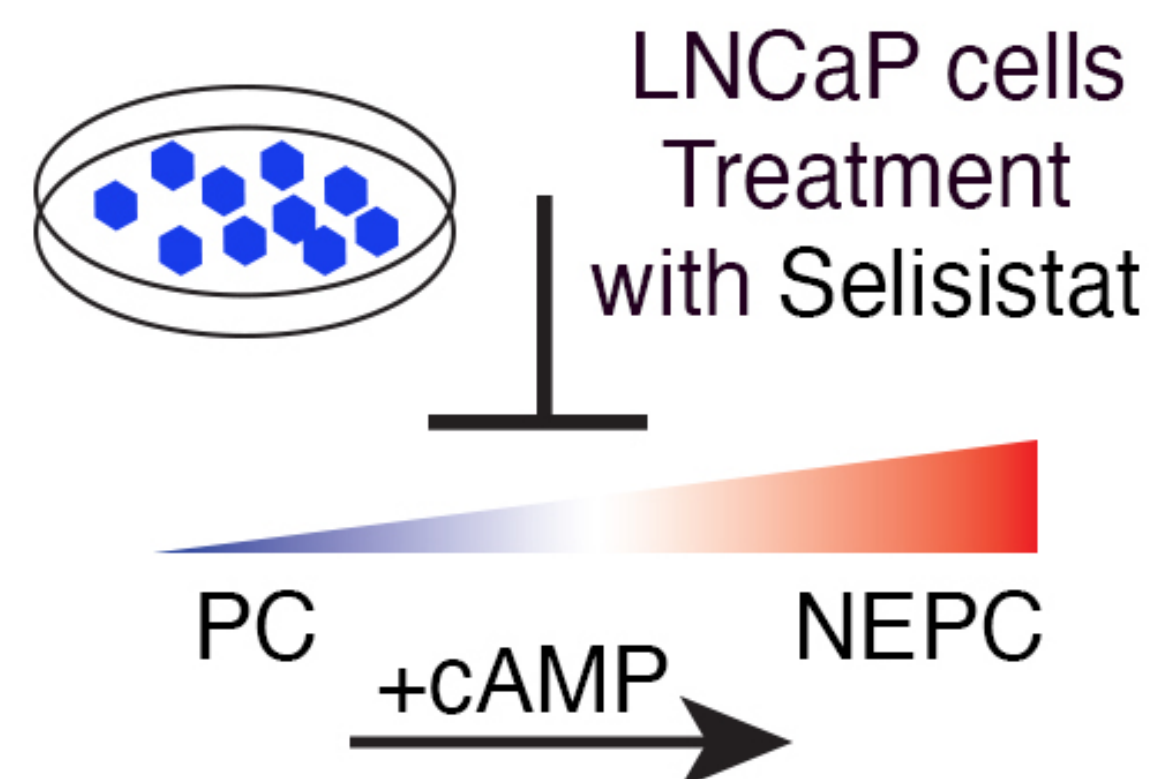
Gain of SIRT1 promotes NEPC
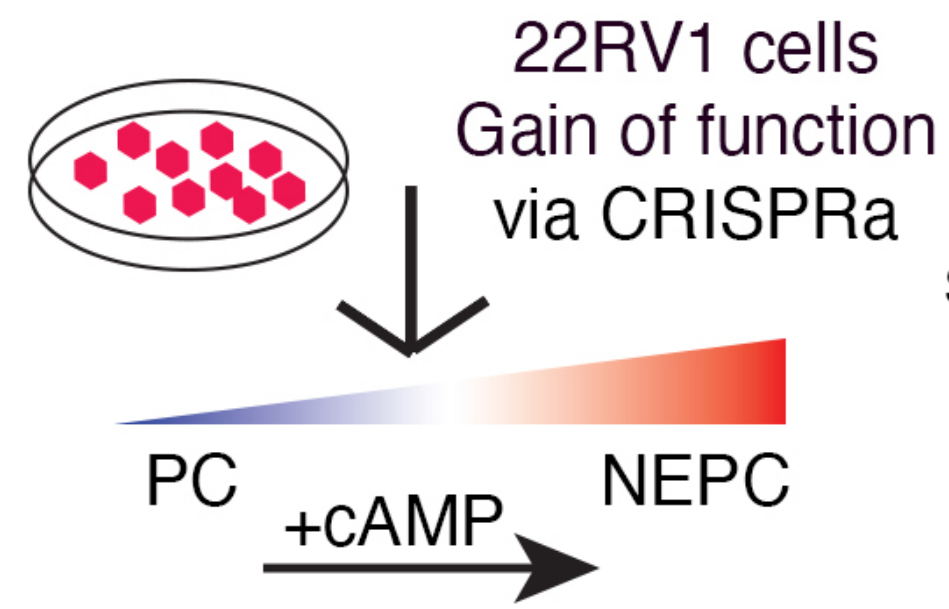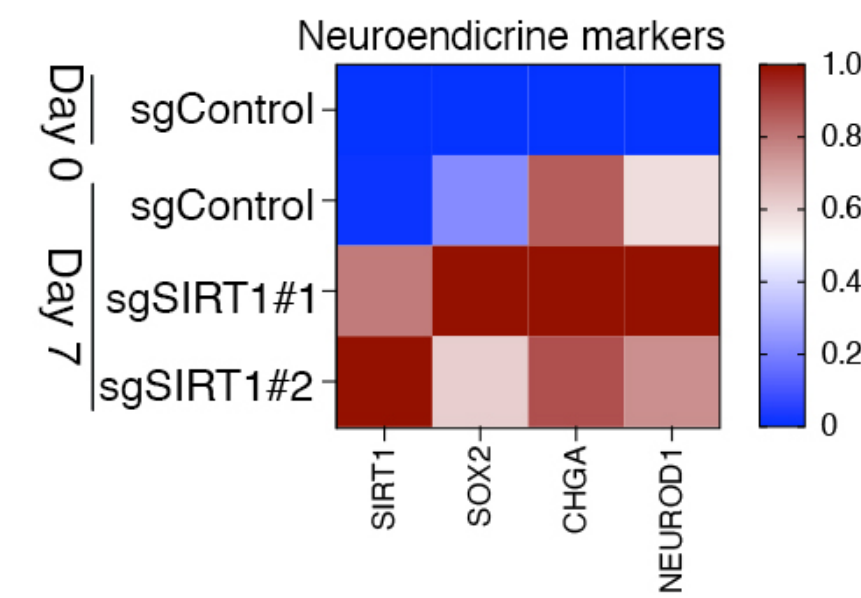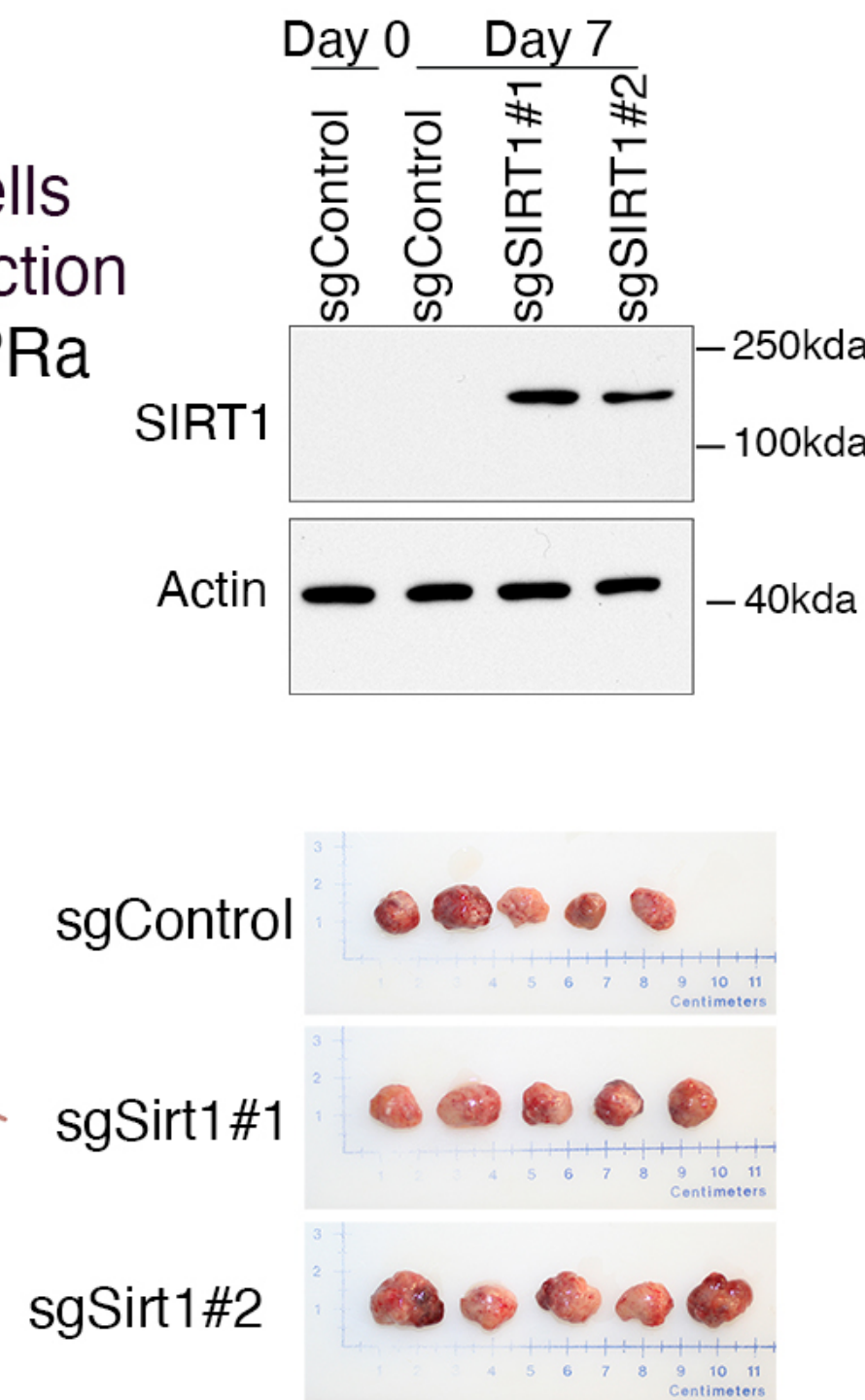
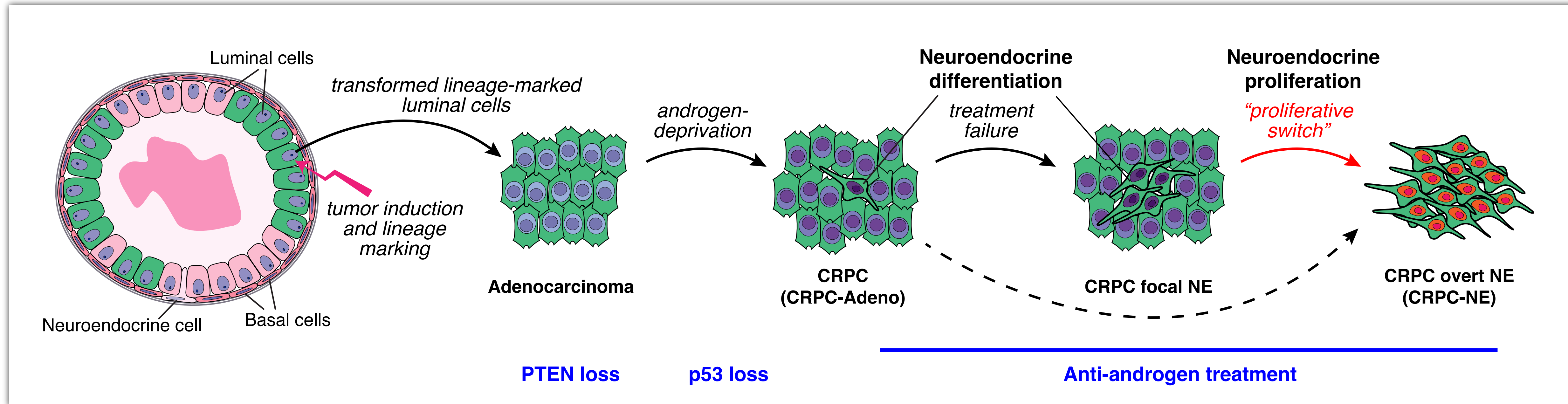# Silencing SIRT1 reverses NEPC
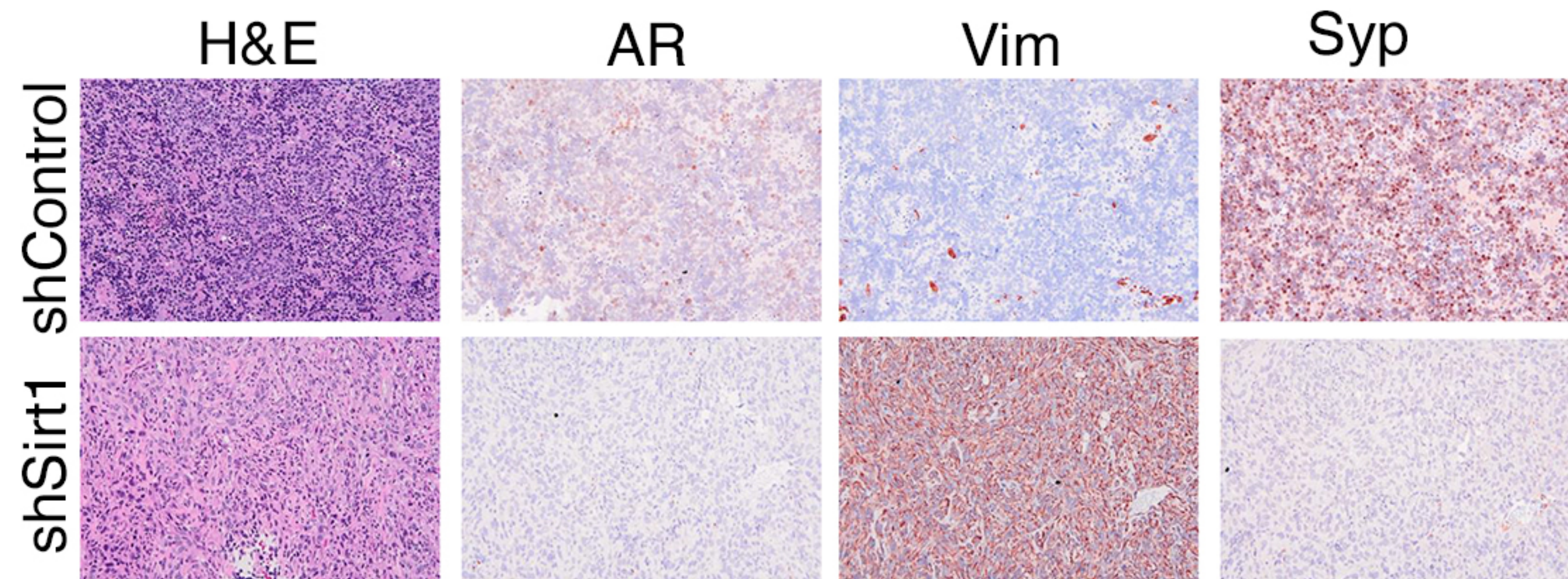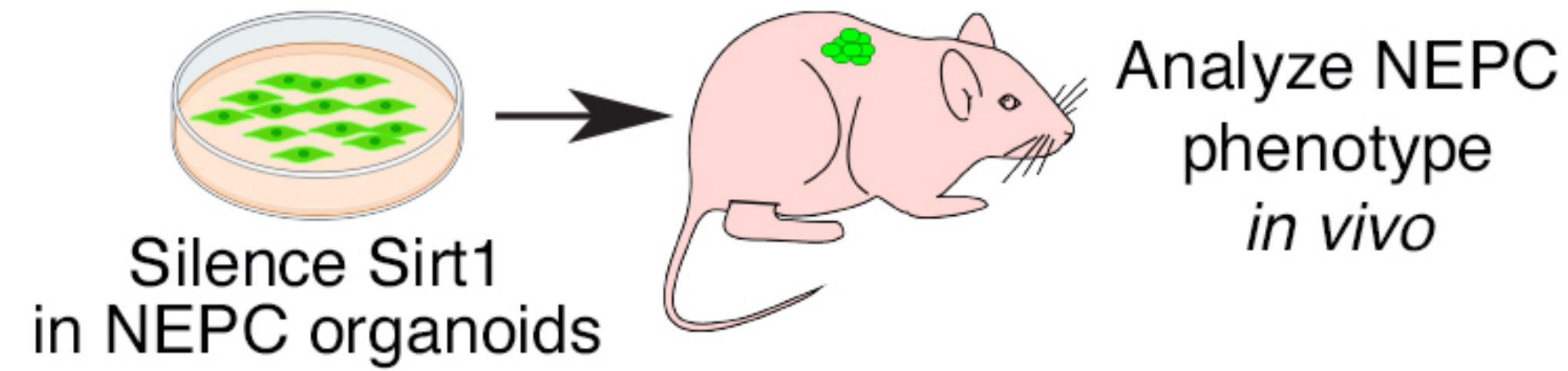
Inhibition of SIRT1 blocks

Treatment resistance leads to NEPC via transdifferentiation