The Science of the Sex Hormone Ecosystem Across a Women's Lifespan

RISE-UP 2024

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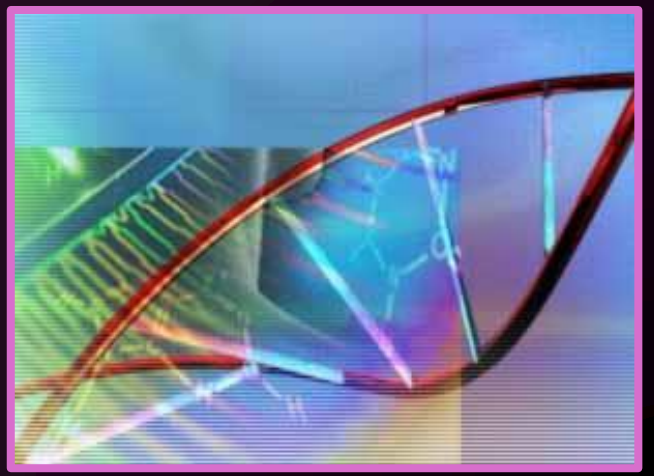
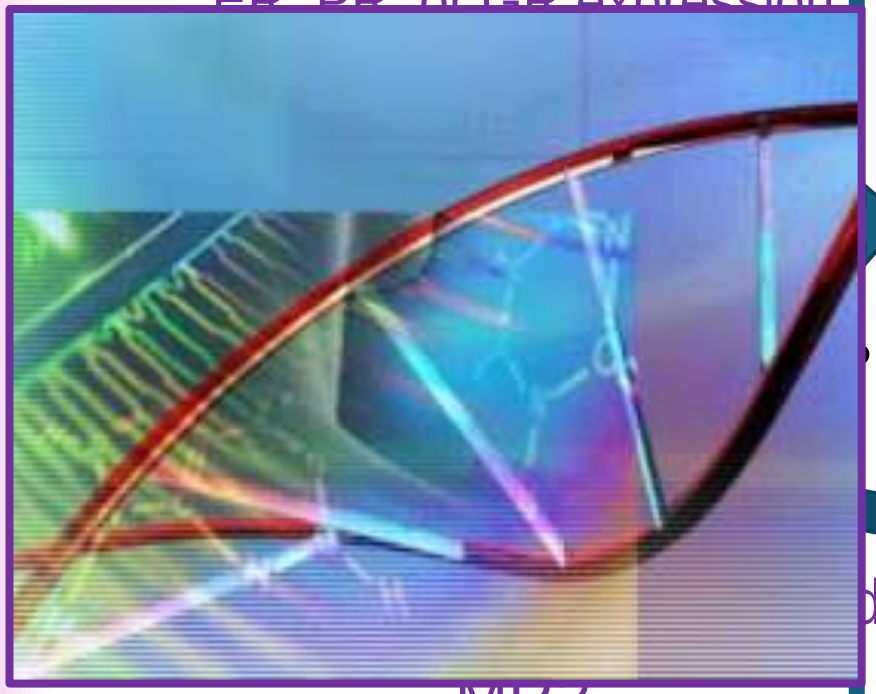
University of Minnesota Masonic Cancer Center



Steroid Hormone Receptors are Ligand-Activated Transcription Factors

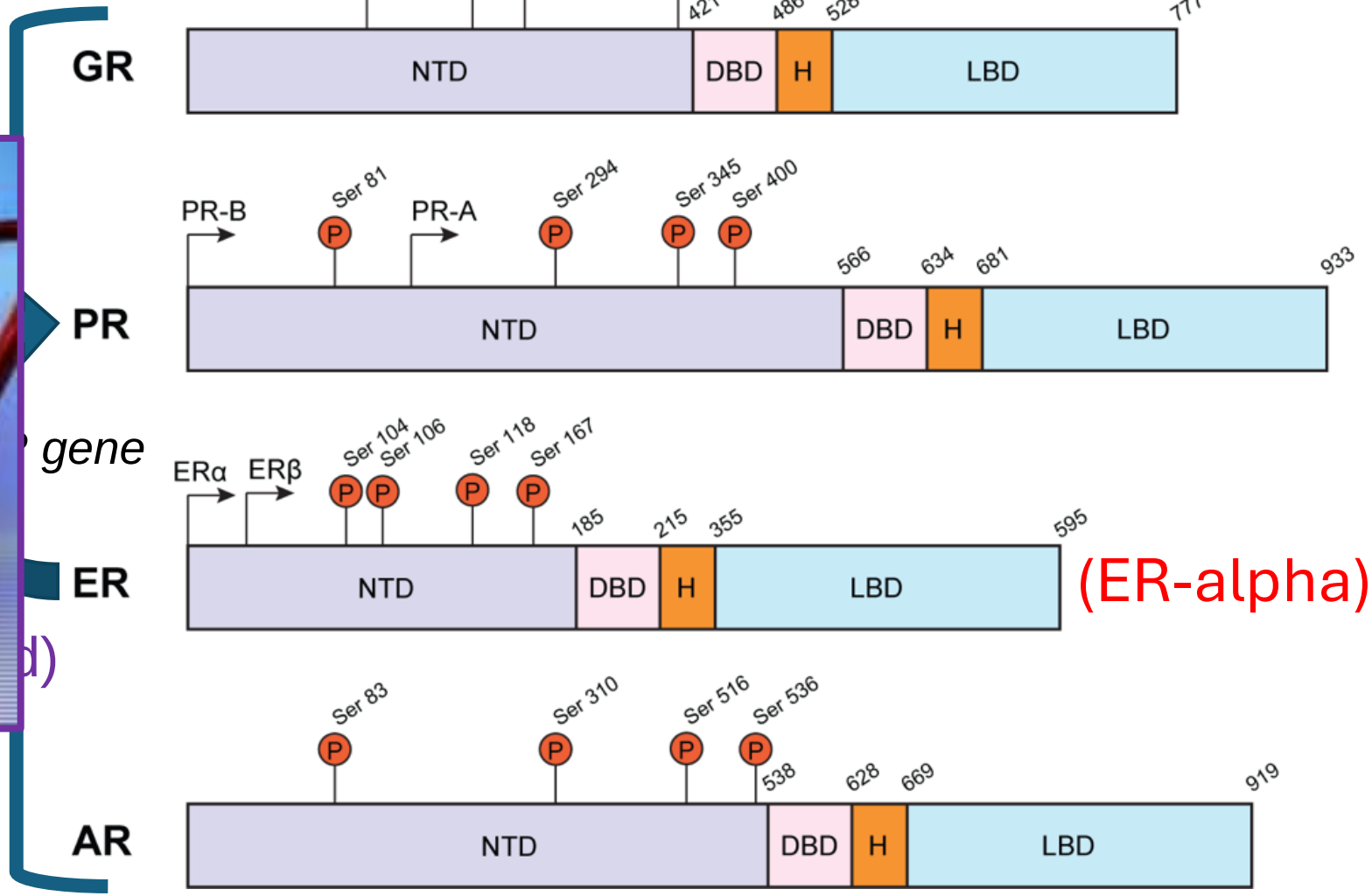
ER, PR, or GR expression



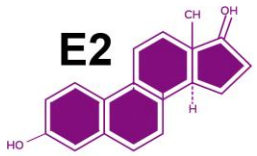
*gene

d)

MR?

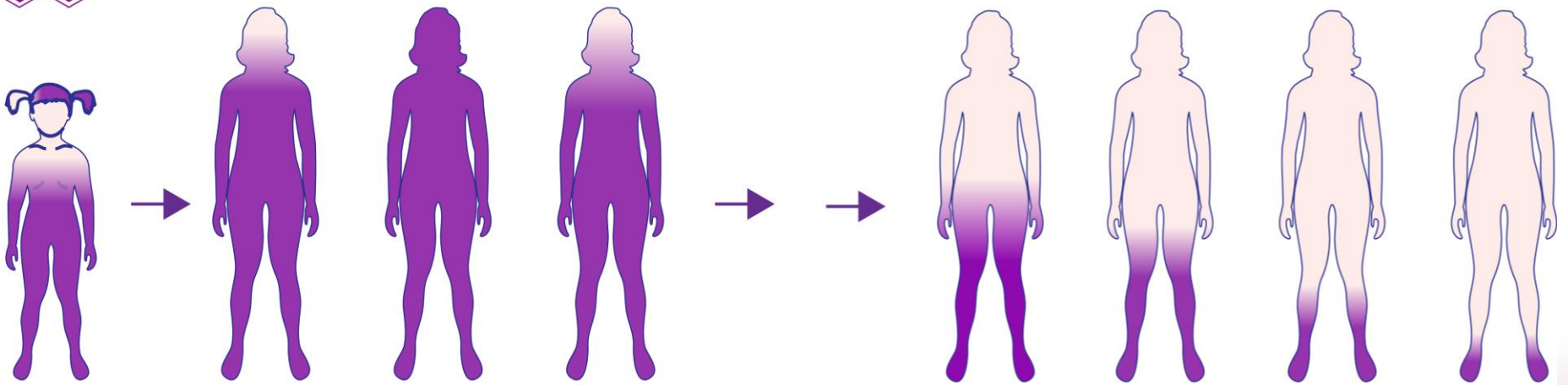


Female Physiology and Women's Health and The Estrogen Lens



Reproductive

Menopause (Anti-Hormone Therapies)



IBS

PCOS

Endometriosis

Preeclampsia

Affective Disorders

Cognitive Disorders

Osteoporosis

CV Disease

Obesity

T2DM

Complements of Dr. Holly Ingraham, PhD (UCSF)

UCSF

Journal of Molecular Endocrinology

From: Brisken C, Scabia V. 90 YEARS OF PROGESTERONE: Progesterone receptor signaling in the normal breast and its implications for cancer. *Journal of Molecular Endocrinology. 2020;65(1):T81-T94. doi:10.1530/JME-20-0091*

Hormonal changes during a woman's life cycle

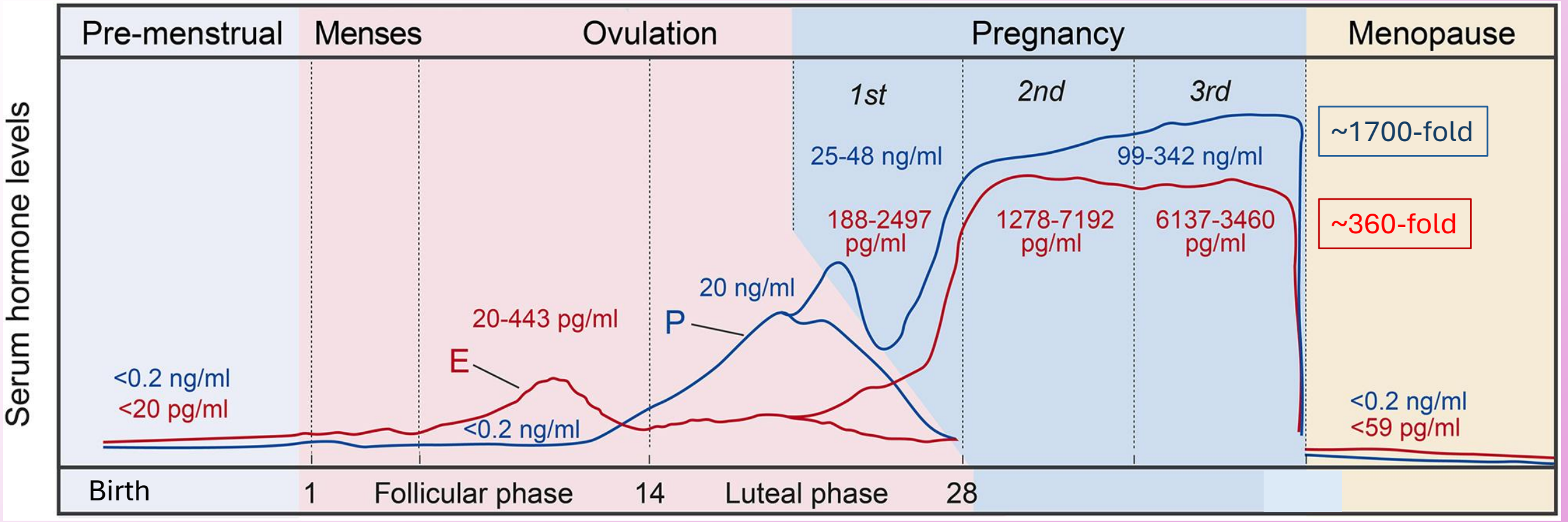


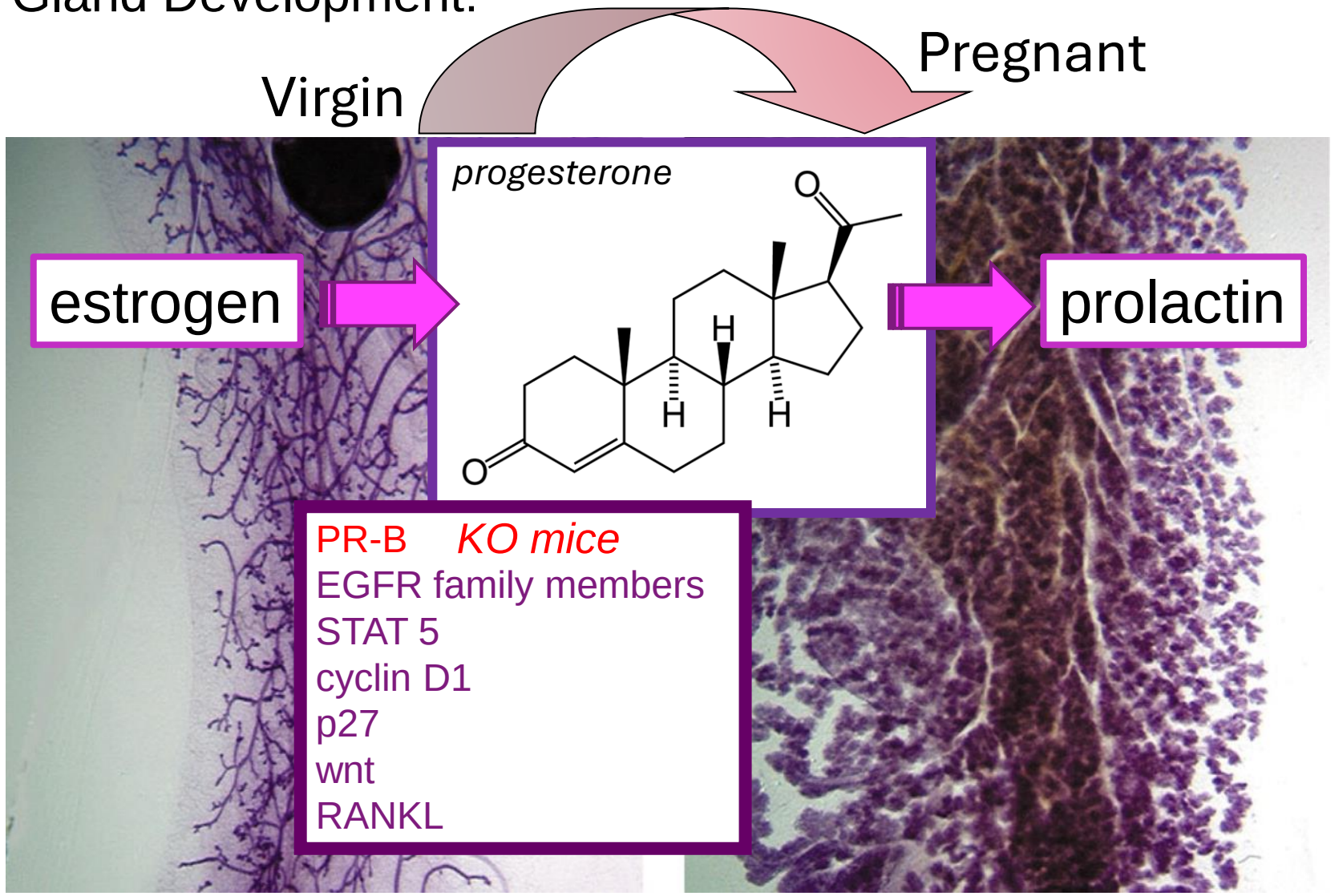
Figure 1 Schema of hormonal changes during a woman's life cycle. Scheme showing the plasma concentrations of the two ovarian hormones E (red) and P (blue) over the lifetime of a woman as a function of reproductive stage of a woman. Data are based on studies on puberty (Elmlinger et al., 2005), during menstrual cycle, menopause (Kratz et al., 2004) and in pregnancy (Abbassi-Ghanavati et al., 2009).

Complements of Dr. Holly Ingraham, PhD (UCSF)

Outline & Learning Objectives

- Lessons from mammary gland development can provide insight to breast cancer prevention strategies!
  - Estrogen and Progesterone act in concert.
  - Progesterone mediates distinct phases of mammary gland development during puberty & pregnancy.
- Both hormone and dose Matter!
  - Steroid hormone receptors (SRs) exhibit “functional allostery” determined by ligand-receptor interaction.
  - Steroid hormones (SR ligand agonists) exhibit biphasic behavior in physiologic dose-response curves.
- Steroid receptors love playmates!
  - Distinct steroid receptor family members interact extensively.
  - SR:SR interactions may be antagonistic or collaborative and depend on the signaling and hormonal context.
- Steroid receptors impact all Hallmarks of Cancer!
  - Unchecked proliferation is one of many well-studied cancer hallmarks.
  - Cytostatic therapies designed to block cell cycle progression (i.e. inhibit proliferation) induce changes in cell fate that favor cell cycle exit, enable metabolic plasticity, and drive EMT, dormancy, and metastasis.
  - It is important to consider multiple readouts of hormone/antihormone action (biomarkers other than Ki67).
- Recent provocative data that incorporate these concepts!
  - SRs drive aggressive phenotypes in breast cancer models via partnership with related SR cousins.
  - Proliferative and Quiescent gene programs are distinct but linked processes (DREAM-on).

Mammary Gland Development:



Hennighausen and Robinson: *Dev. Cell* 2001

Journal of Molecular Endocrinology

From: Brisken C, Scabia V. 90 YEARS OF PROGESTERONE: Progesterone receptor signaling in the normal breast and its implications for cancer. *Journal of Molecular Endocrinology. 2020;65(1):T81-T94. doi:10.1530/JME-20-0091*

The progesterone signaling hub in the adult mammary epithelium

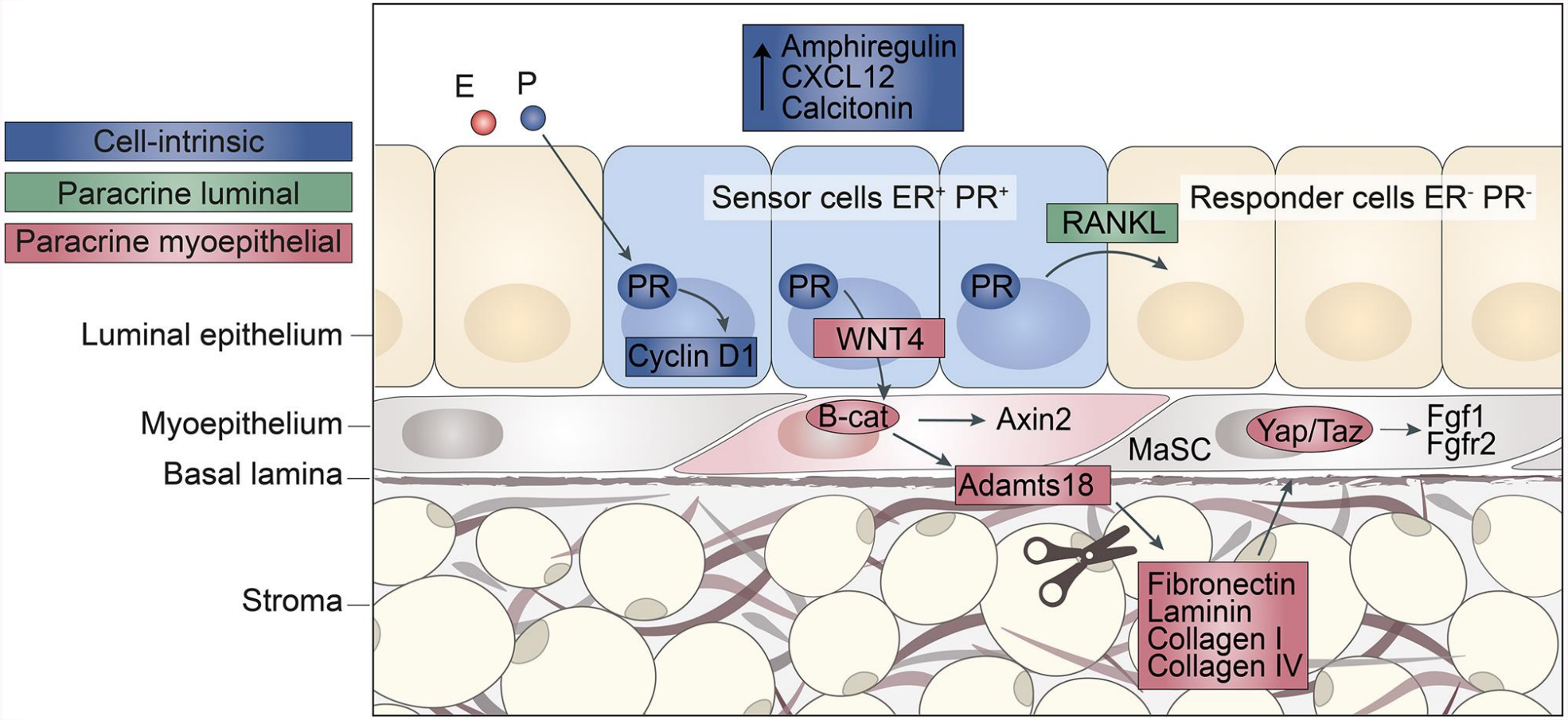
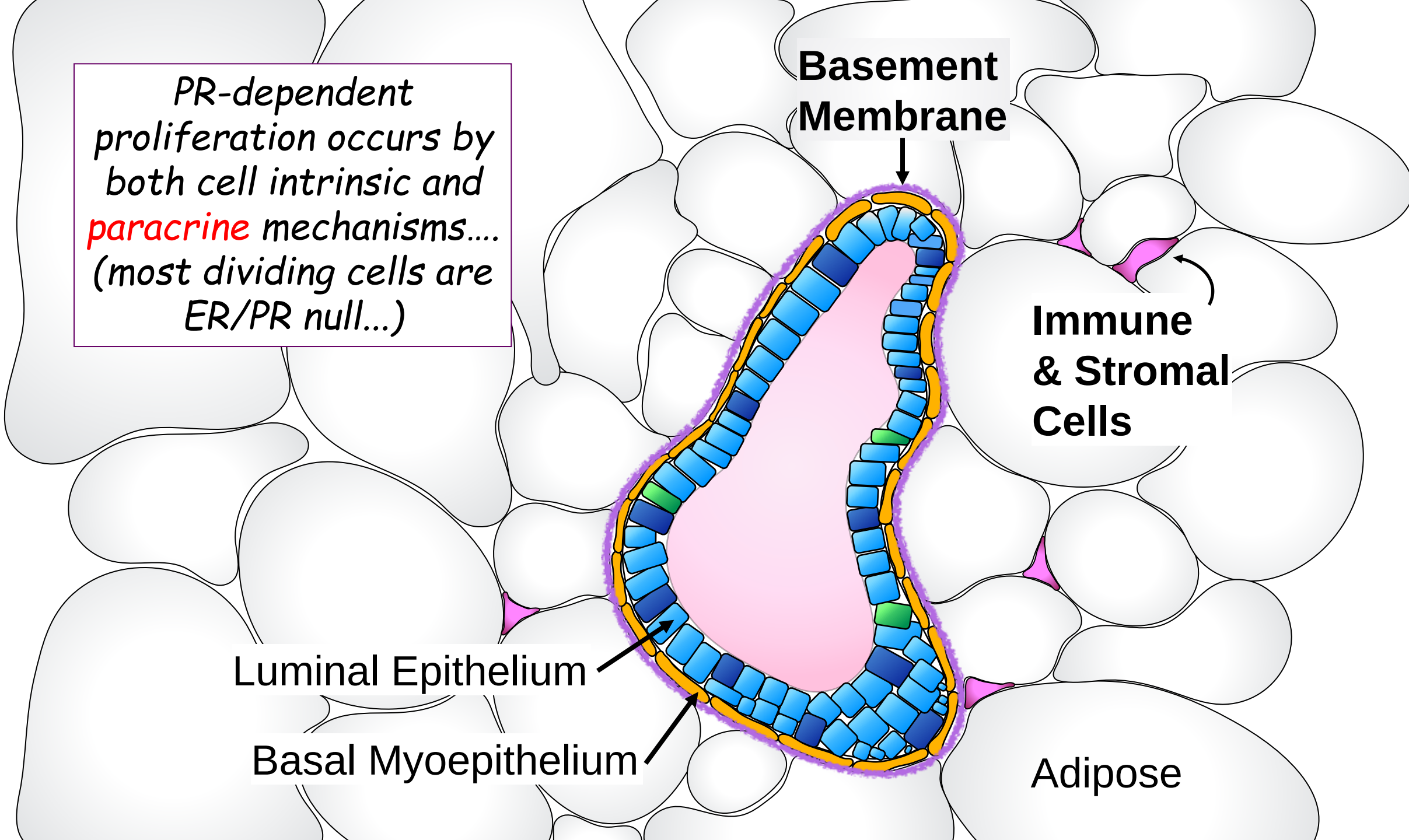
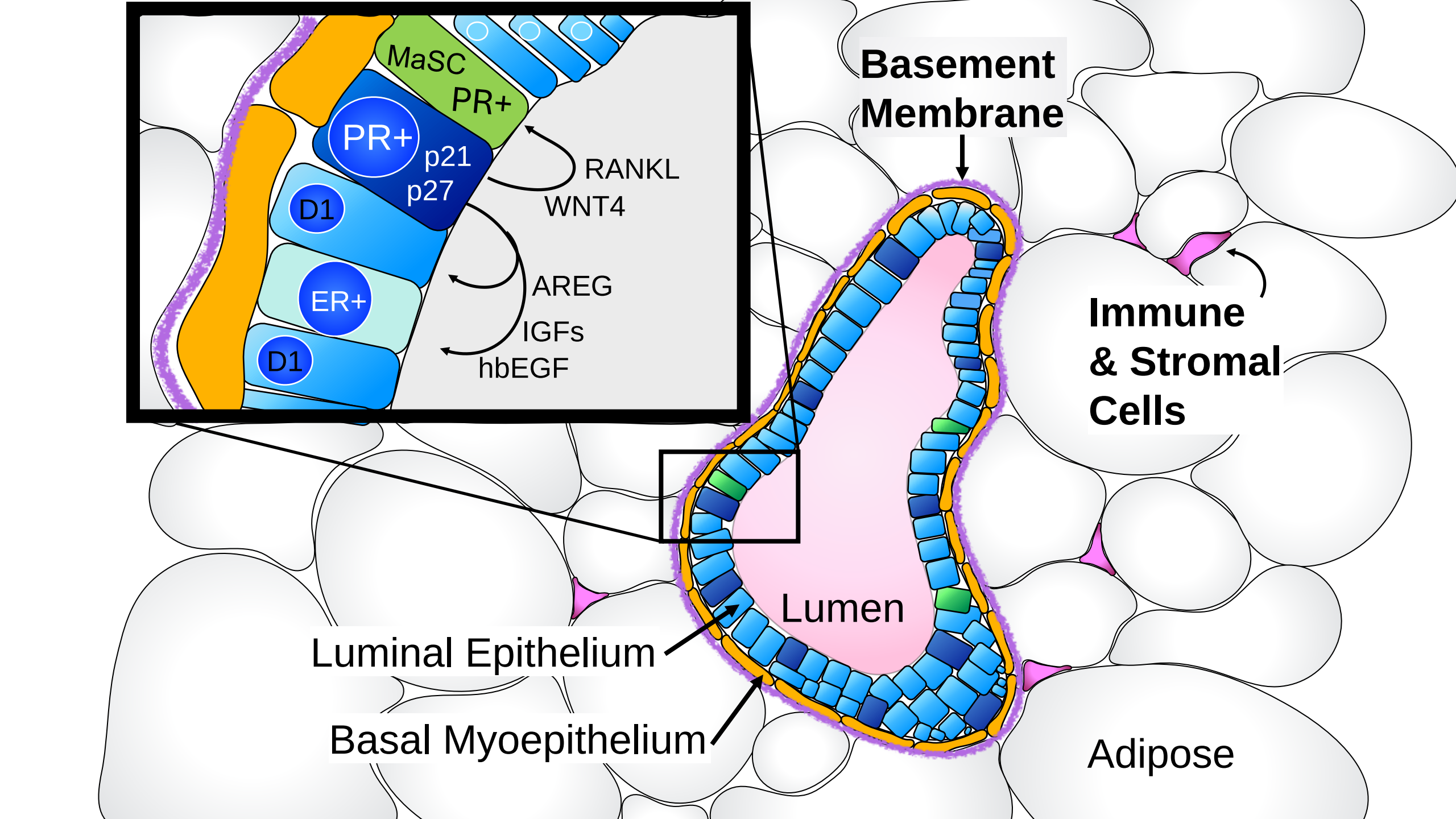
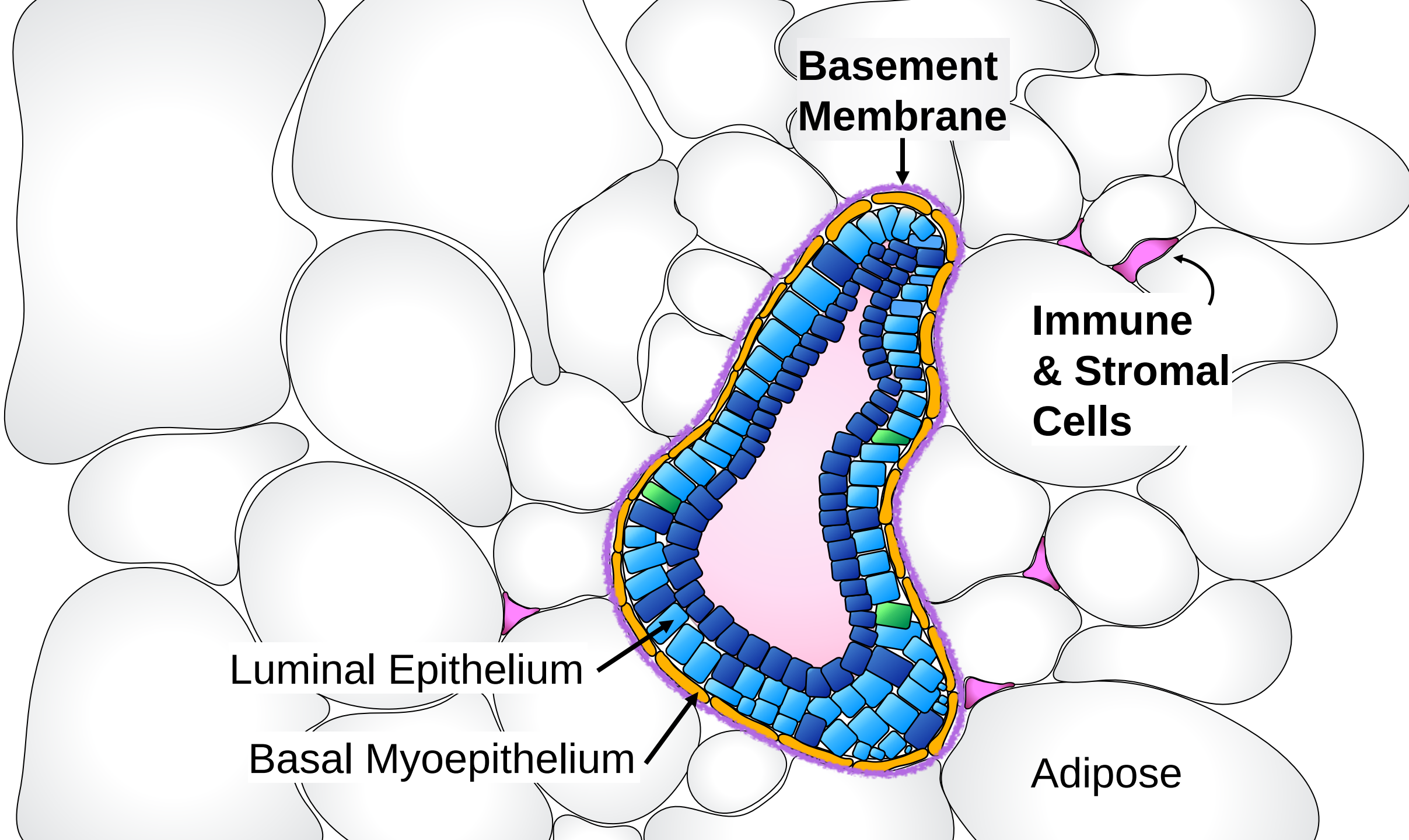
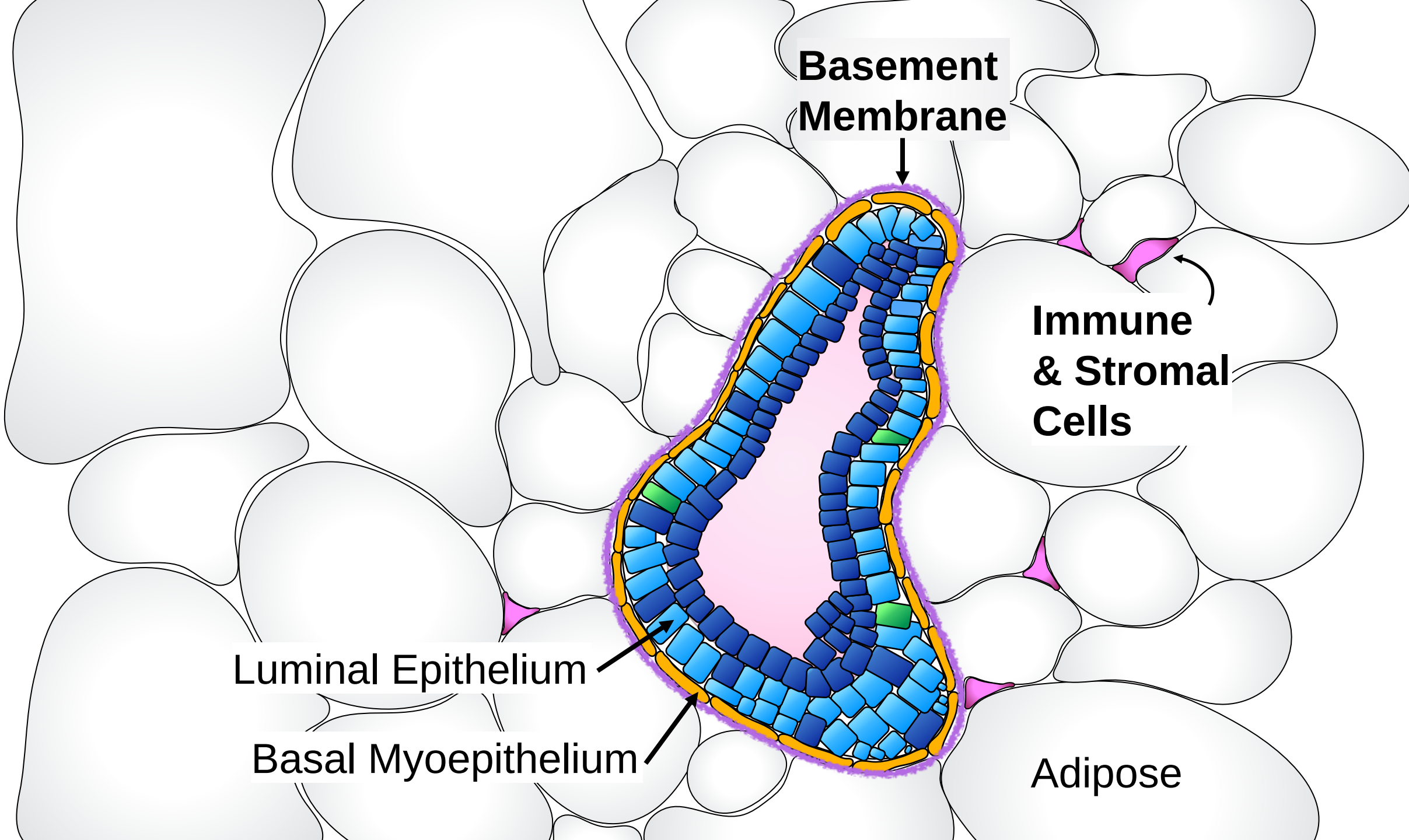


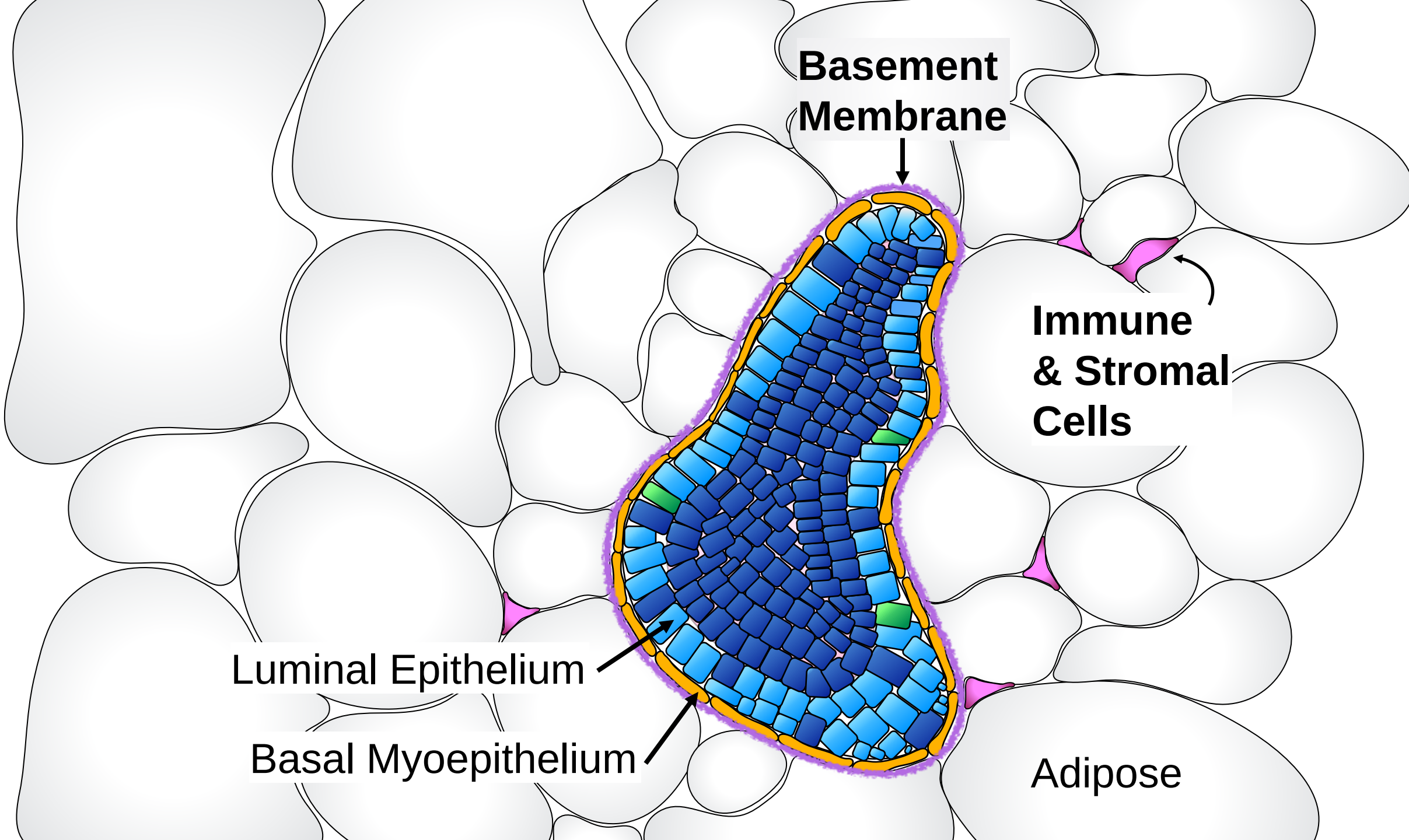
Figure 3 The progesterone signaling hub in the adult mammary epithelium progesterone, upon binding to its receptor in the ER+/PR+ sensor cells (blue) activates different signaling pathways. It can stimulate cell-intrinsic proliferation by a cyclin D1-dependent mechanism (blue) and induce secreted factors like Amphiregulin, CXCL12, or Calcitonin (blue). Distinct PR+ cells induce Wnt4, which acts on the myoepithelium where it activated canonical Wnt signaling, which results in the expression of the secreted protease Adamts18 that cleaves fibronectin. As a result the ECM, part of the stem cells niche, is biochemically altered with resulting activation of the hippo signalling pathway and increased transcription of FGFR signaling components (red). In other PR+ cells, Rankl is induced that induces the proliferation of neighboring ER−/PR− responder cells (green).


PR-dependent proliferation occurs by both cell intrinsic and paracrine mechanisms…. (most dividing cells are ER/PR null…)
Basement Membrane
Immune & Stromal Cells
Luminal Epithelium
Basal Myoepithelium
Adipose


MaSC
PR+
PR+
p21
p27
D1
ER+
D1
RANKL
WNT4
AREG
IGFs
hbEGF
Basement Membrane
Immune & Stromal Cells
Lumen
Luminal Epithelium
Basal Myoepithelium
Adipose


Basement Membrane
Immune & Stromal Cells
Luminal Epithelium
Basal Myoepithelium
Adipose


Basement Membrane
Immune & Stromal Cells
Luminal Epithelium
Basal Myoepithelium
Adipose


Basement Membrane
Immune & Stromal Cells
Luminal Epithelium
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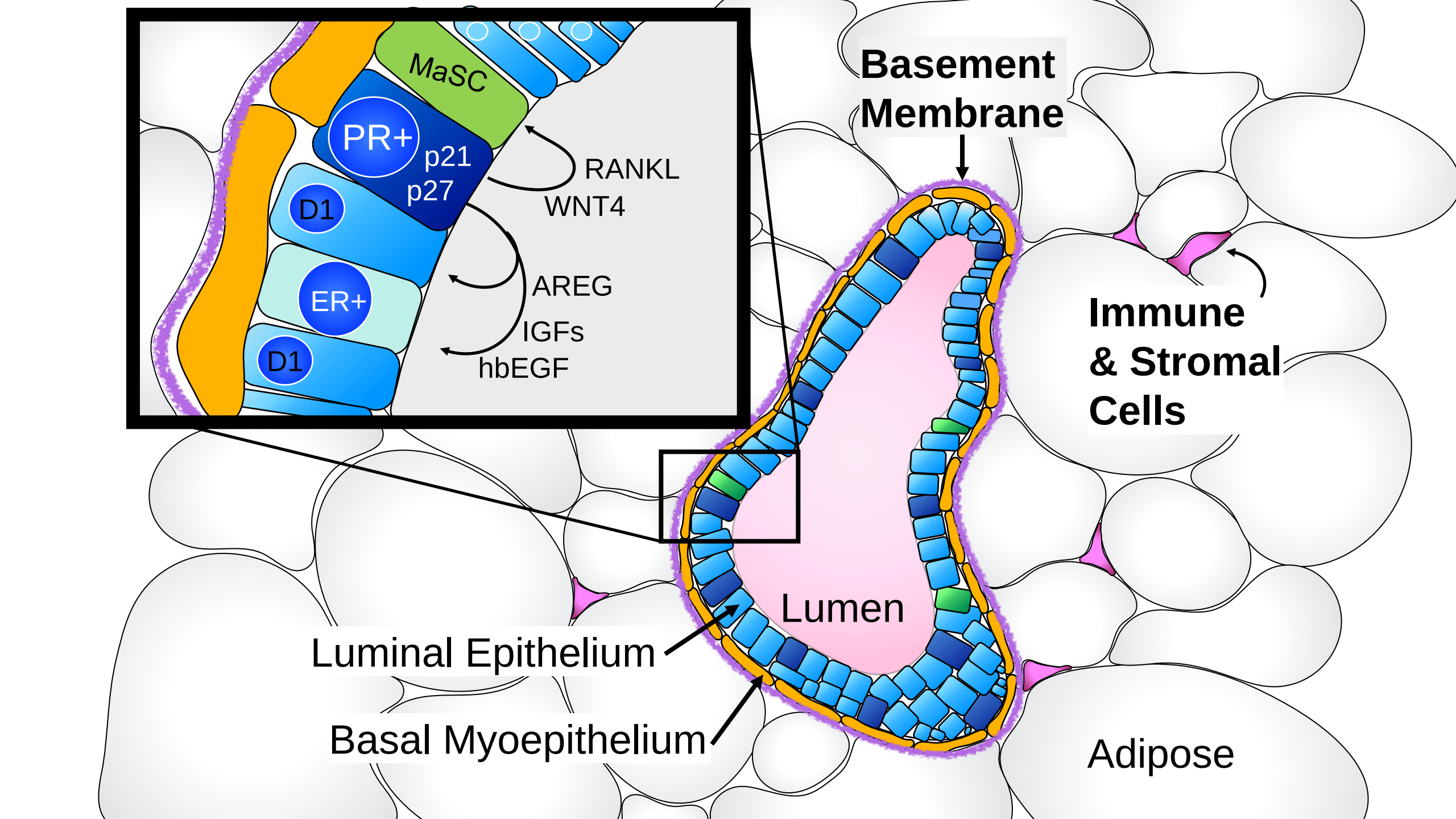
Adipose


MaSC
PR+
p21
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ER+
D1
RANKL
WNT4
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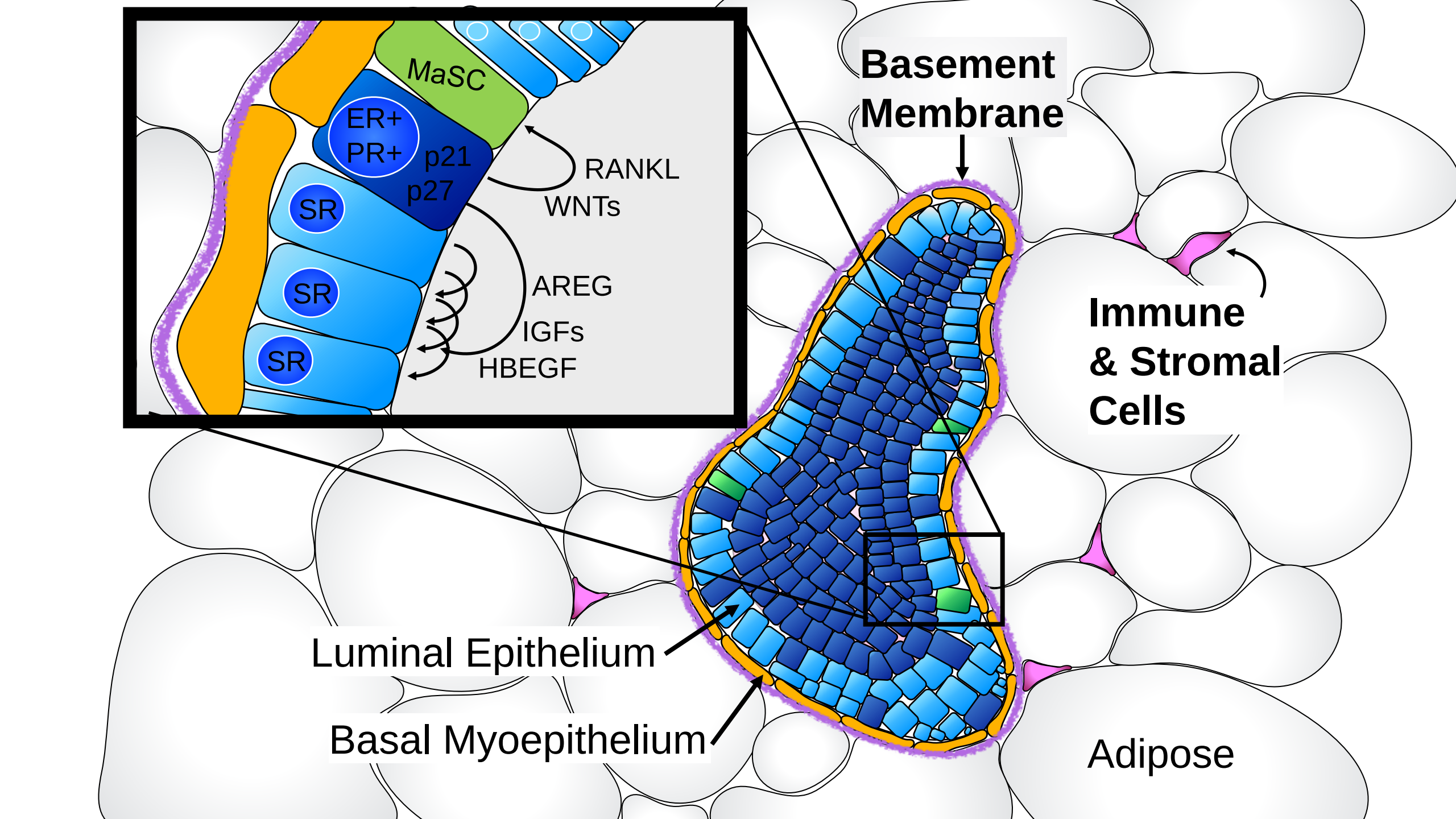
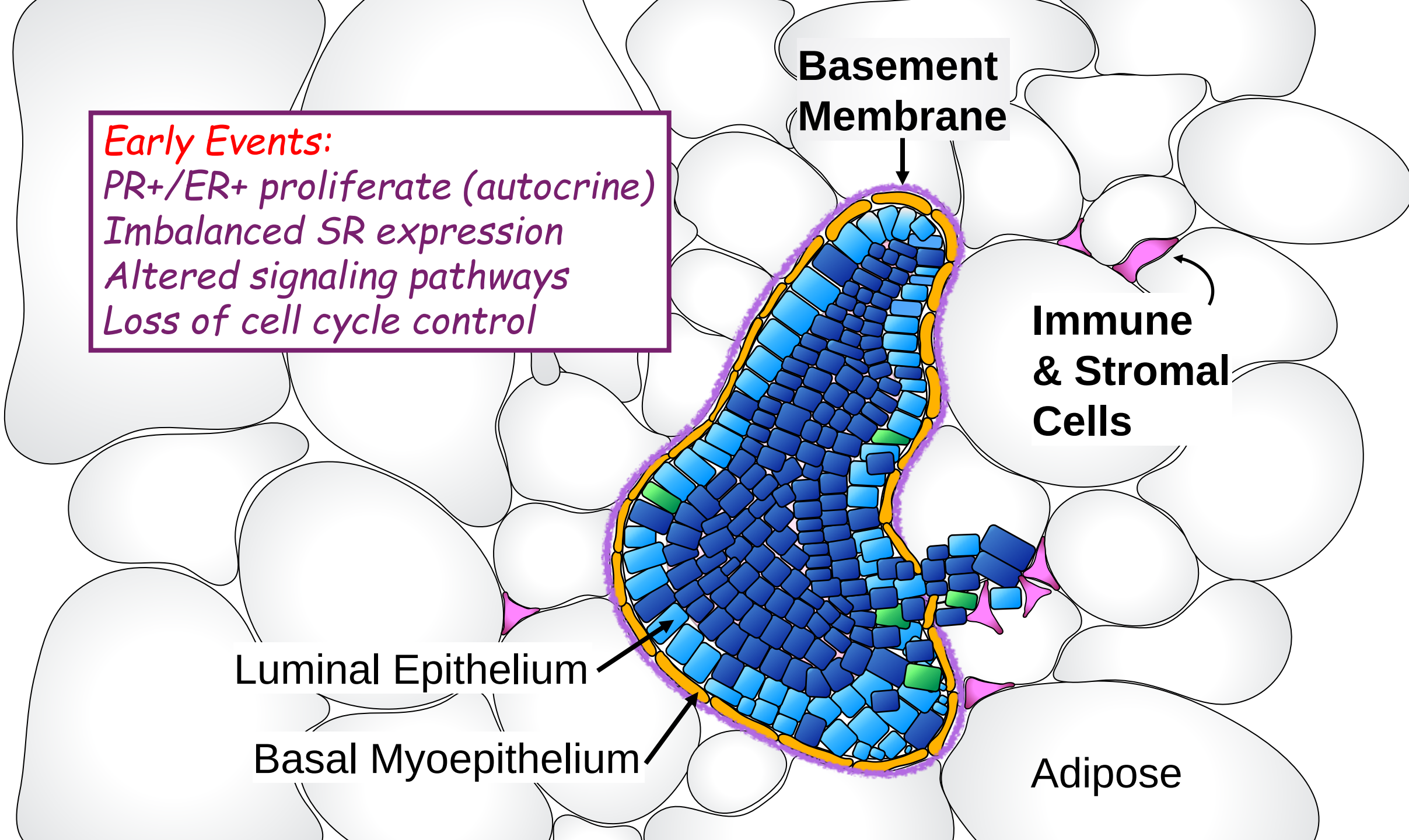
Immune & Stromal Cells
Lumen
Luminal Epithelium
Basal Myoepithelium
Adipose

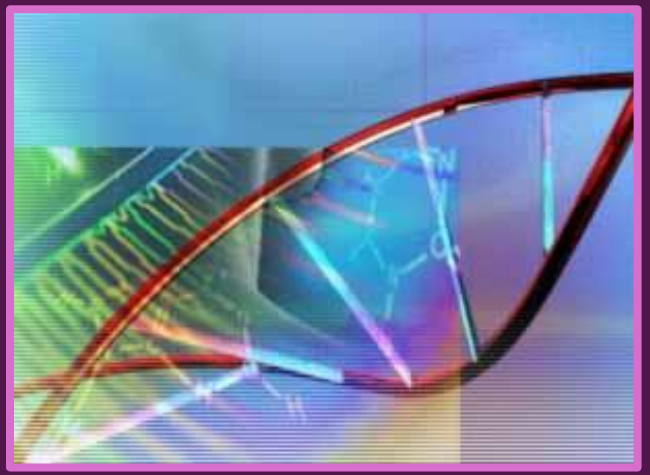

MaSC
ER+
PR+
p21
p27
SR
SR
SR
RANKL
WNTs
AREG
IGFs
HBEGF
Basement Membrane
Immune & Stromal Cells
Luminal Epithelium
Basal Myoepithelium
Adipose


Early Events:
PR+/ER+ proliferate (autocrine)
Imbalanced SR expression
Altered signaling pathways
Loss of cell cycle control
Basement Membrane
Immune & Stromal Cells
Luminal Epithelium
Basal Myoepithelium
Adipose

Lessons from Mammary Gland Development

- Expansion of mammary stem cells (MaSC) is P4-dependent (wnts, RANKL)
- Early events include:
  ER+/PR+ cells are abundant and divide by autocrine mechanisms
  PR isoforms (PR-A and PR-B) are imbalanced (frequently PR-A>PR-B)
- Tremendous complexity and plasticity defines mammary gland cell lineages
  Explains the heterogeneity and adaptability of breast cancers

This information can be leveraged to
reduce breast cancer risk (hormone exposures)
by tailored “instruction” of lineages
We should pay more attention to other hormones (Prolactin)



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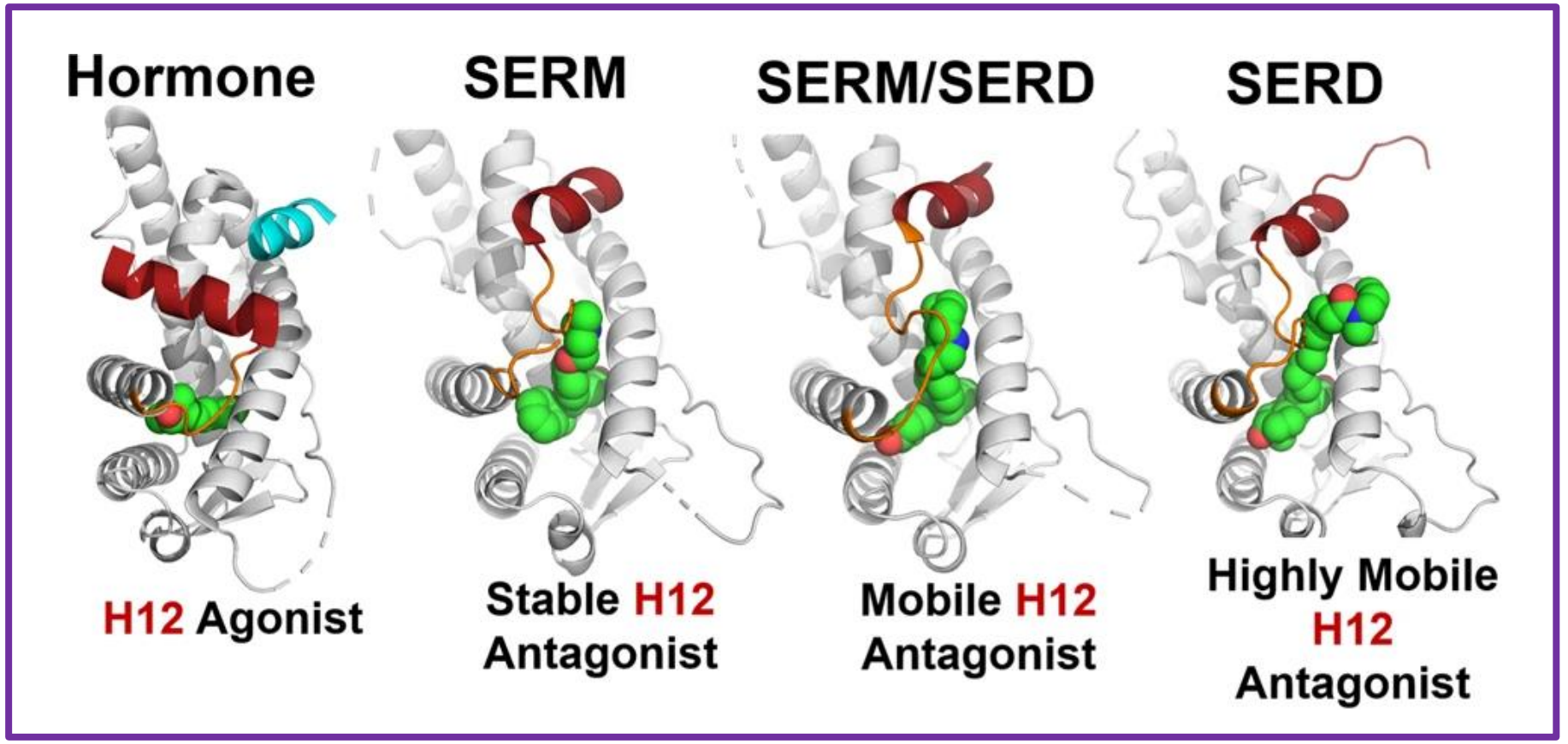
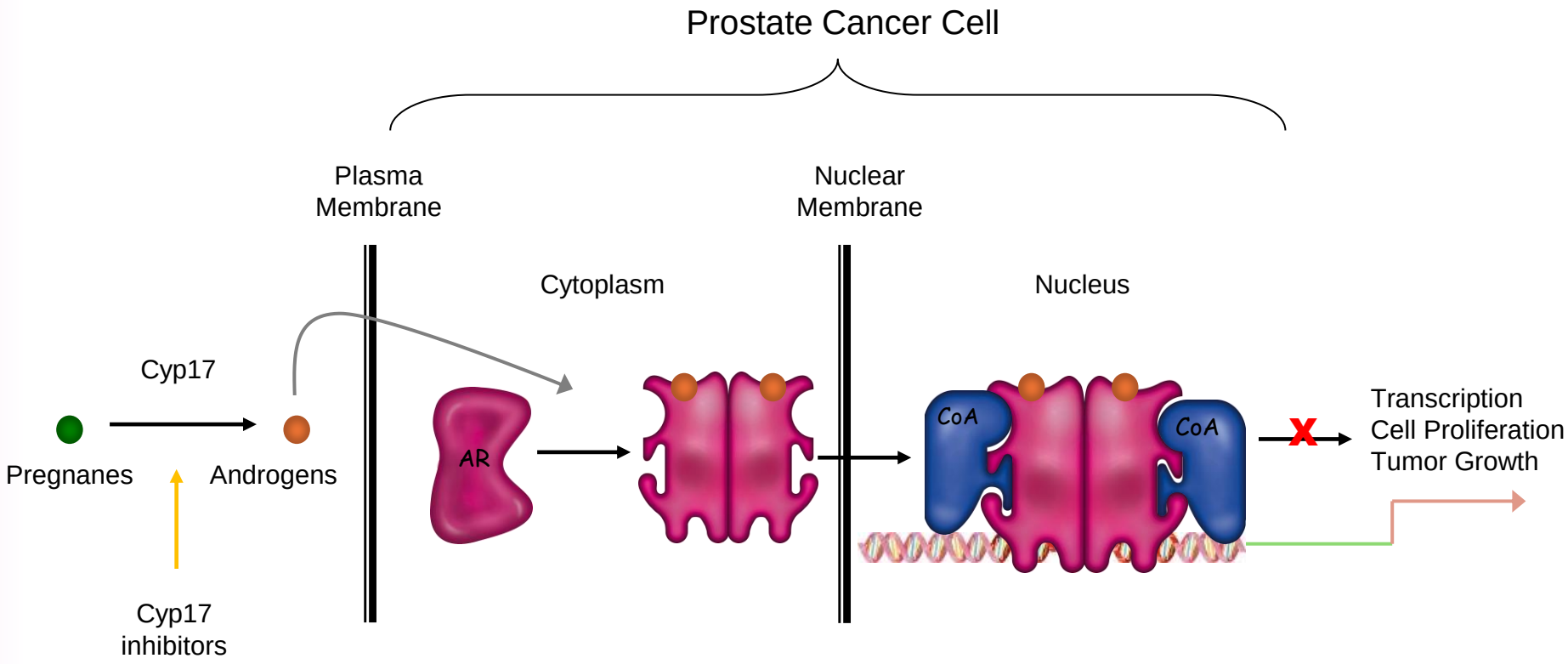
SRs exhibit functional allostery (they are shape shifters)



Hancock, G.R., Young, K.S., Hosfield, D.J. *et al.* Unconventional isoquinoline-based SERMs elicit fulvestrant-like transcriptional programs in ER+ breast cancer cells. *npj Breast Cancer* **8**, 130 (2022). https://doi.org/10.1038/s41523-022-00497-9

Current Model of Steroid Hormone Receptor Action and Pharmacology (exp: AR in Prostate Cancer)



Complements of Dr. Donald McDonnell (Duke University)

Prostate Cancer Cells Respond in a Non-Linear Manner to Androgens

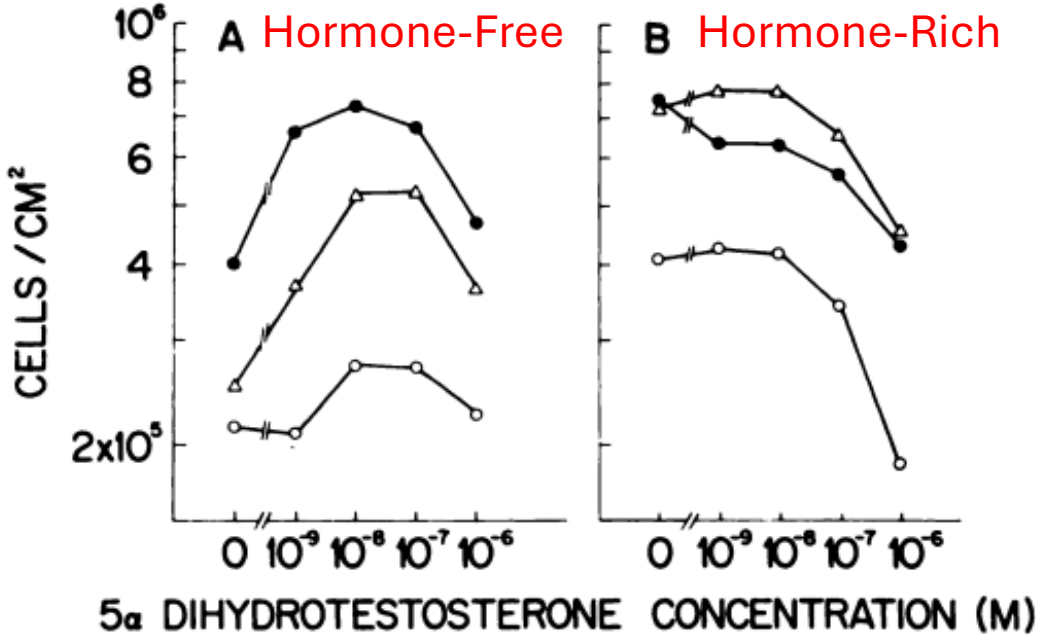
Complements of Dr. Donald McDonnell (Duke University)

[CANCER RESEARCH 43, 1809–1818, April 1983]
0008-5472/83/0043$02.00

LNCaP Model of Human Prostatic Carcinoma[1]

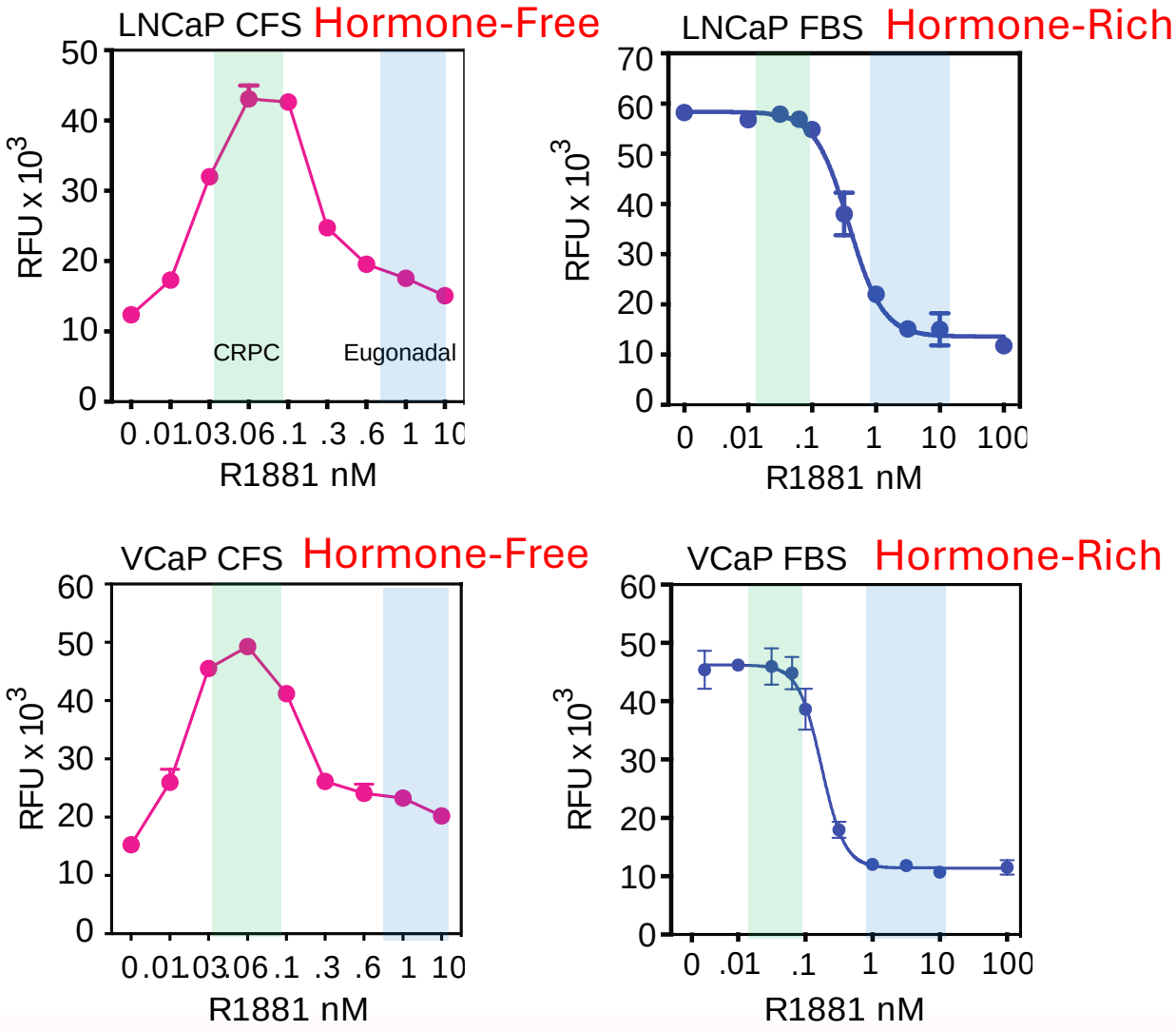
Julius S. Horoszewicz,[2] Susan S. Leong, Elzbieta Kawinski, James P. Karr, Hannah Rosenthal, T. Ming Chu, Edwin A. Mirand, and Gerald P. Murphy

Departments of Biological Resources [J. S. H., S. S. L., E. K., E. A. M.], Experimental Surgery [J. P. K., G. P. M.], Genetics and Endocrinology [H. R.], and Diagnostic Immunology and Biochemistry [T. M. C.], Roswell Park Memorial Institute, Buffalo, New York 14263



Complements of Dr. Donald McDonnell (Duke University)

Cells Possess Mechanisms to Allow Them to Respond Differently to Different Doses of Androgens



Complements of Dr. Donald McDonnell (Duke University)

Shutsung Liao Proposed the Idea of HD Androgens as a Therapeutic Strategy in Prostate Cancer 35 Years Ago!

Suppression of Prostate Cancer Growth by Androgen

(Androgen Suppression and Reversion (ASR) Therapy)

Memo by S. Liao

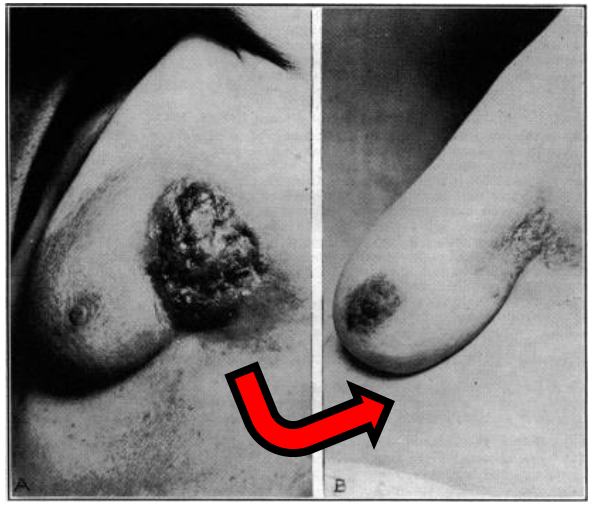
Basic aspects:

1. After androgen ablation therapy, androgen-dependent PC cells can progress to androgen-independent cells that do not need androgen for their growth and proliferation.
2. These cells may have increased amounts of androgen receptors (AR) due to negative control of AR gene expression by androgen.
3. These androgen-independent PC cells, with high AR content, may be sensitive to androgen repression and, therefore, are called PC-R cells.
4. The serum PSA levels of individuals with these PC-R tumors may increase after androgen administration. As the tumor size decreases, PSA levels may go down.
5. Androgen may also reverse the PC-R cells back to androgen-dependent cells that do not grow well without androgen.
6. Our new idea is based on the suppression of the growth of androgen-independent tumor and reversion of the androgen-independent tumors back to androgen-dependent tumors that can be treated again by androgen ablation therapy.
7. Our approach, therefore, may be called 'Androgen Suppression and Reversion (ASR) Therapy'.
8. The 'Intermittent Androgen Replacement Therapy' of the Vancouver (Bruchovsky) group was based on the maintenance (and stimulation) of the growth of androgen-dependent tumor cells by androgen to release the 'pressure' for the tumor cells to become androgen-independent.
9. Our results also indicated the danger of blindly using Proscar, Casodex or other antiandrogens that may stimulate the growth of PC-R tumors.
10. Flutamide withdrawal syndrome may be due to: (a) AR mutation, or (b) progression to R cells in chemically castrated patients (still with testis).

(Credit to Dr. Gail Prins for finding this document)

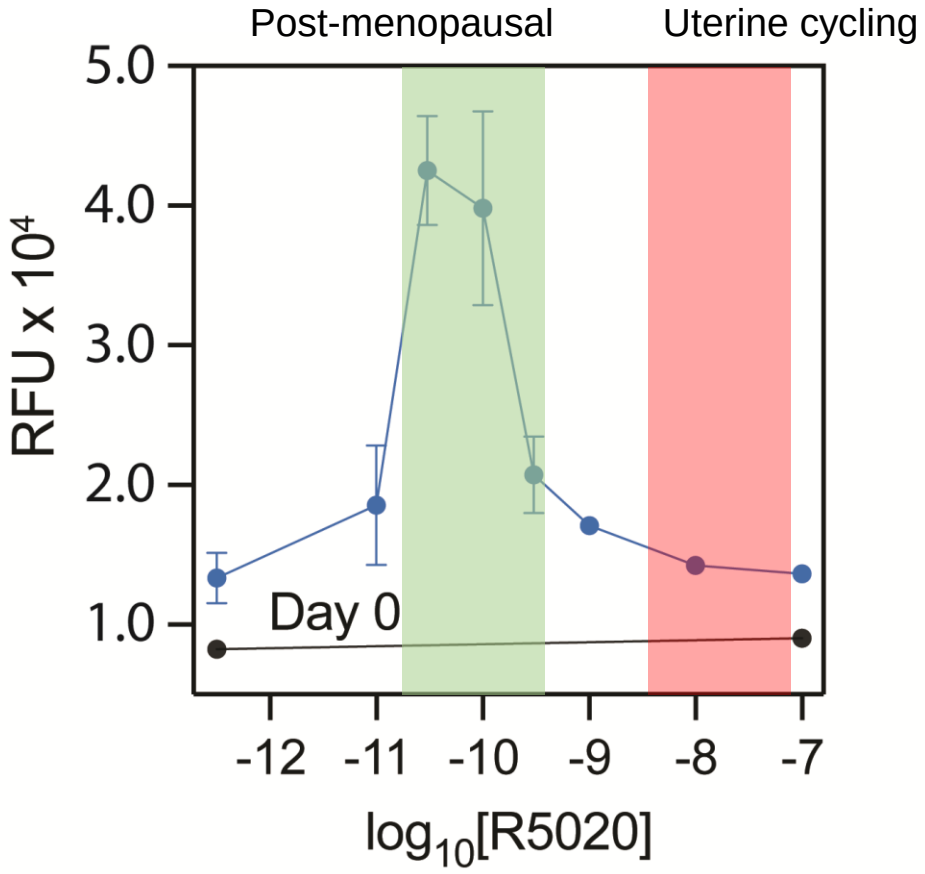
HD estrogens were proposed over 80 years ago!

Haddow A, Watkinson JM, Paterson E, Koller PC. **Influence of Synthetic Oestrogens on Advanced Malignant Disease.** Br Med J. 1944 Sep 23;2(4368):393-8. doi: 10.1136/bmj.2.4368.393. PMID: 20785660; PMCID: PMC2286289.

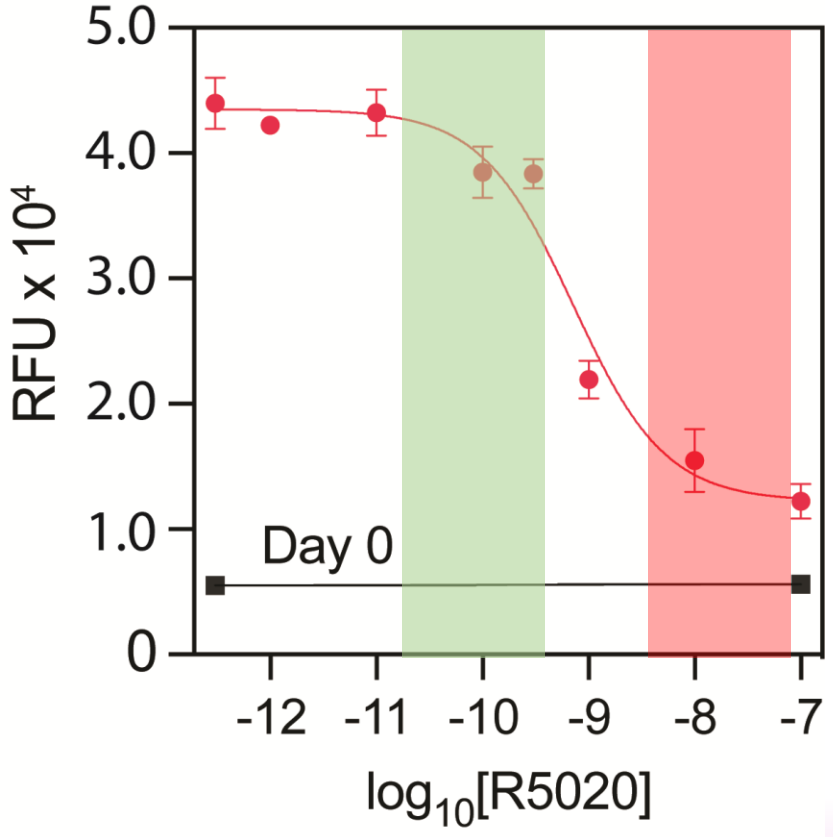


Cells Possess Mechanisms to Allow Them to Respond Differently to Different Doses of Progestins

T47D CFS (hormone-free)

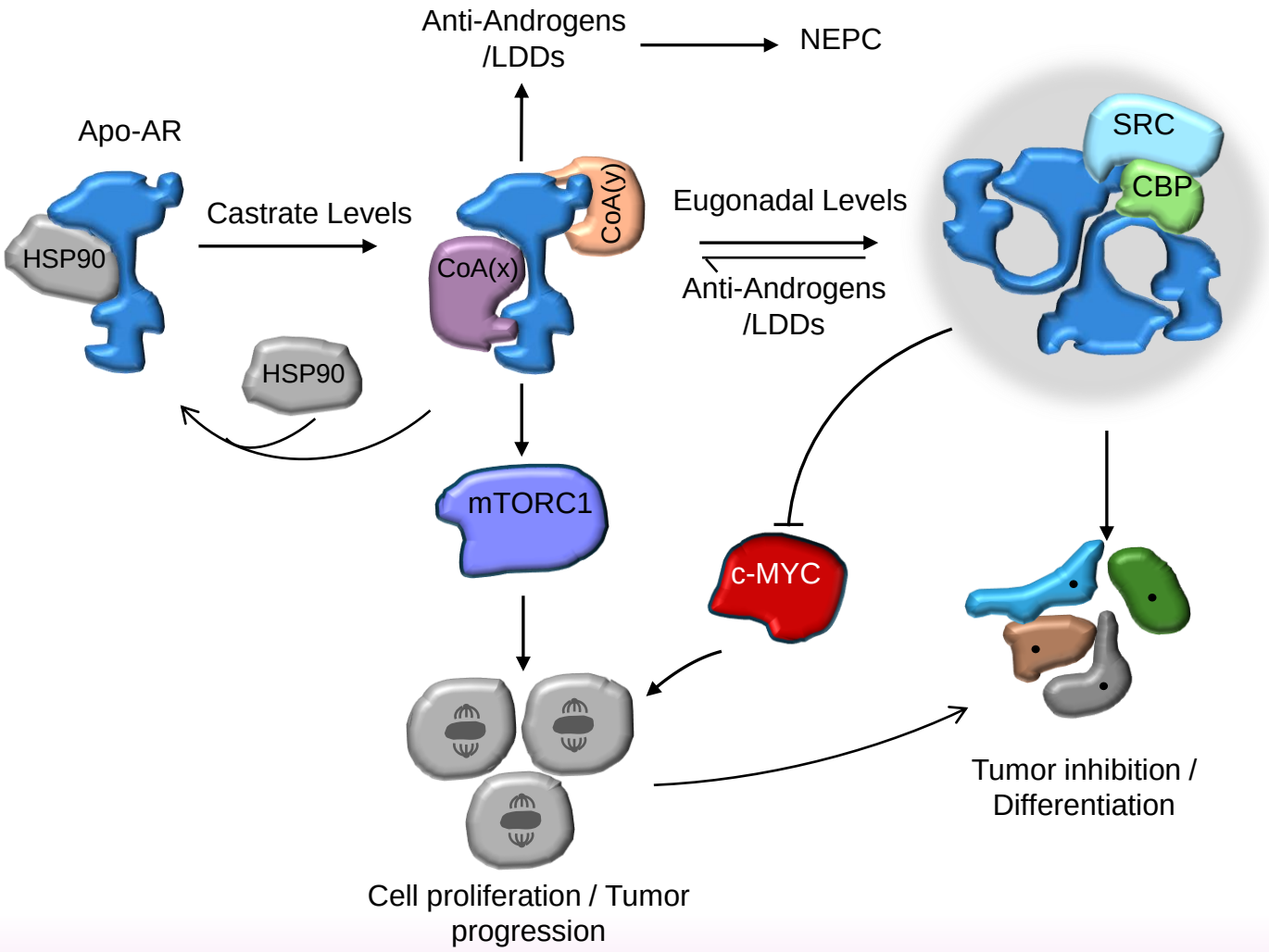


T47D FBS (hormone-rich)



Complements of Dr. Donald McDonnell (Duke University)

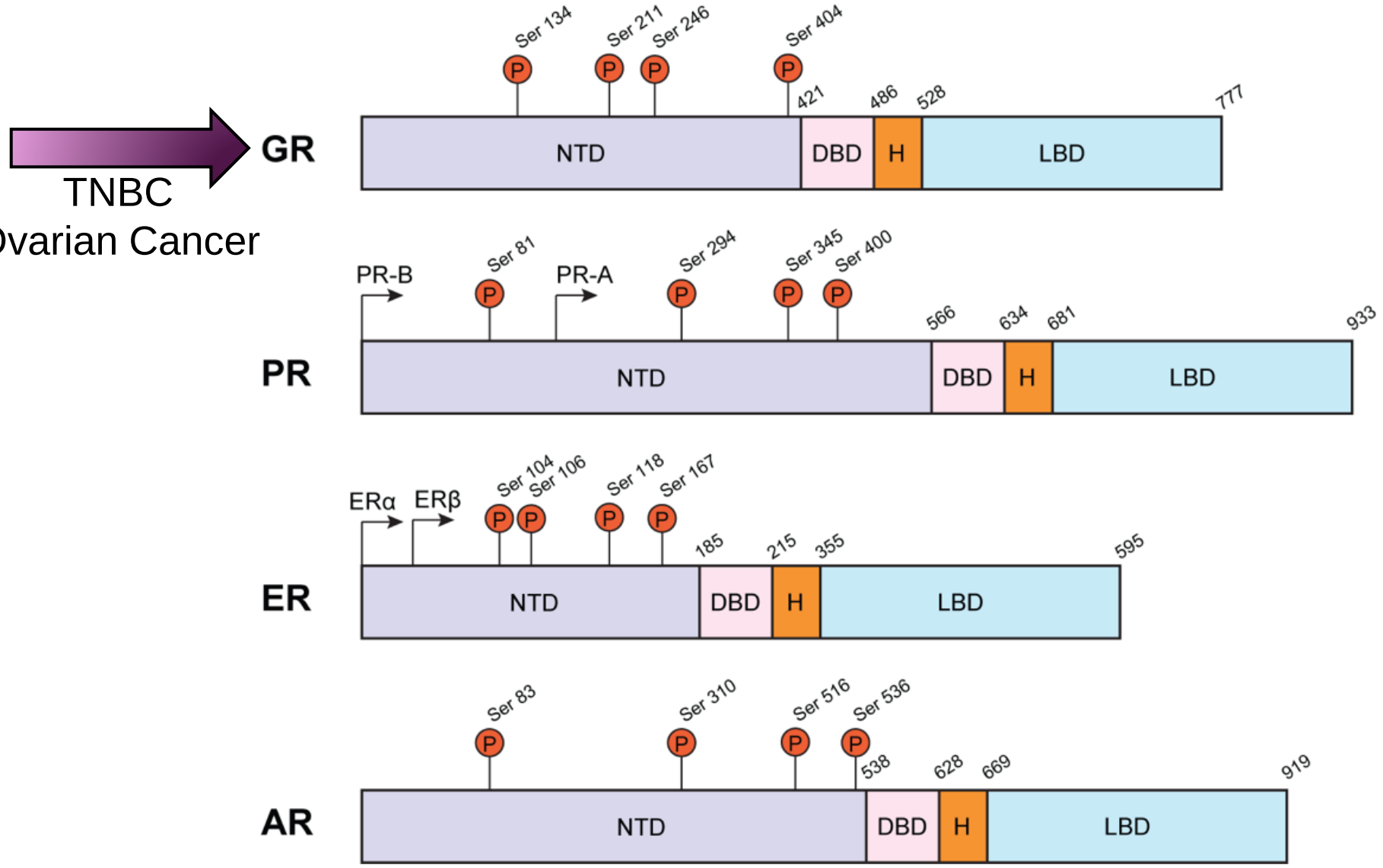
Take Advantage of the Normal Biology of Androgens



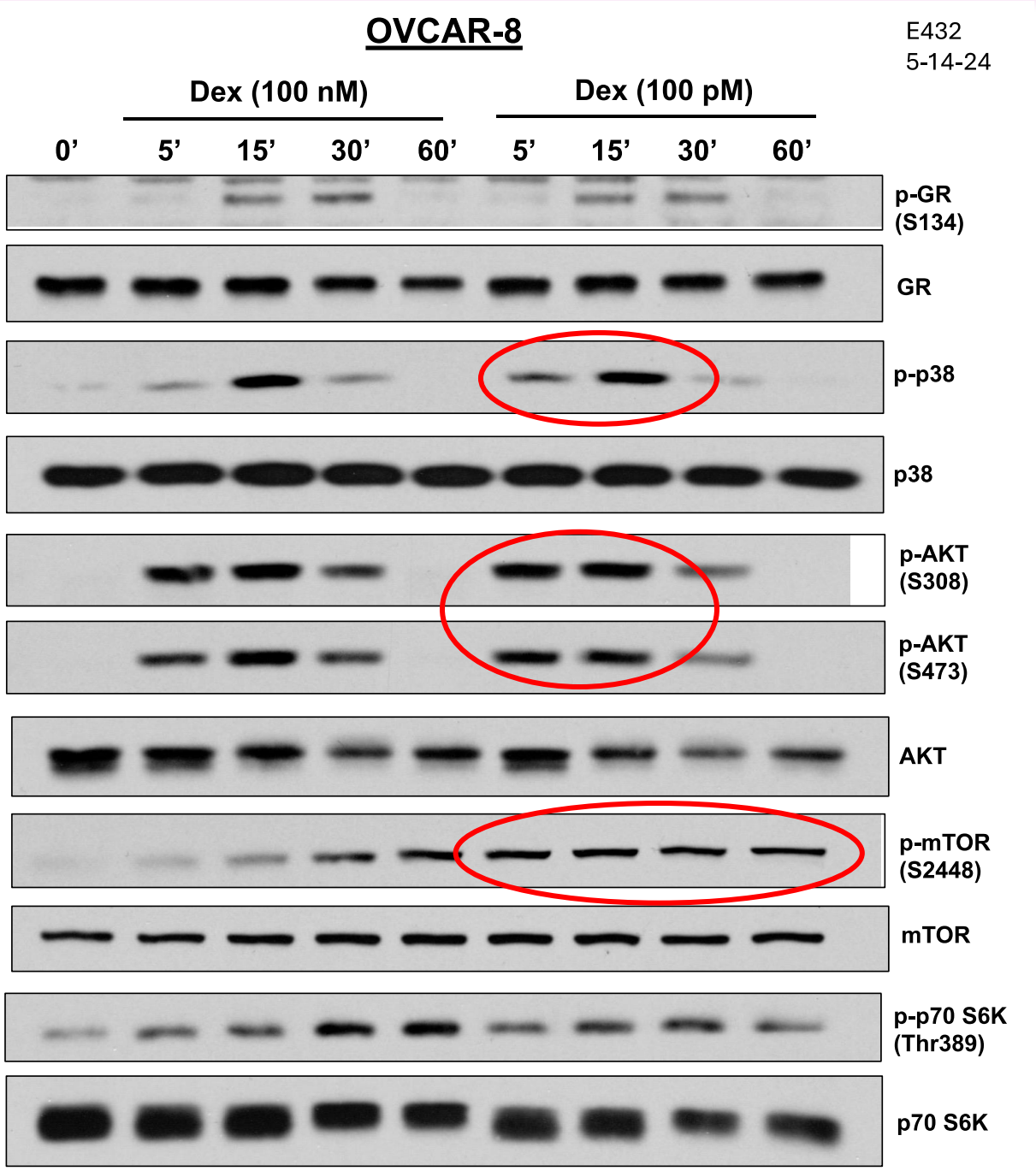
Complements of Dr. Donald McDonnell (Duke University)

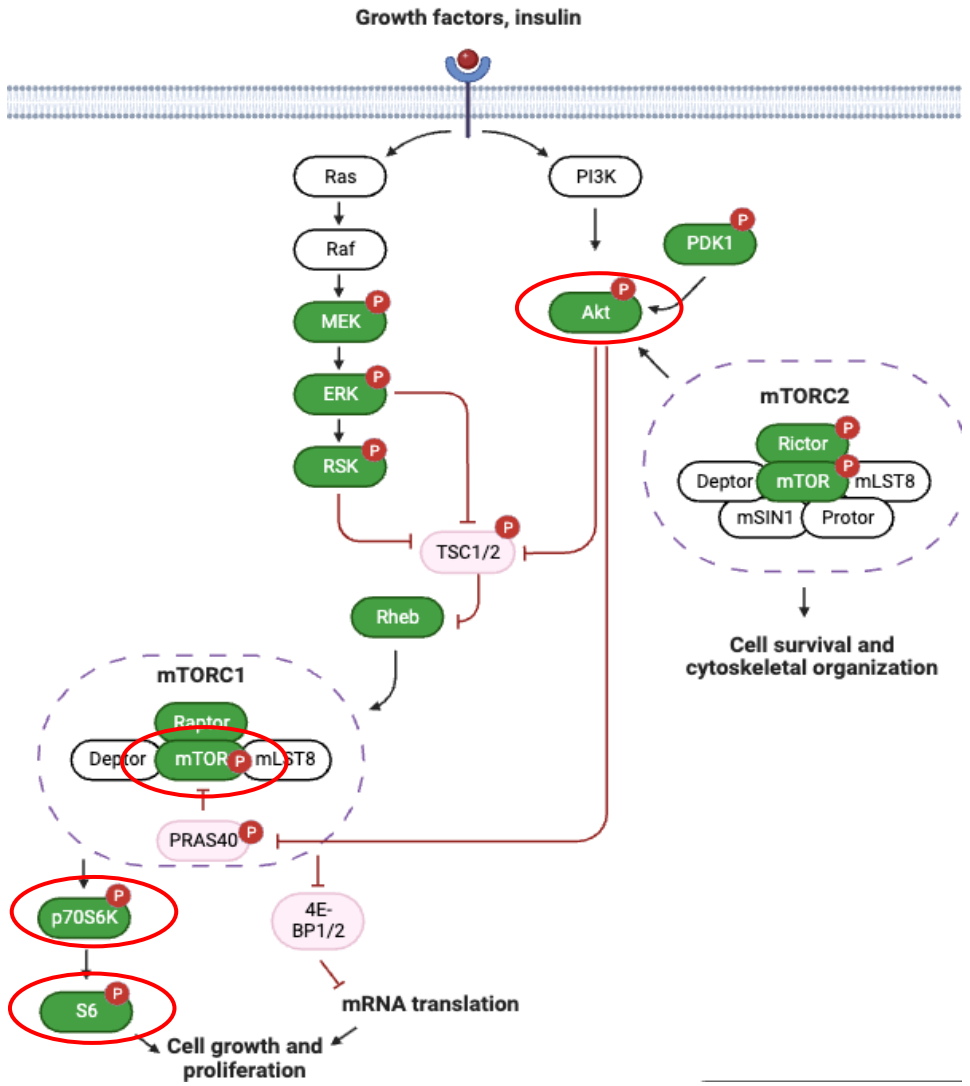
Closely Related Steroid Hormone Receptor Family Members

TNBC
Ovarian Cancer



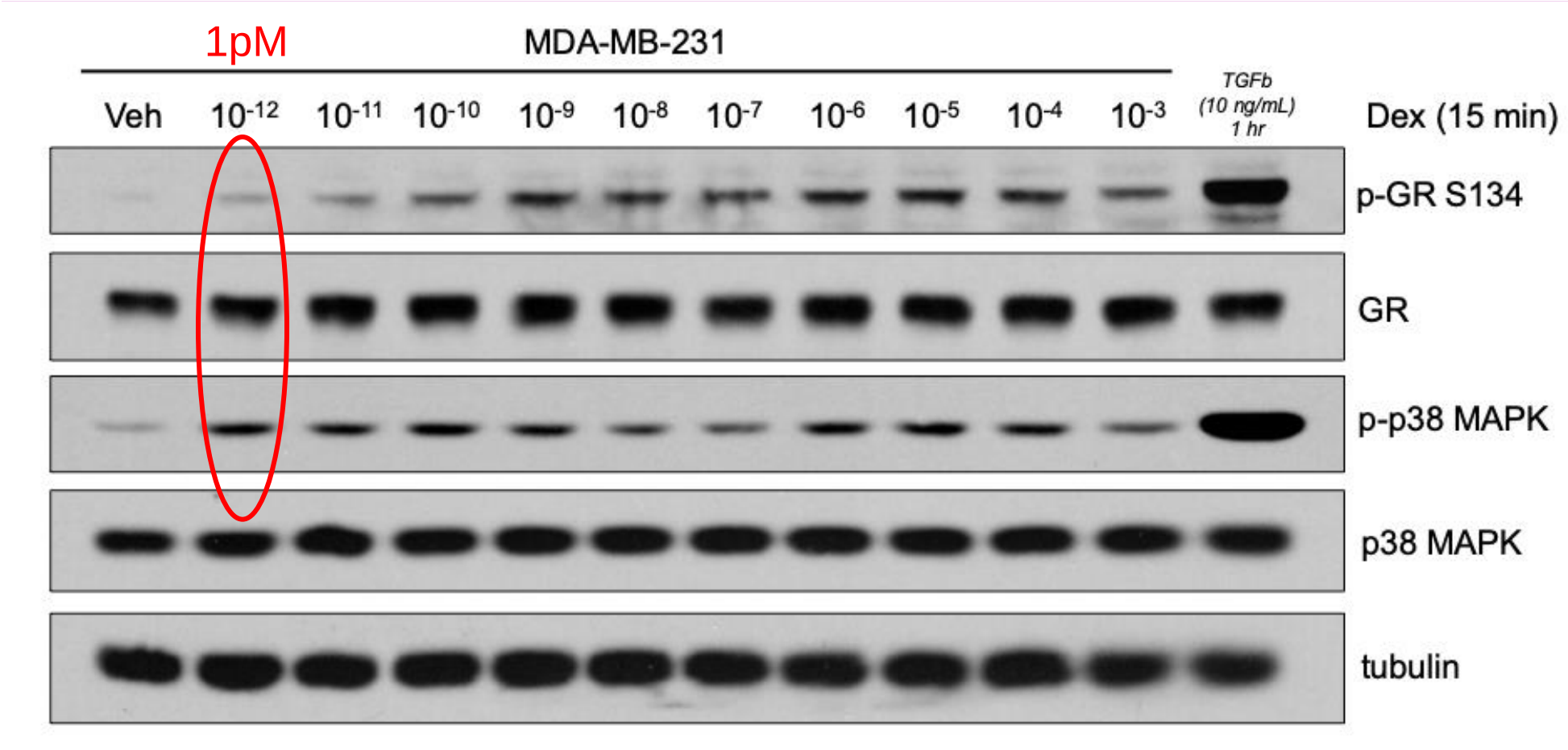
High (100 nM) vs low (100 pM) Dex treatment rapidly activates GR, p38, and mTOR pathways in ovarian cancer cells





Dr. Caroline Diep, Lange lab (unpublished)

Dex dose curve in TNBC Models (MDA-MB-231)
(Dex treatment time = 15 min)



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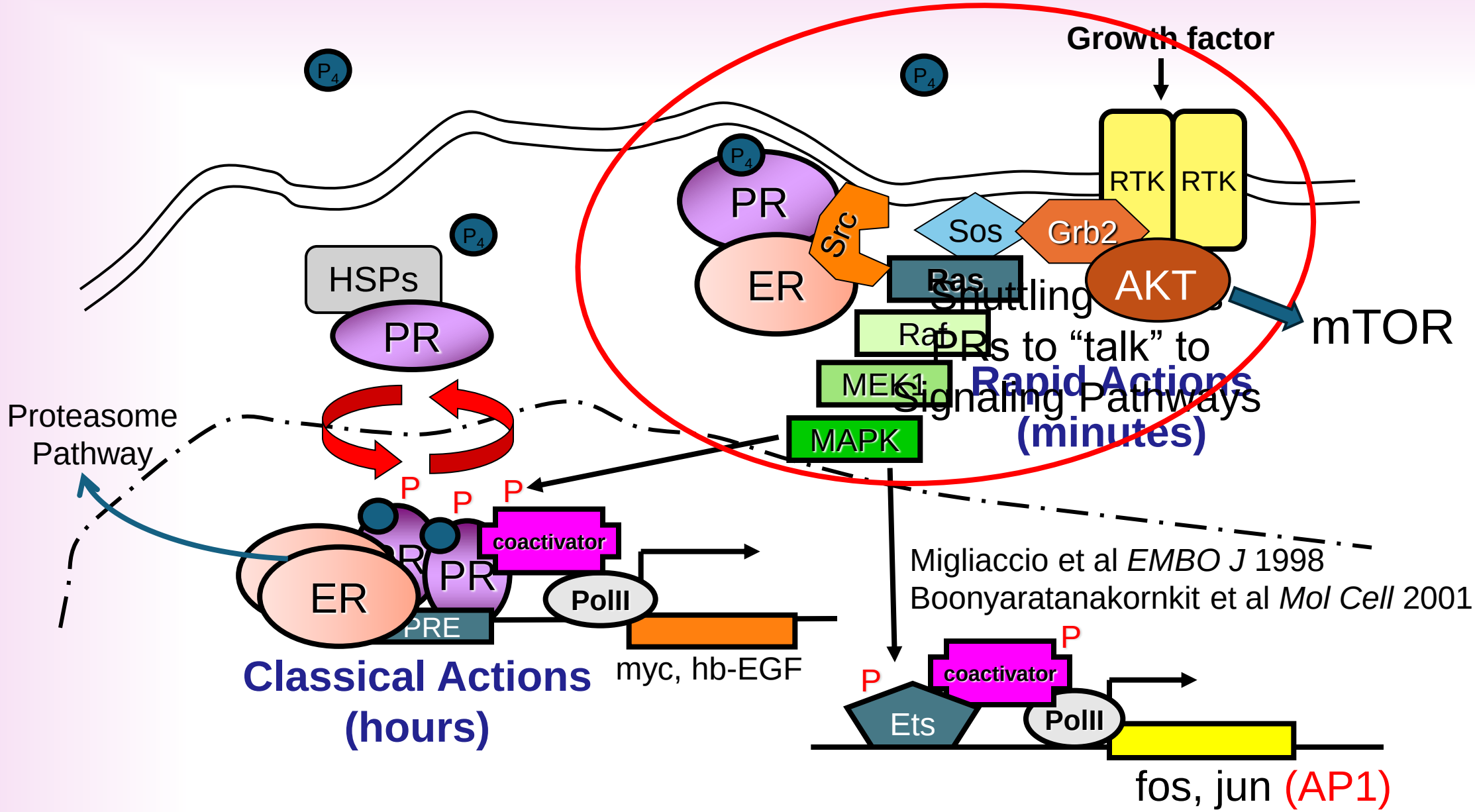
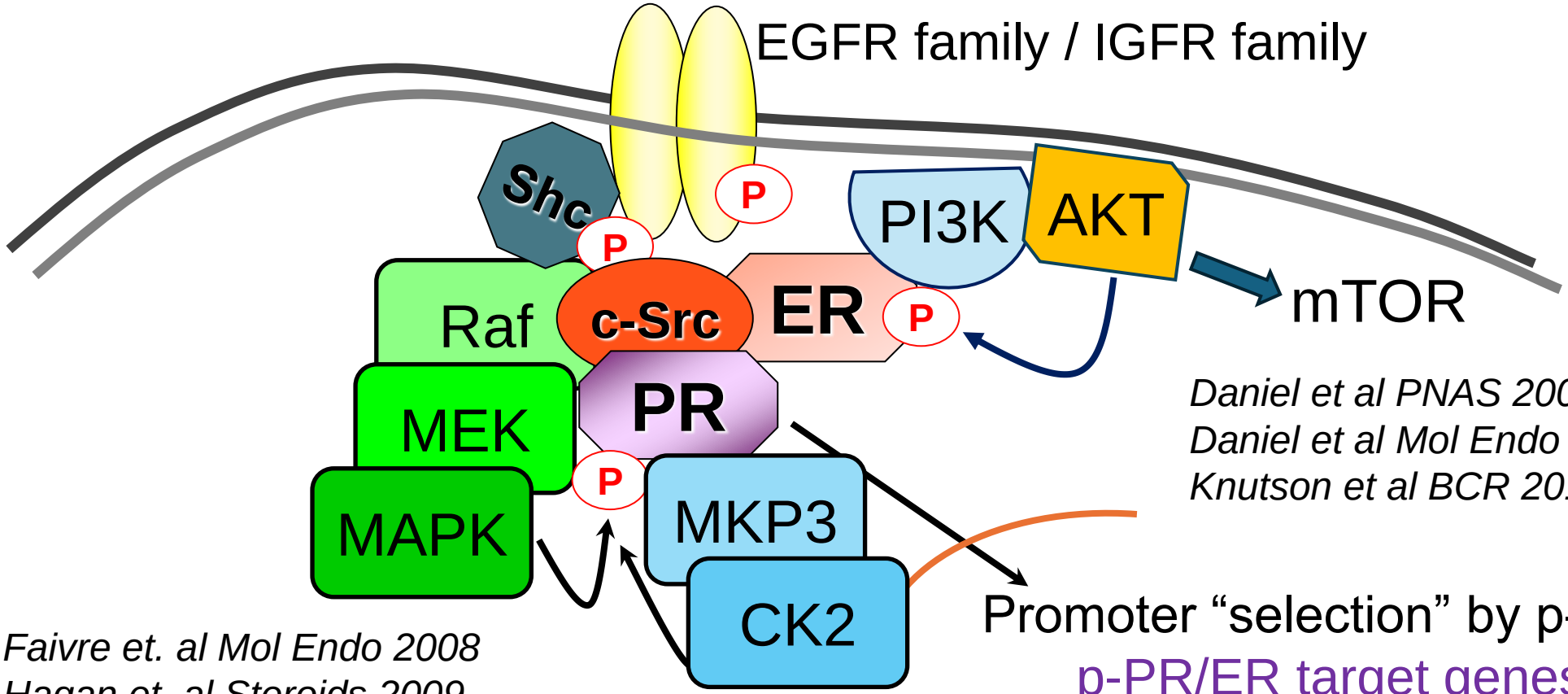
All SRs function in both the nucleus and the cytoplasm

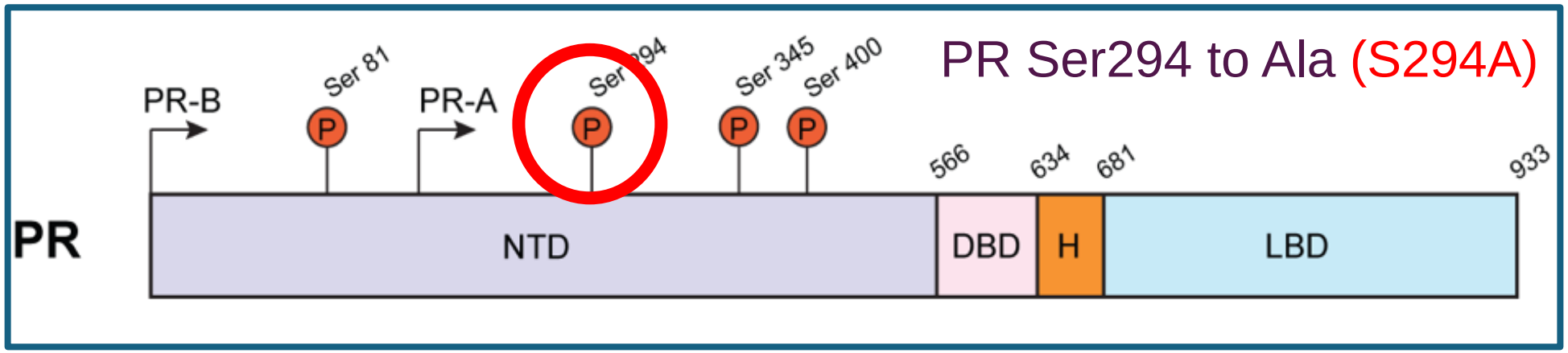


AR Daniel et al Oncogene 2015

PR and ER in membrane-associated complexes are capable of rapidly activating c-Src and MAPKs *that phosphorylate PR and ER…. (highly regulated!)*



Progesterone Receptors are phosphorylated by oncogenic protein kinases

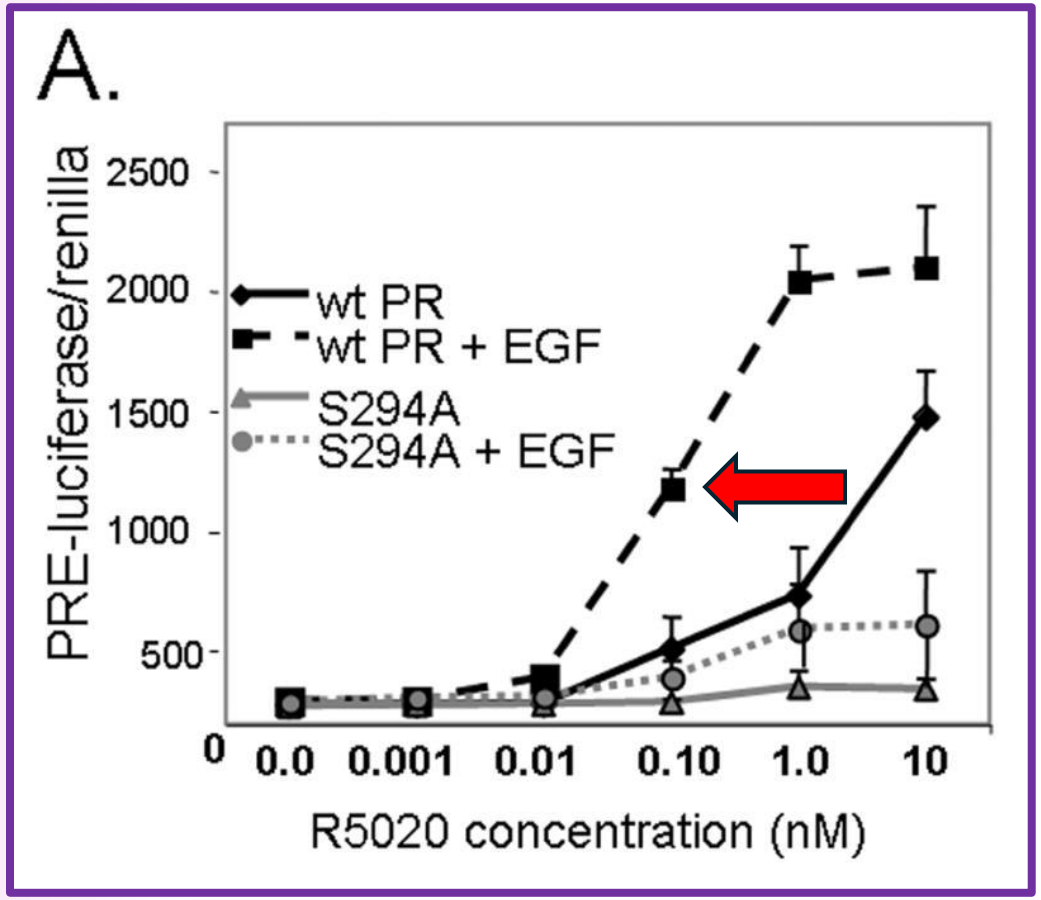


Studies with phospho-mutant S294A PRs:

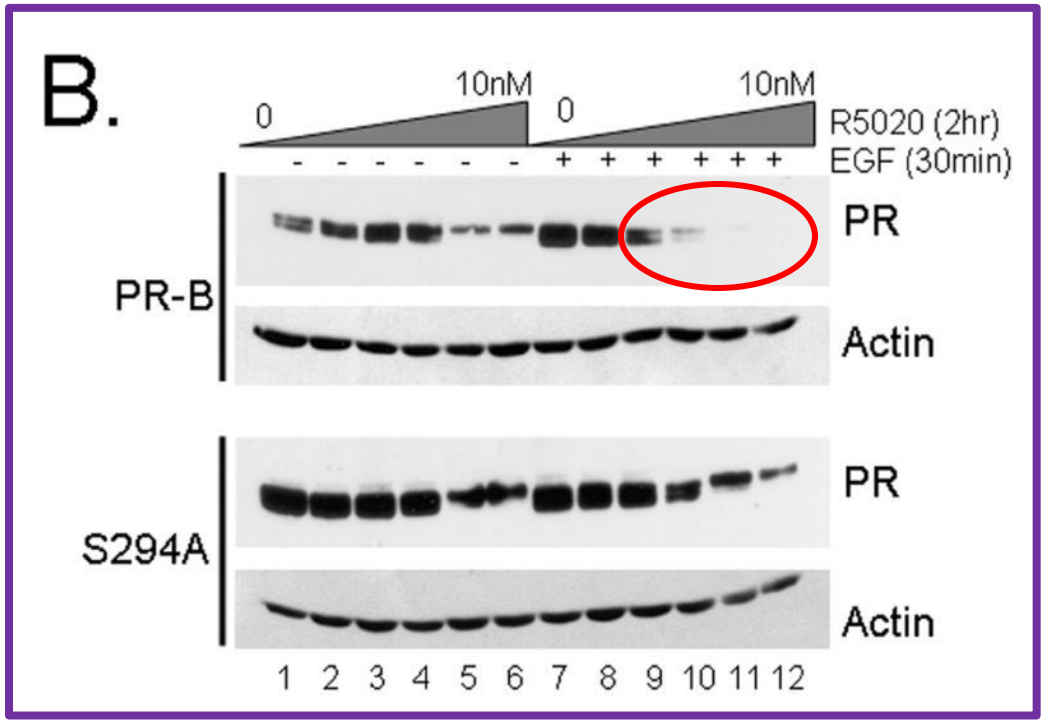
- Phosphorylated PR are hyper-activated (low dose progestins)

Phosphorylation events left-shift the dose-response curve

This is a feed-forward loop that amplifies the signal!

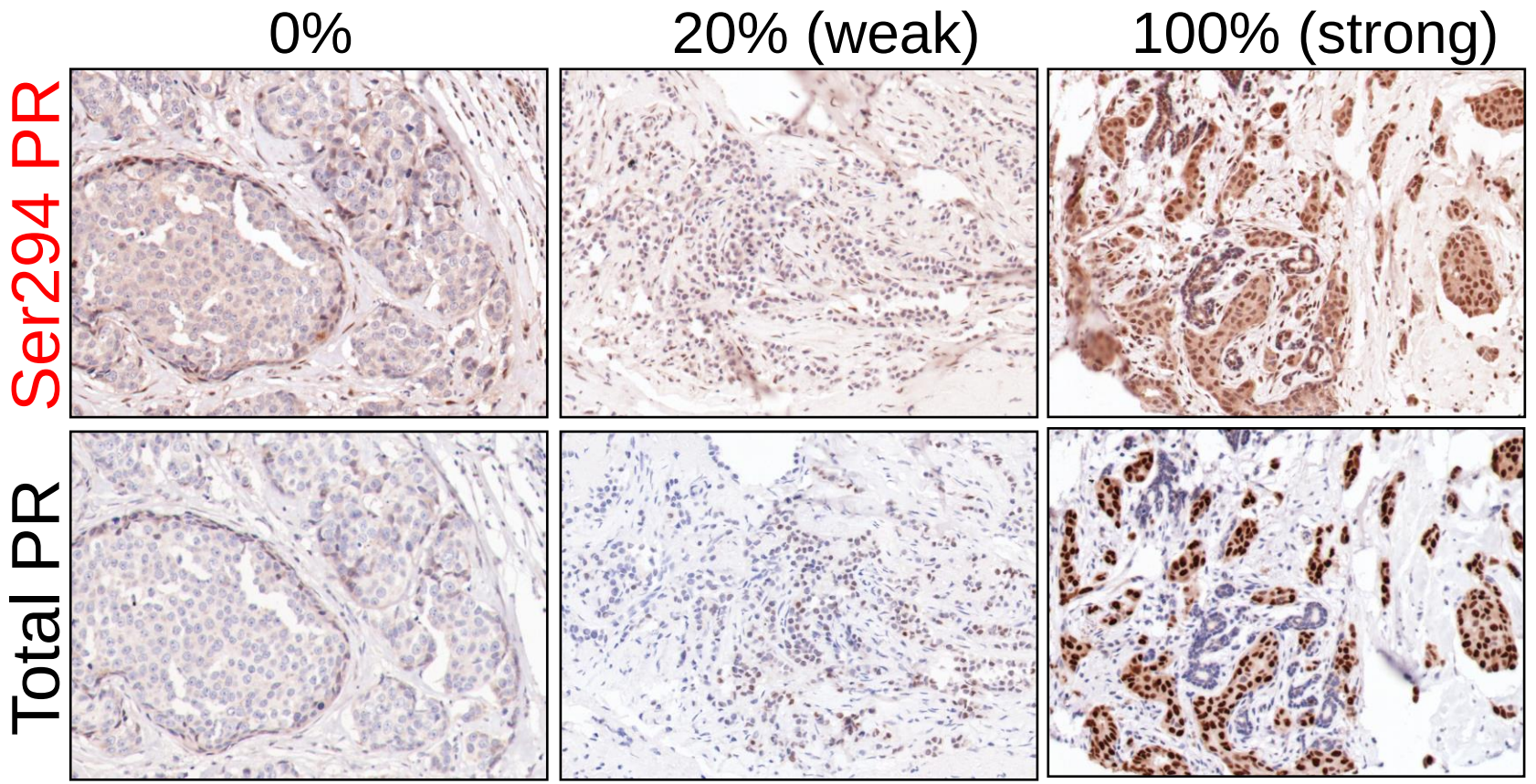


Activated phospho-PRs undergo rapid turnover!



M. Qiu et al, 2003

54% of ER+ luminal tumors express >20% phospho-Ser294 PRs

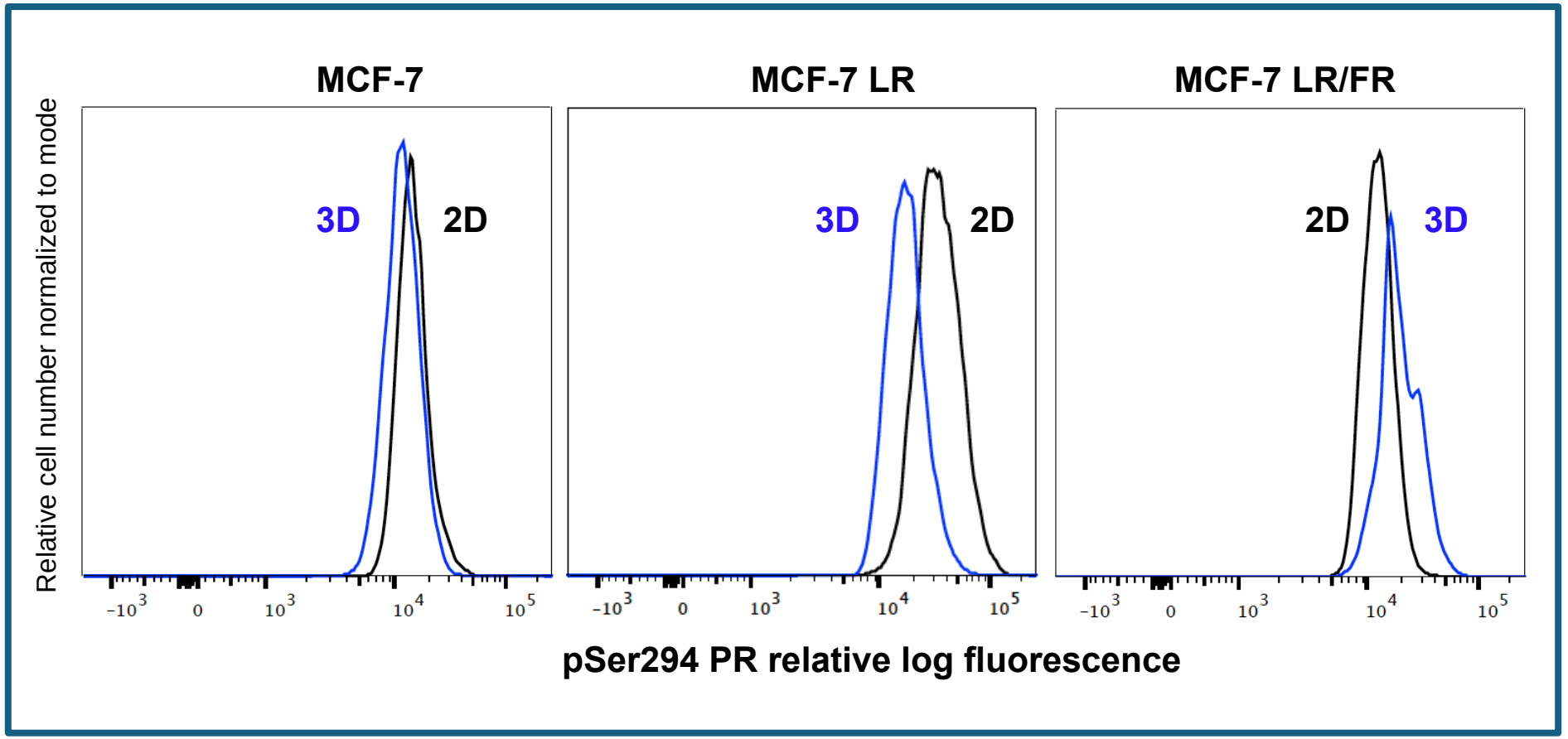


Kaylee Schwertfeger & Nick Brady; n=207 luminal tumors (TMA)
TP Knutson et al JHO 2017

Endocrine Resistant Models: Letrozole (LR) & Fulvestrant (FR)

- ER-very low/PR-null?

Flow Cytometry (p-Ser294-PR)



(Unpublished – Dr. Caroline Diep)

All steroid hormones exhibit biphasic behavior

- Low dose hormone exposures favor SR monomers
  - Steroid hormones are made within the TME and during therapeutic hormone ablation
  - SR monomers elicit highly proliferative signaling programs known to drive tumorigenesis
- Phosphorylation events may favor monomers that support cytoplasmic signaling
- Phosphorylated SRs provide useful biomarkers of rapid signaling behavior

New ligands are being designed that “lock in”
SR dimers to drive differentiation programs
These could be used in prevention strategies to lower risk!

Outline & Learning Objectives

- Lessons from mammary gland development can provide insight to breast cancer prevention strategies!
  - Estrogen and Progesterone act in concert.
  - Progesterone mediates distinct phases of mammary gland development during puberty & pregnancy.
- Both hormone and dose Matter!
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- Steroid receptors love playmates!
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  - SR:SR interactions may be antagonistic or collaborative and depend on the signaling and hormonal context.
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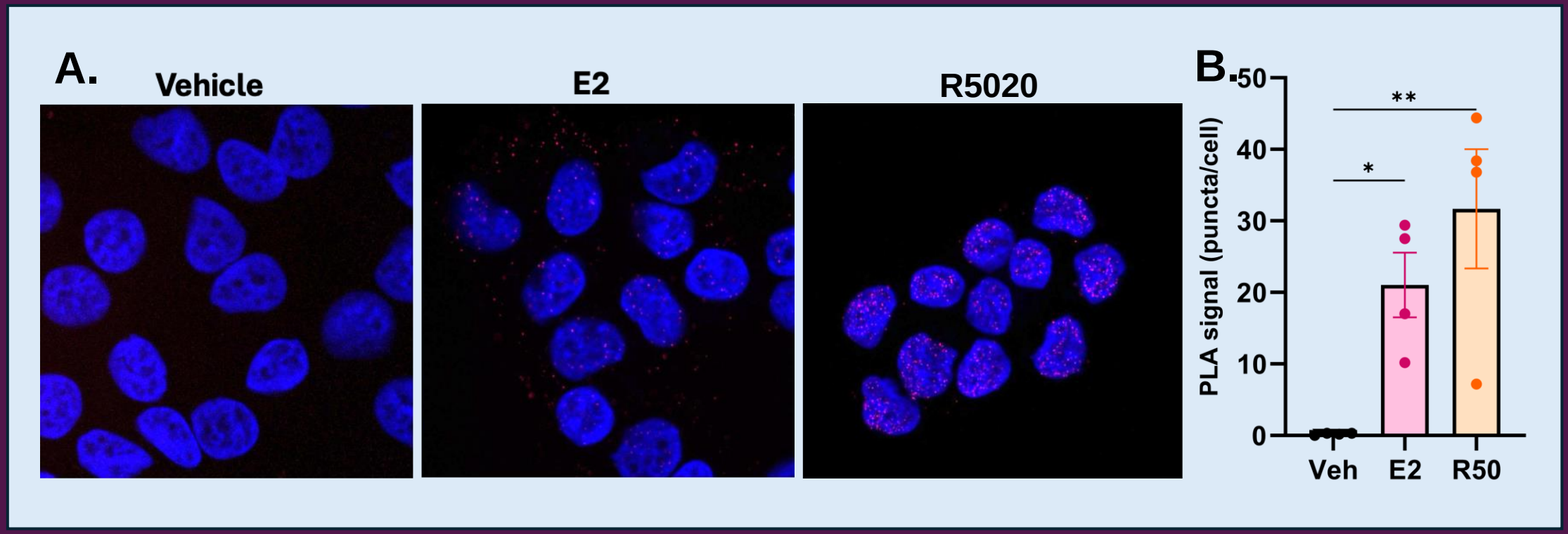
  - It is important to consider multiple readouts of hormone/antihormone action (biomarkers other than Ki67).
- Recent provocative data that incorporate these concepts!
  - SRs drive aggressive phenotypes in breast cancer models via partnership with related SR cousins.
  - Proliferative and Quiescent gene programs are distinct but linked processes (DREAM-on).

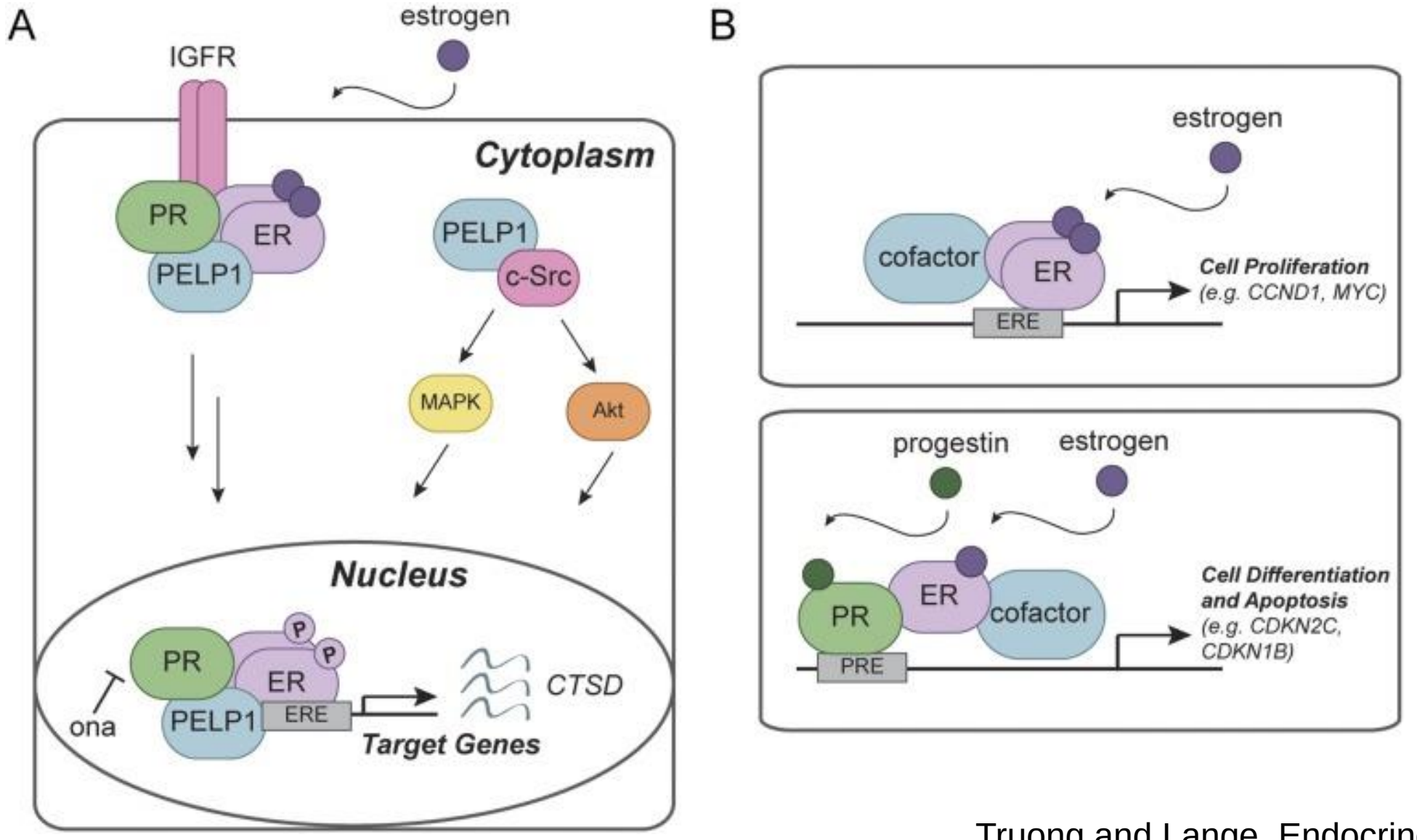
ER:PR interactions are induced by either estrogen (E2) or progestin (R5020)



Proximity Ligation Assay (PLA) shows hormone-induced ER:PR nuclear puncta

Posani and Lange; Unpublished

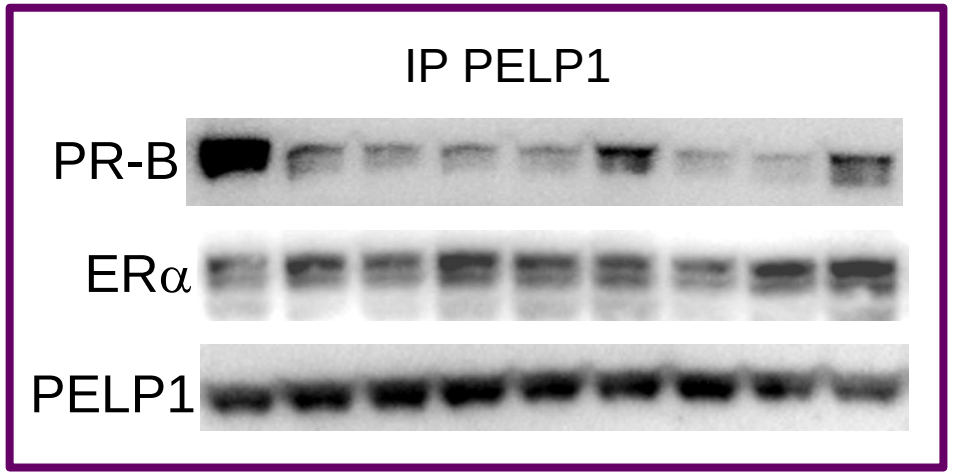
Models of ER:PR crosstalk



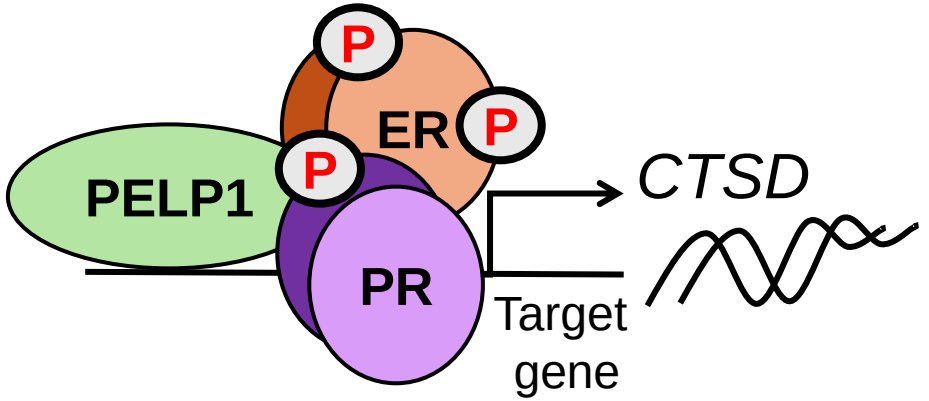
Truong and Lange, Endocrinology 2018

ER and PR are intimate partners:

ER/PR signaling complexes occur constitutively in human tumors



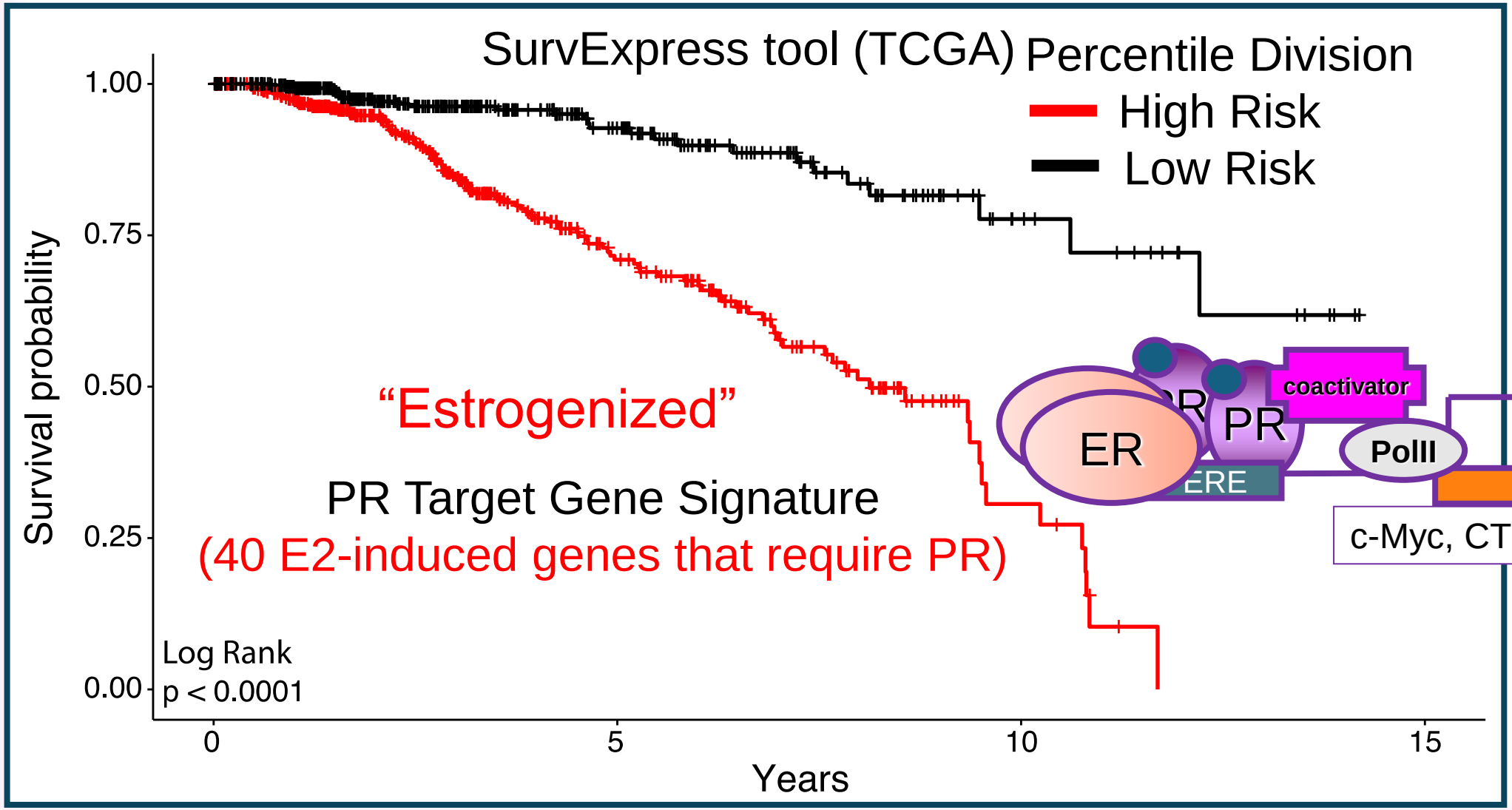
Human breast tumor tissue



ER:PR interaction requires PR phosphorylation
PR scaffolding augments ER phosphorylation

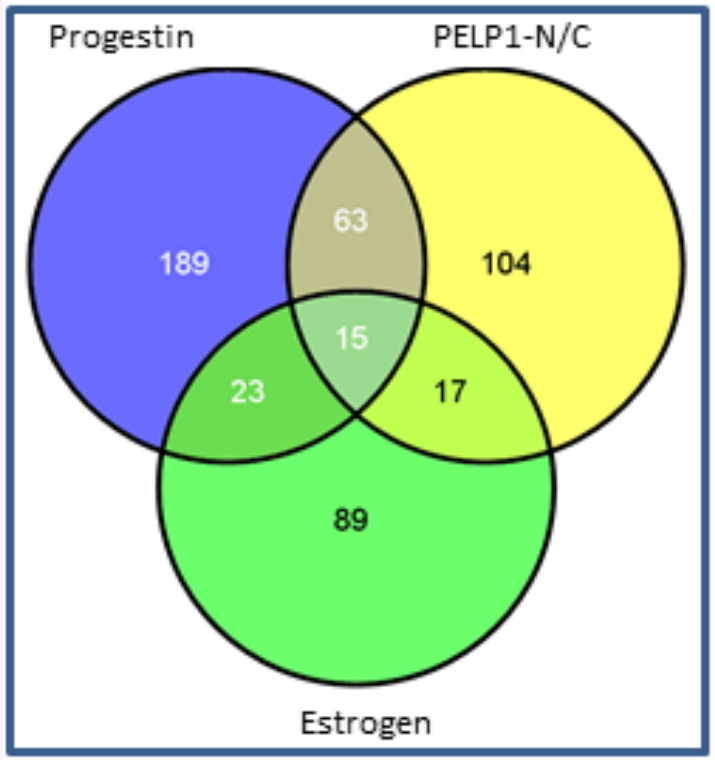
Daniel et. al *Oncogene* 2015
With collaborators G Raj and SH Ma (UTSW)

Cooperative “ER/PR” gene signature predicts poor outcome



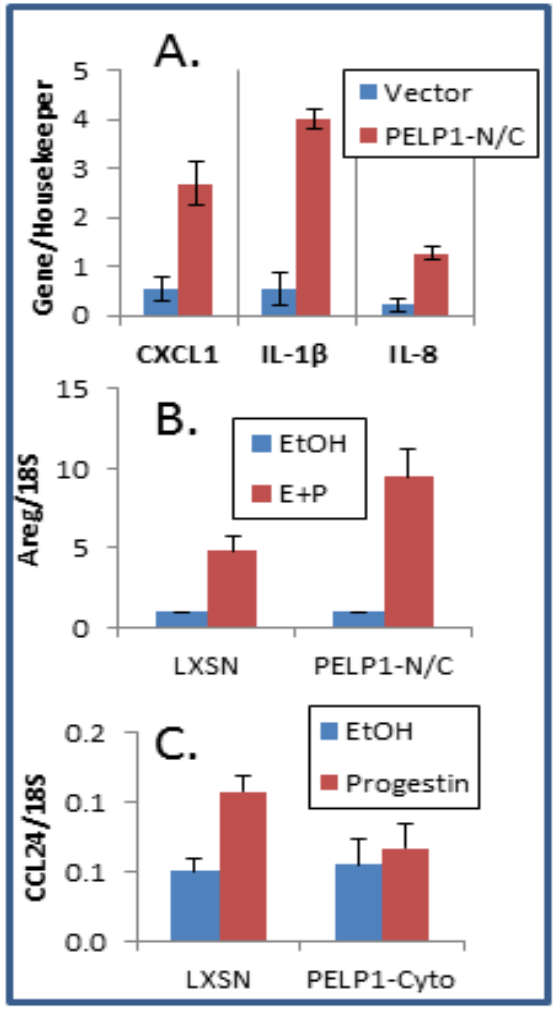
Carlos Perez Kerkvliet; Lange Lab Unpublished

Significant overlap between ER, PR, and PELP1-N/C target genes



15 overlapping gene sets

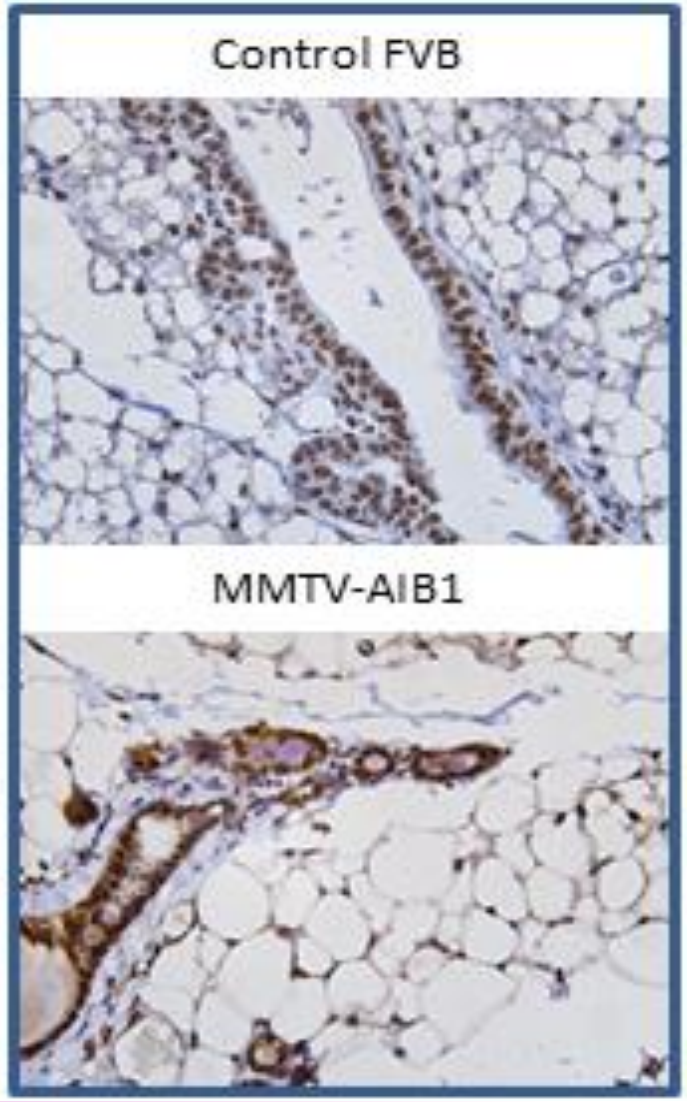
Pro-Inflammatory genes



MCF-7 Models

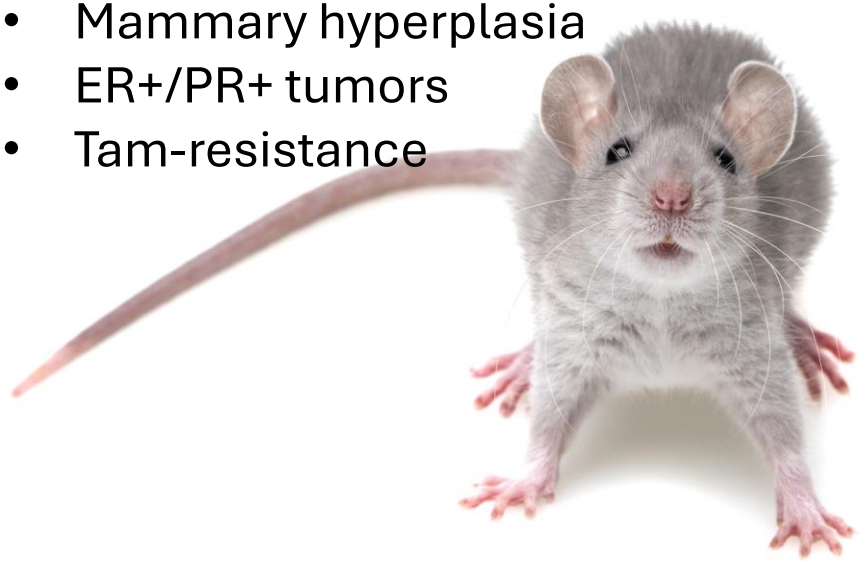
Julie Ostrander and Carol Lange

Pro-Inflammatory Signaling drives progression of hyperplastic lesions *in vivo*

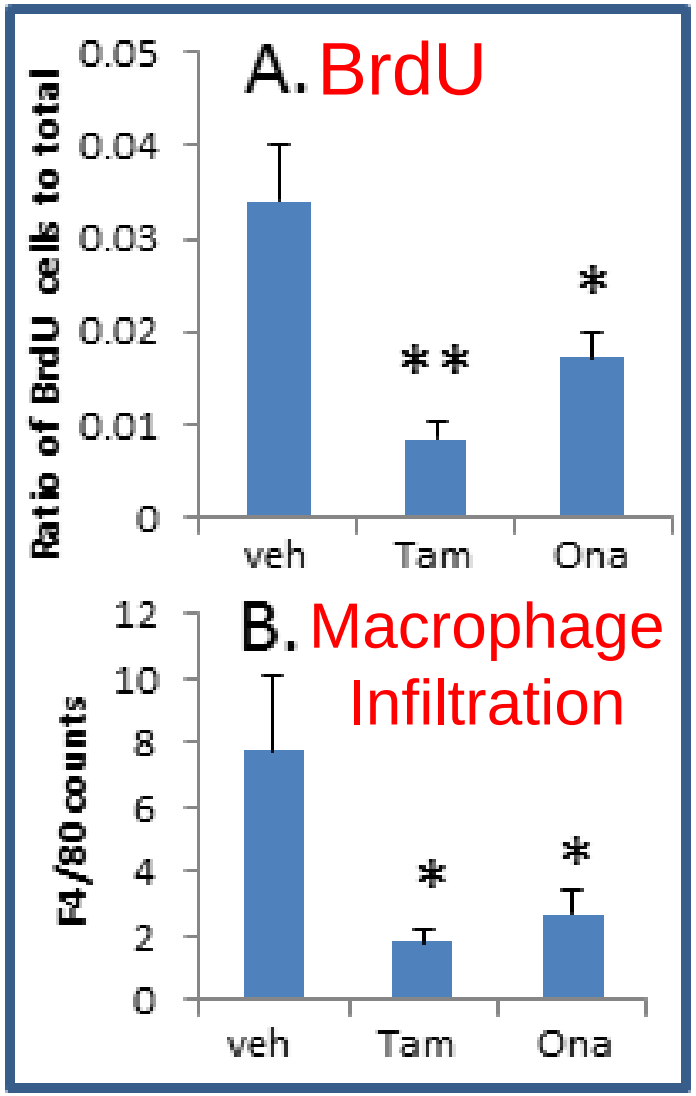


AIB-1 transgenic mouse model (Brown Lab)

- Mammary hyperplasia
- ER+/PR+ tumors
- Tam-resistance



Cytoplasmic PELP1



Julie Ostrander and Carol Lange (unpublished)

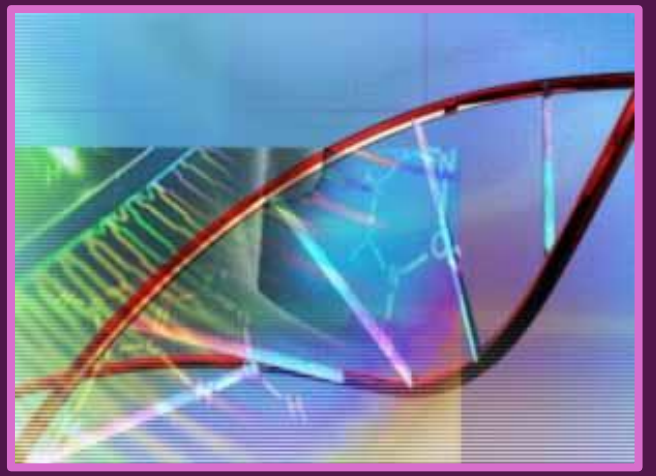
Steroid hormone receptor family members interact extensively

- Anything goes! (the biochemistry and biology of SR crosstalk is complex)
  - SR:SR interactions can be Inhibitory or Cooperative
  - Ligand-dependent or Independent (Scaffolding Actions are common)

- Evaluation of the full SR repertoire will be extremely useful
  - SR:SR interactions create unique gene signatures (biomarkers)
  - SR Degraders target the Scaffolding Actions of unliganded SR partners

SR:SR interactions represent a new frontier but have not been well-characterized in normal breast tissues or during mammary gland development

Targeting pro-inflammatory pathways to reduce risk?



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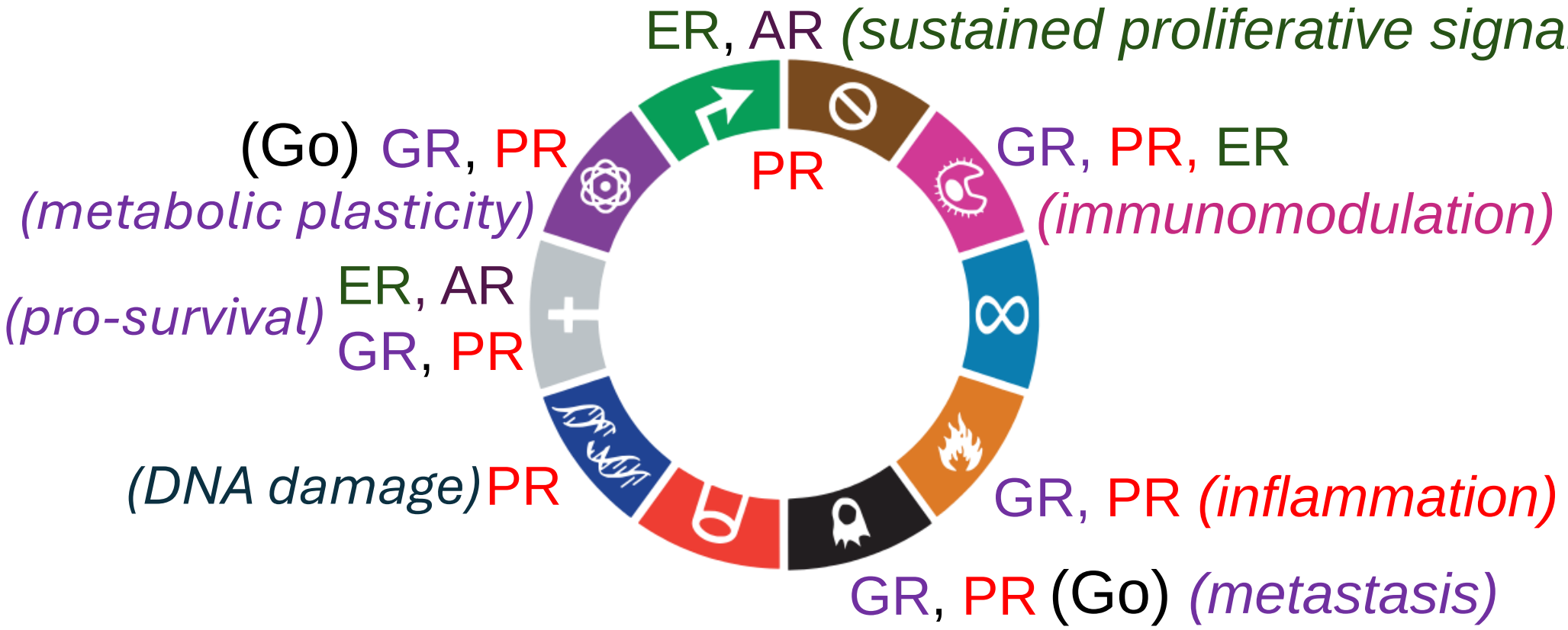
  - It is important to consider multiple readouts of hormone/antihormone action (biomarkers other than Ki67).
- Recent provocative data that incorporate these concepts!
  - SRs drive aggressive phenotypes in breast cancer models via partnership with related SR cousins.
  - Proliferative and Quiescent gene programs are distinct but linked processes (DREAM-on).

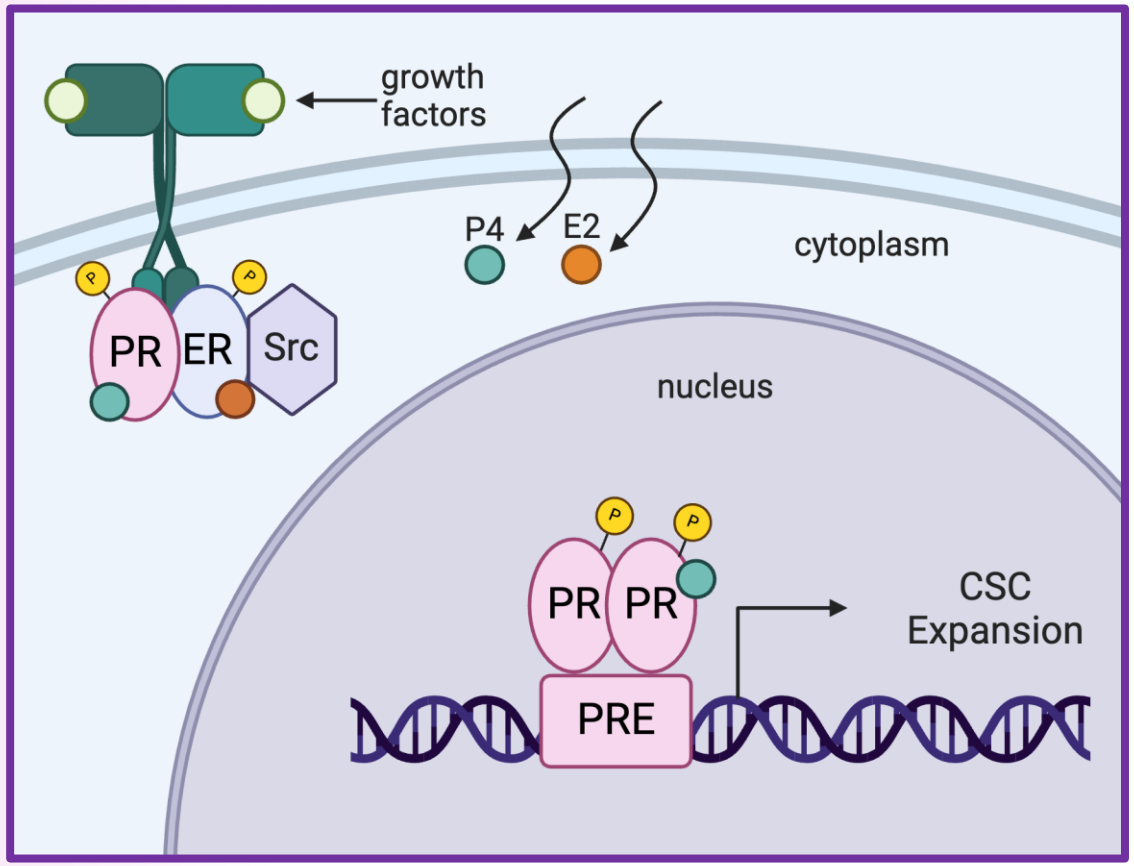
Functionally redundant SRs Drive many Hallmarks of Cancer

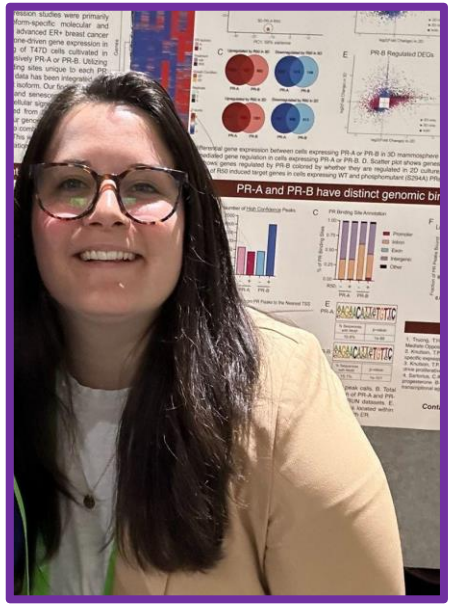
Mammary Stem Cells and Cancer Stem Cells are weakly/non-proliferative



Cell 2011 144646-674DOI: (10.1016/j.cell.2011.02.013)

Regulation of Super Enhancers by Phosphorylated Progesterone Receptors Drives Breast Cancer Stem Cell Expansion



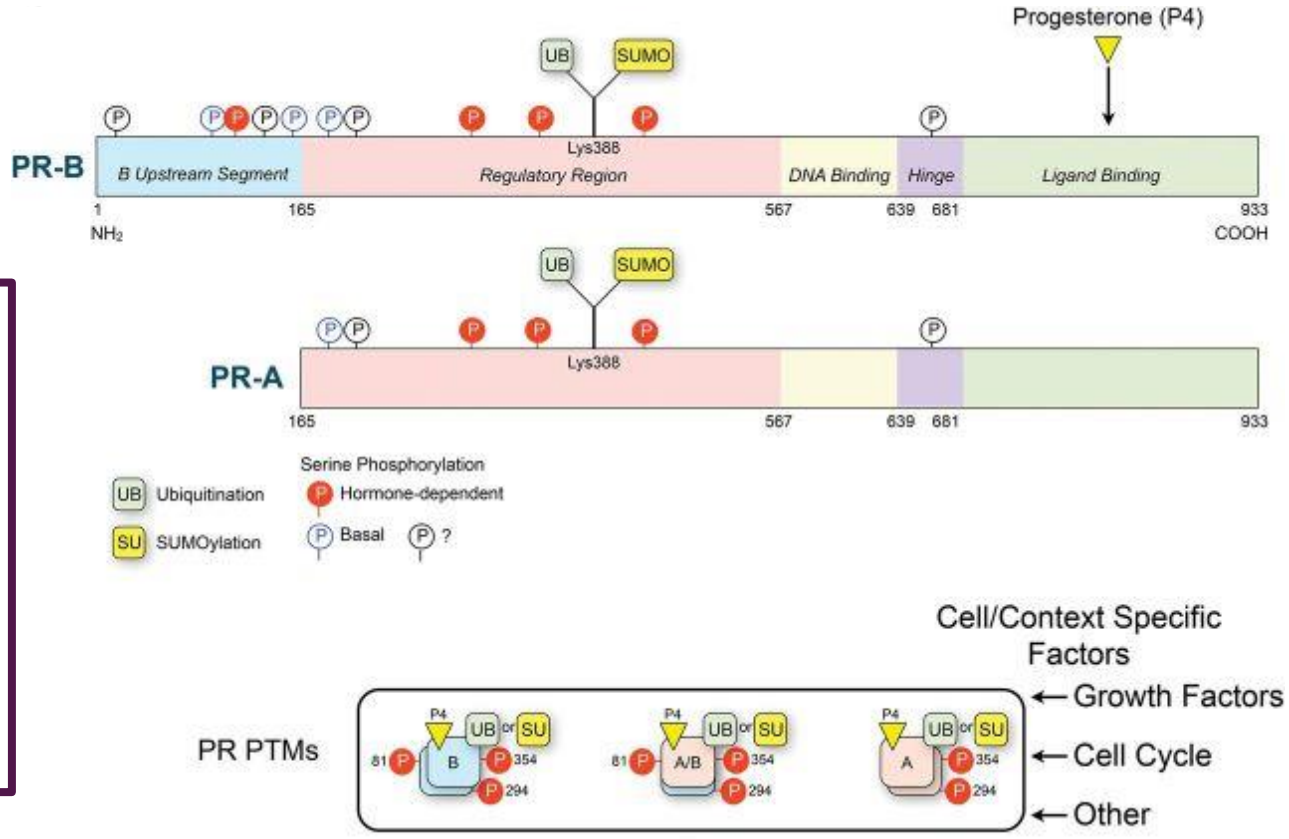


Dr. Noelle Gillis, PhD

University of Minnesota

PR Isoforms play distinct roles in breast cancer biology

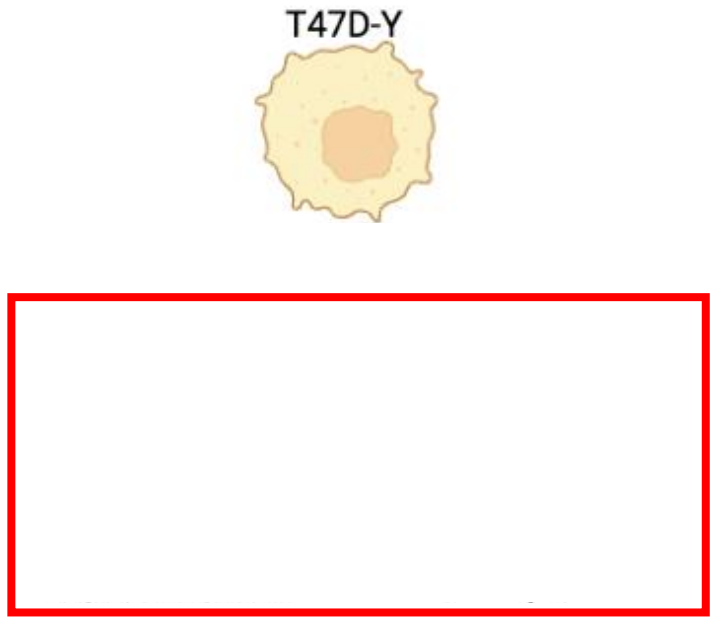
- PRs are expressed at equal levels in ***normal*** breast tissue (1:1 ratio).
- In ***breast cancer***, an imbalanced ratio (typically PR-A>PR-B) is observed early in tumor development.
- PR isoforms regulate **distinct transcriptomes** that enable distinct breast cancer phenotypes.

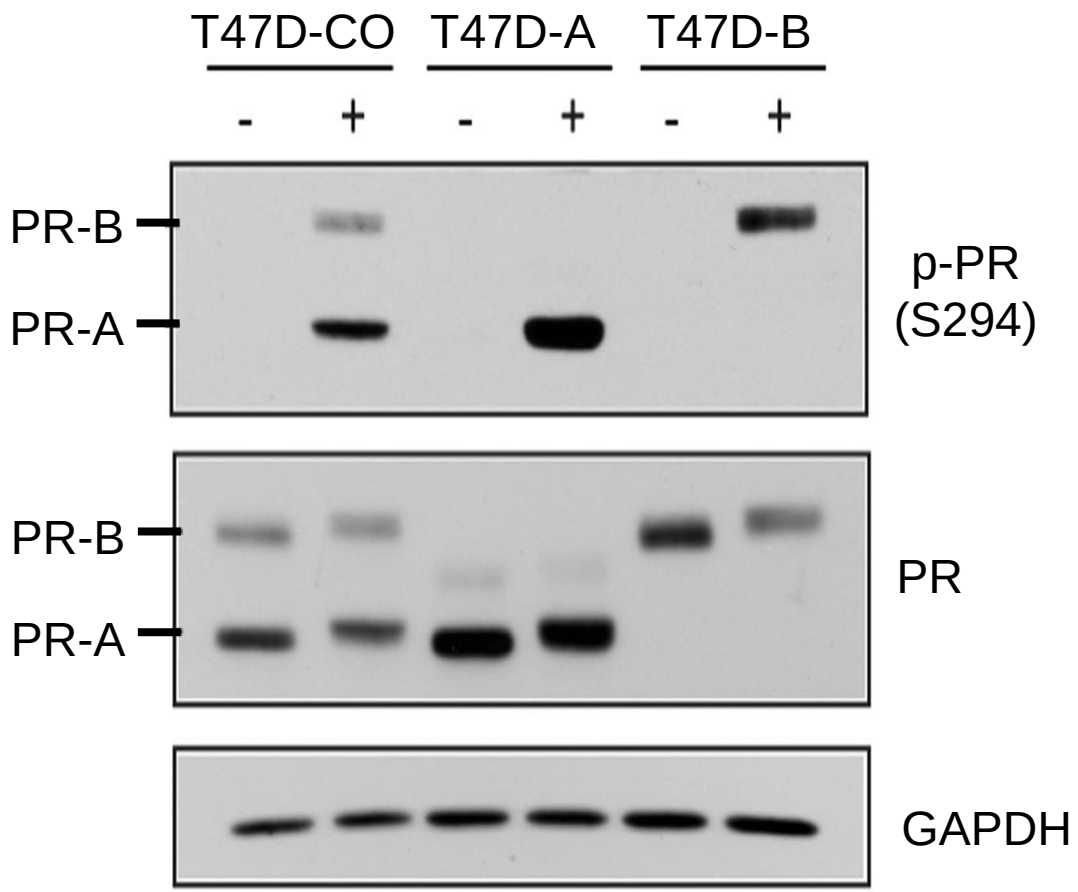


adapted from Patel, B., et al (2014) Hum Repro Update

Truong, T.H. & Dwyer, A.R., et al (2018) *Endocrinology;* Knutson, T.P., et al. (2017) *J Hematol Oncol;* Knutson, T.P., et al (2012) *Breast Cancer Res*

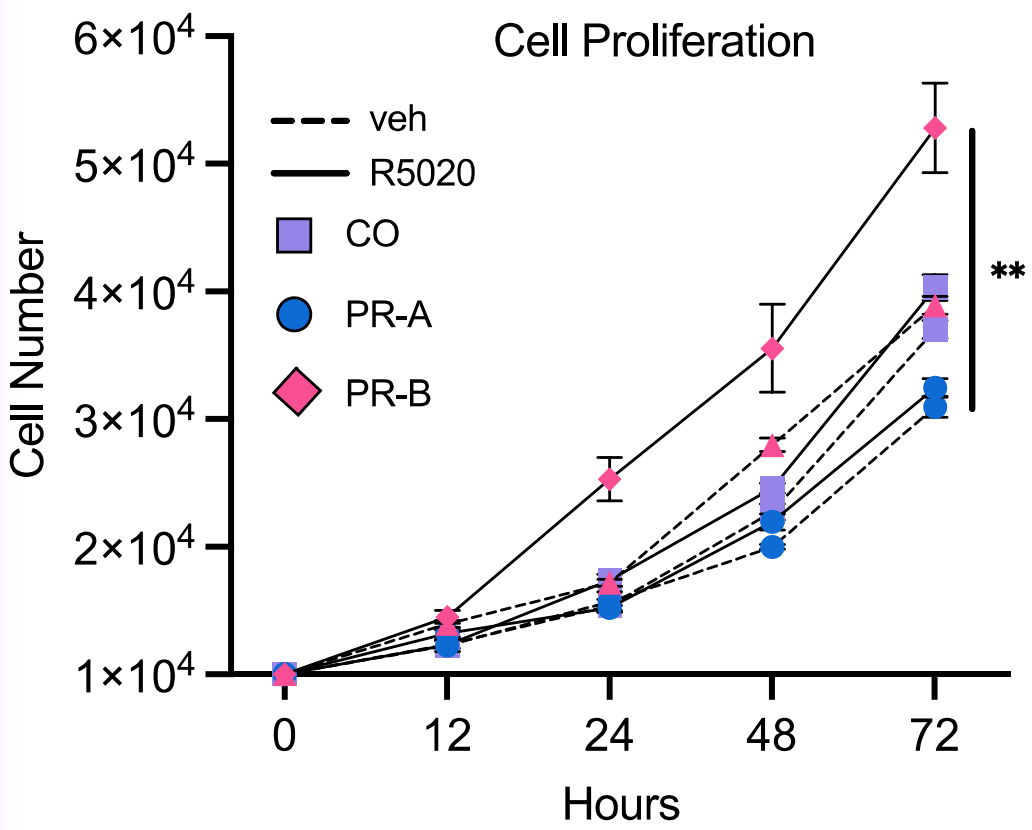
Cell Line Models of PR Isoform-Specific Expression



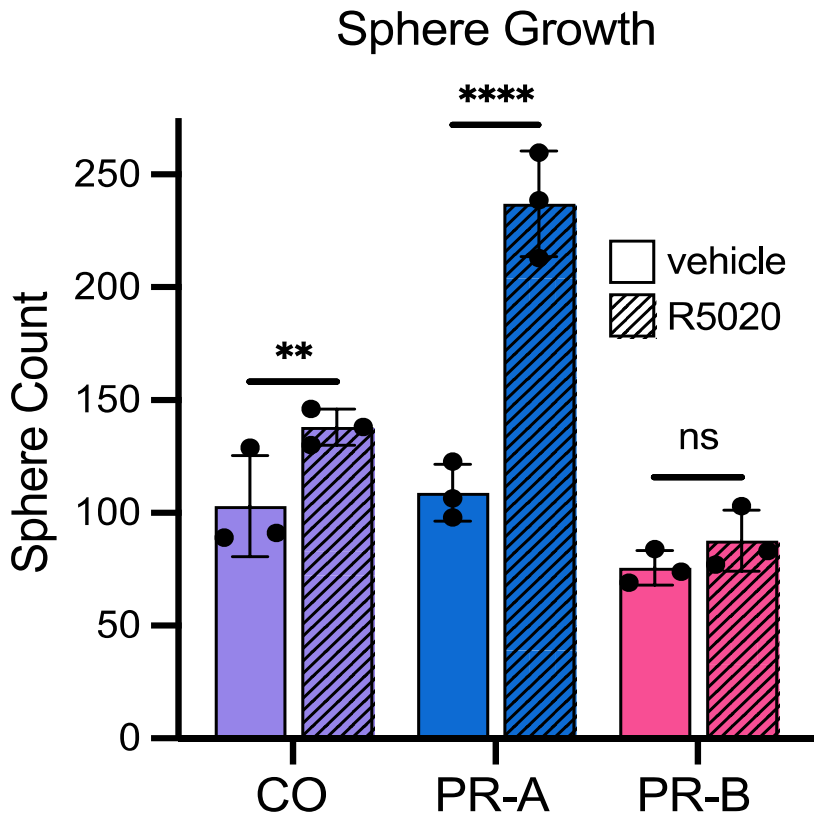


T47D-Y cells characterized by Sartorius, C.A., et al. (1994) *Cancer Res.*

PR-A and PR-B regulate opposing cell phenotypes



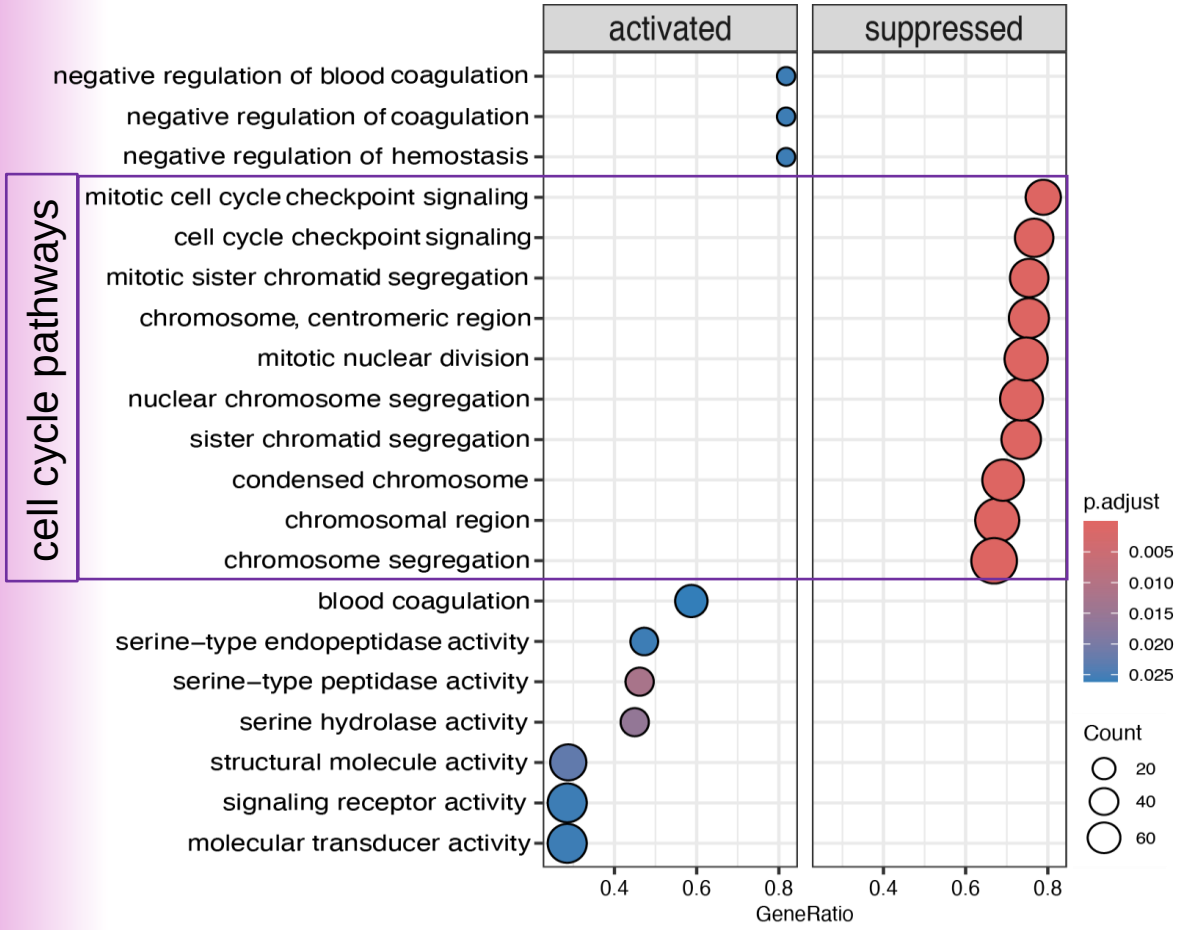
PR-B+ cells proliferate faster than PR-A+ cells.

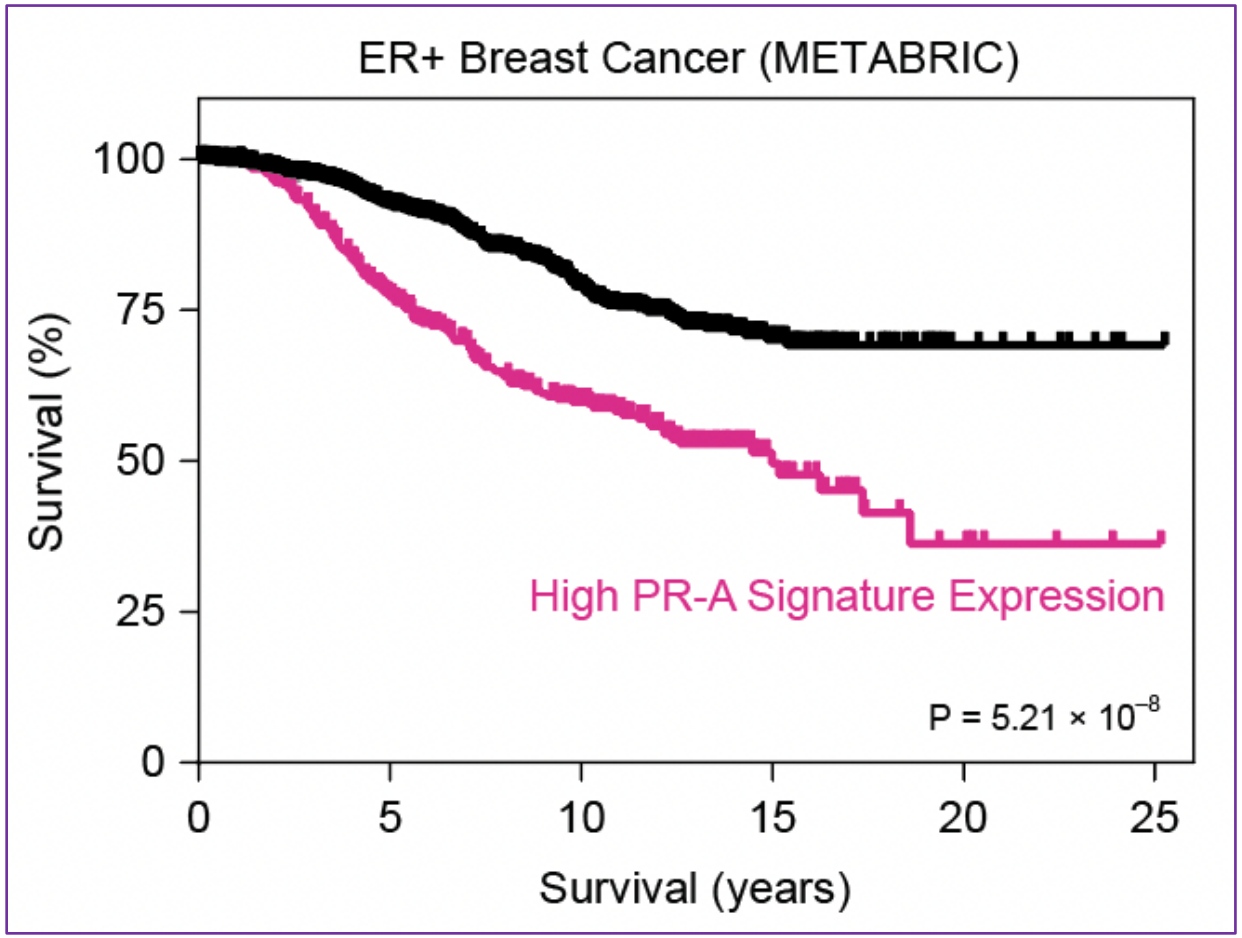


PR-A+ cells make more spheres than PR-B+ cells.

Gillis, N.E. et al, manuscript in preparation

The PR-A (3D) transcriptome is growth-inhibitory…

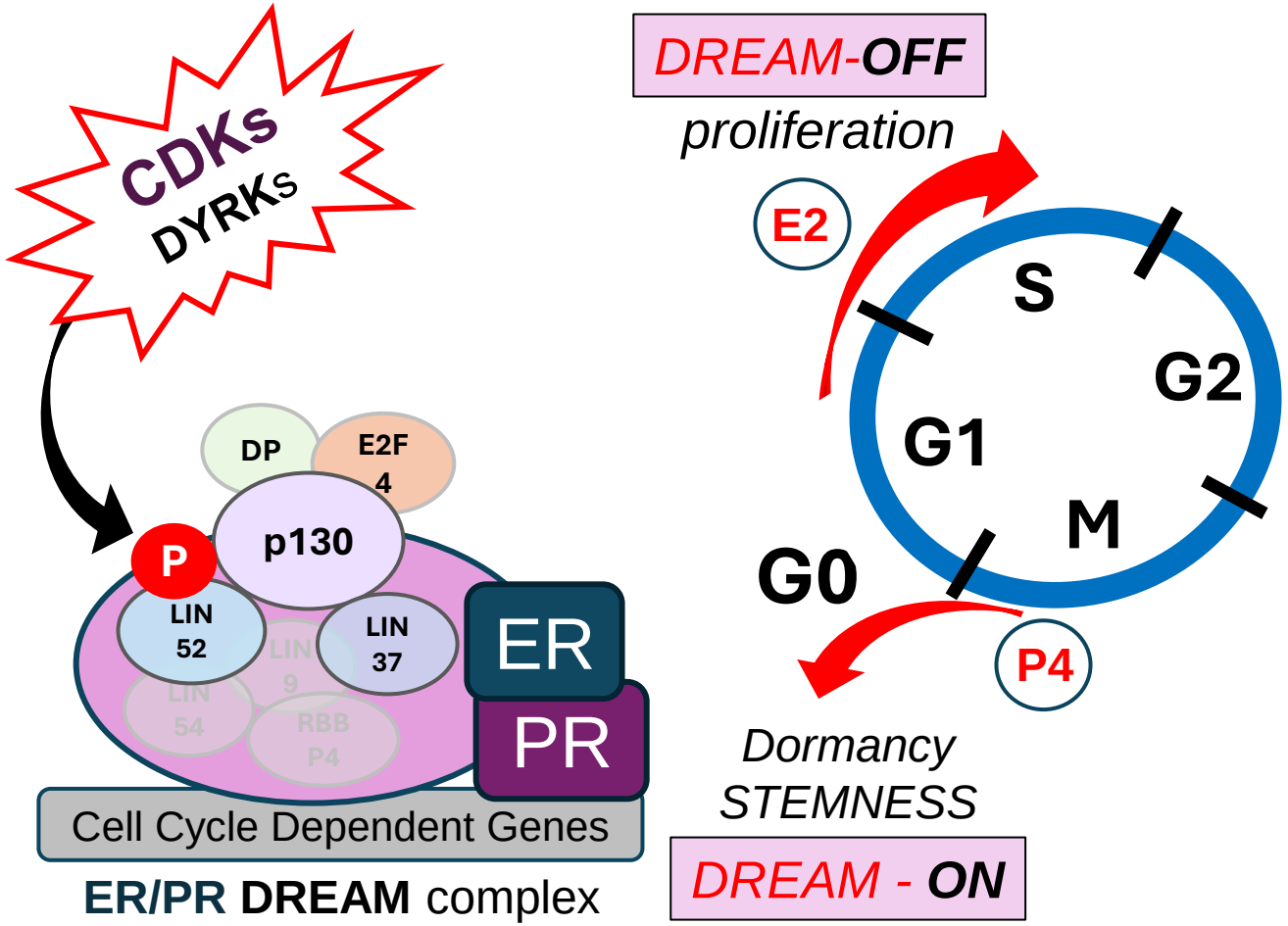




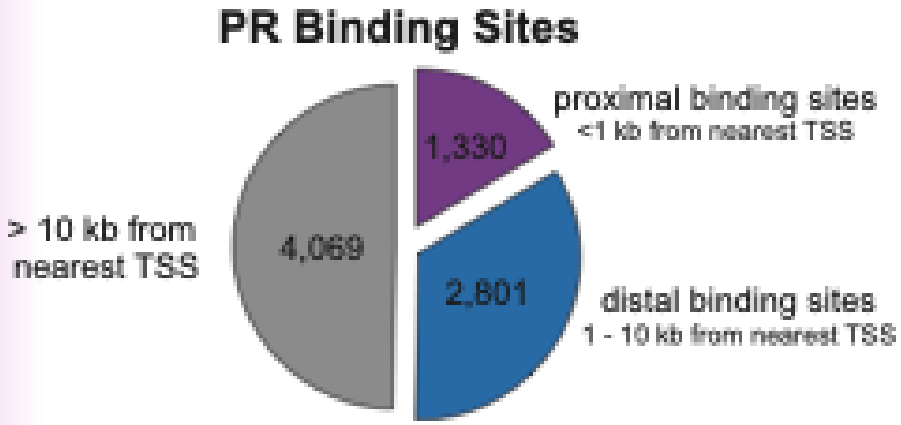
Noelle Gillis, PhD

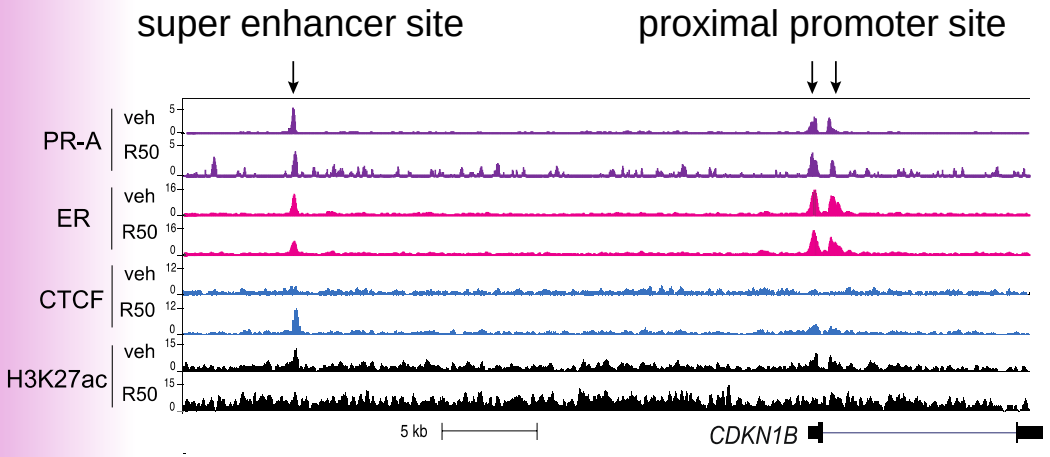
Hypothesis:

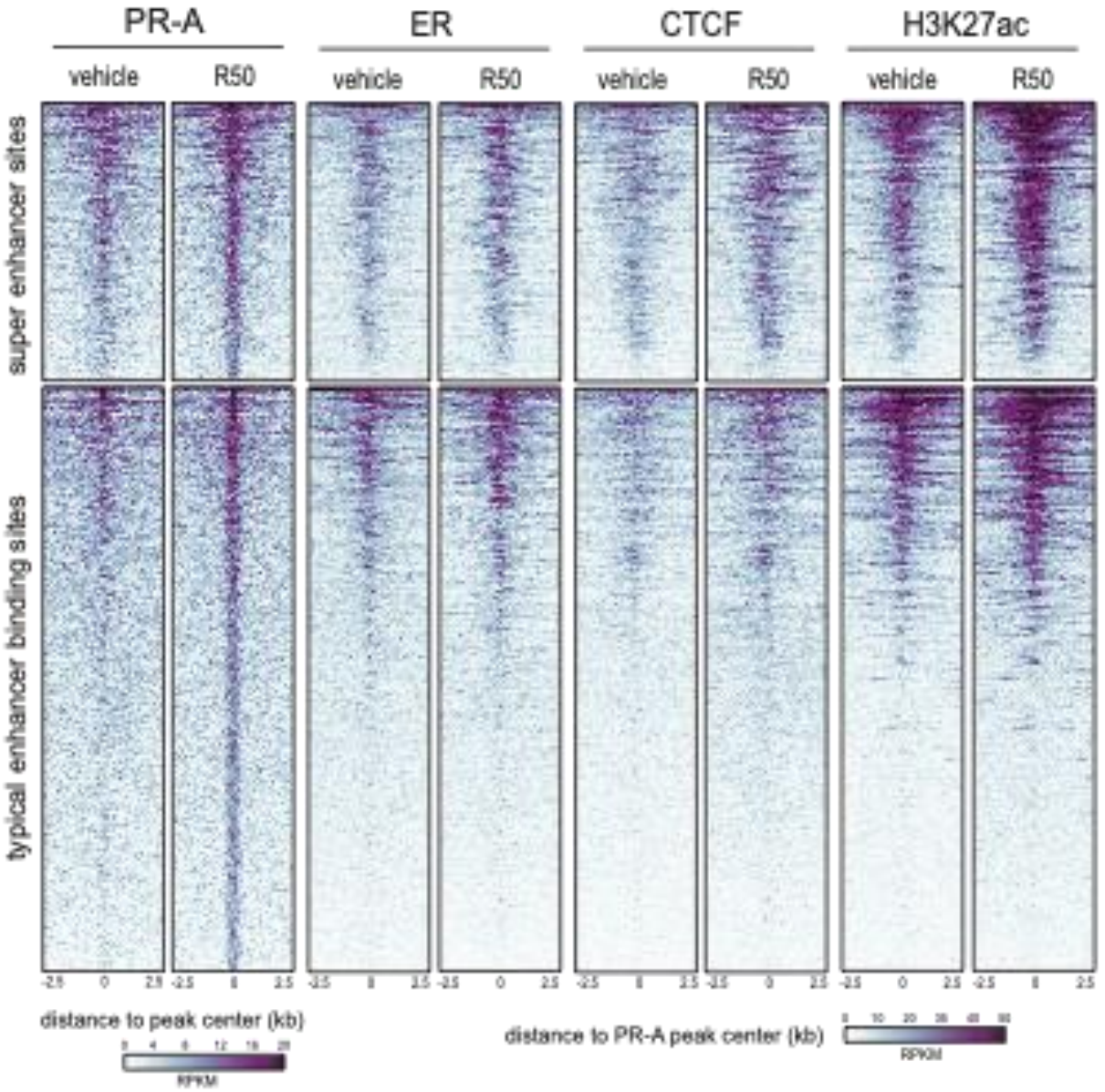
PR-A mediates durable quiescence/dormancy that explains late recurrence



PR-A Recruits ER and CTCF to Super Enhancers



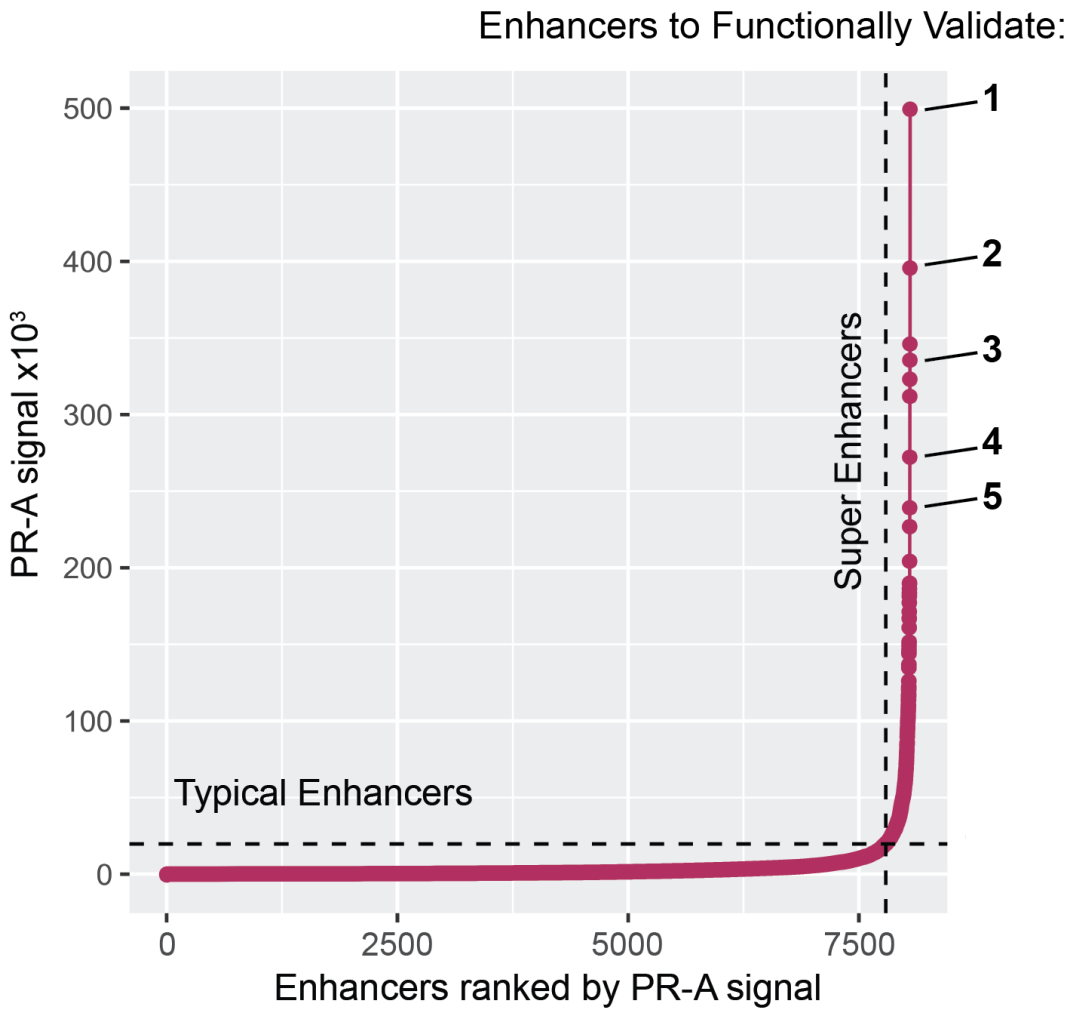




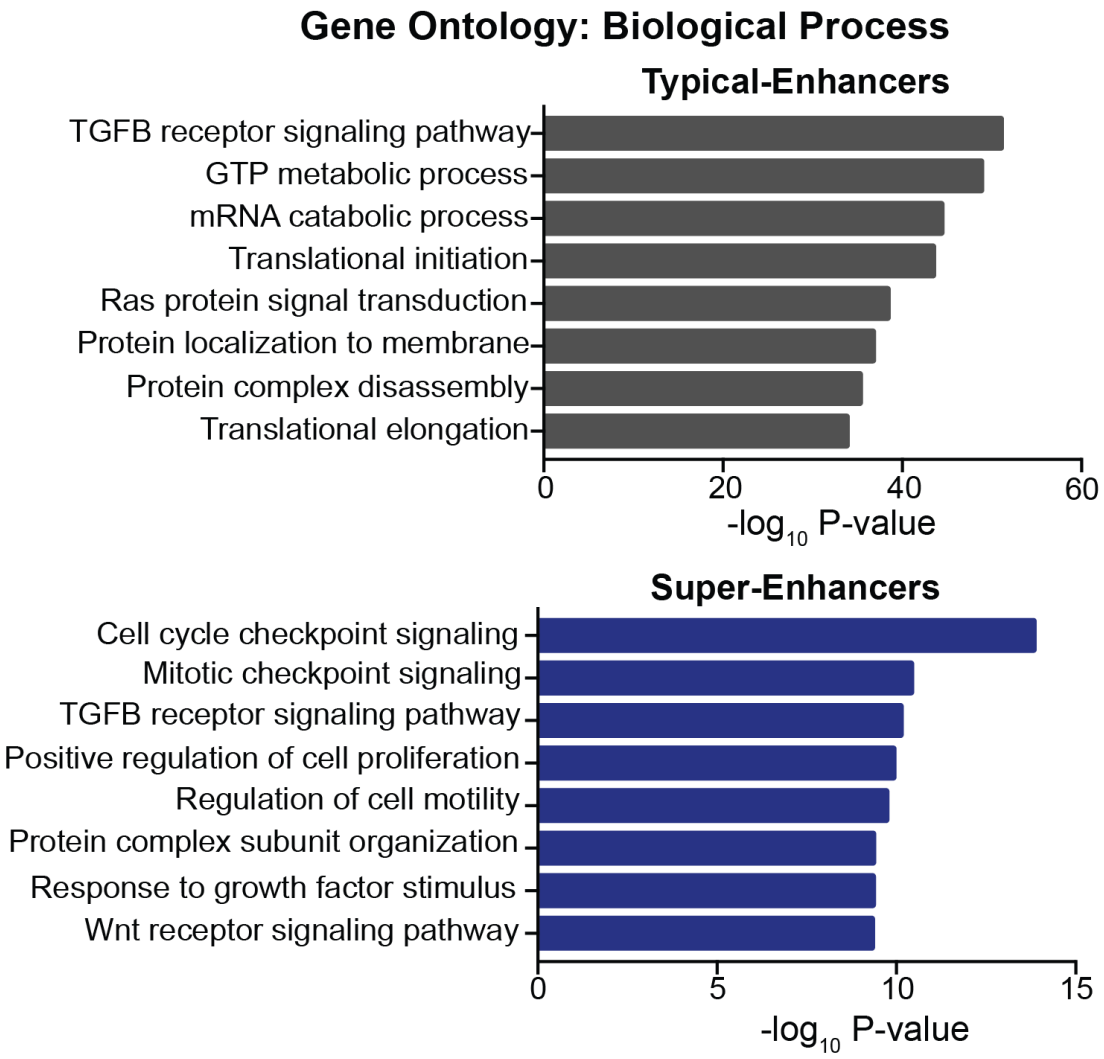
Noelle Gillis, PhD

PR-A binding sites are frequently within Super Enhancers

ROSE Analysis of PR-A Binding Sites



Pathways *likely* affected by PR-bound Enhancers

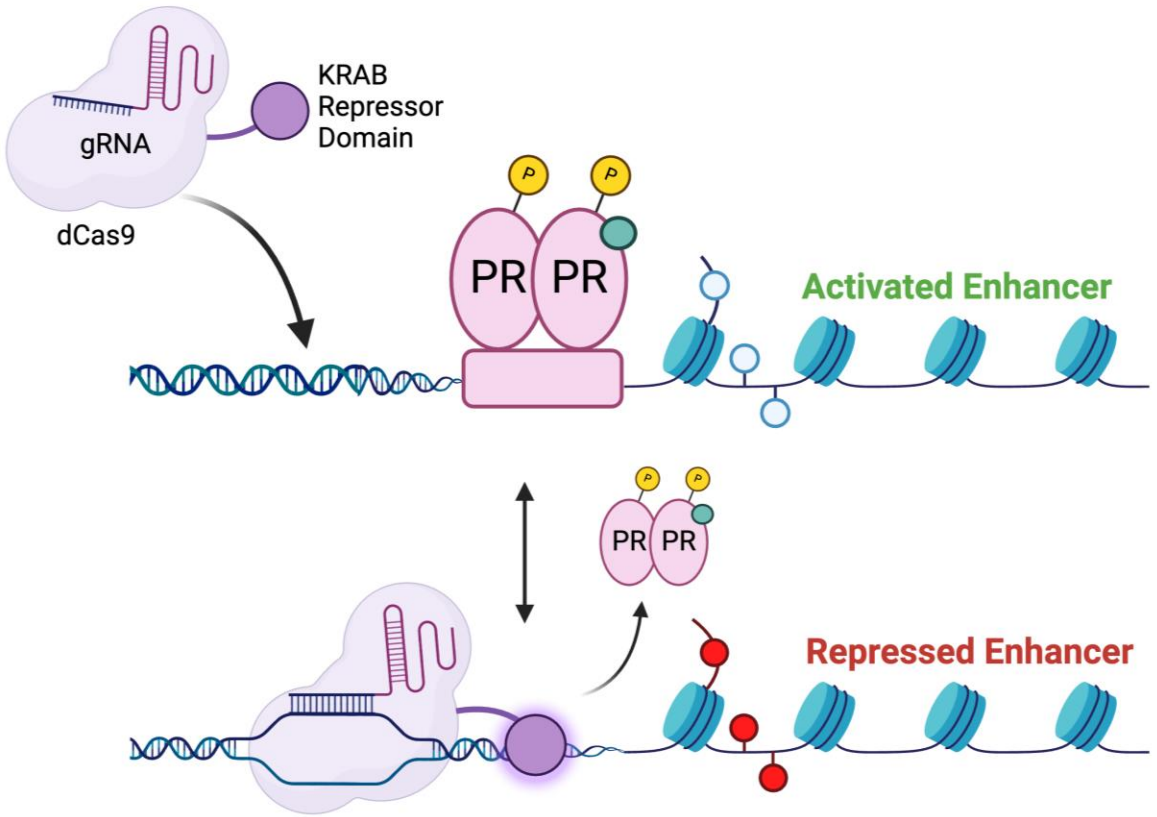


ROSE Analysis: Whyte, W.A., et al. (2013) *Cell* & Lovén, J., et al. (2013) *Cell*

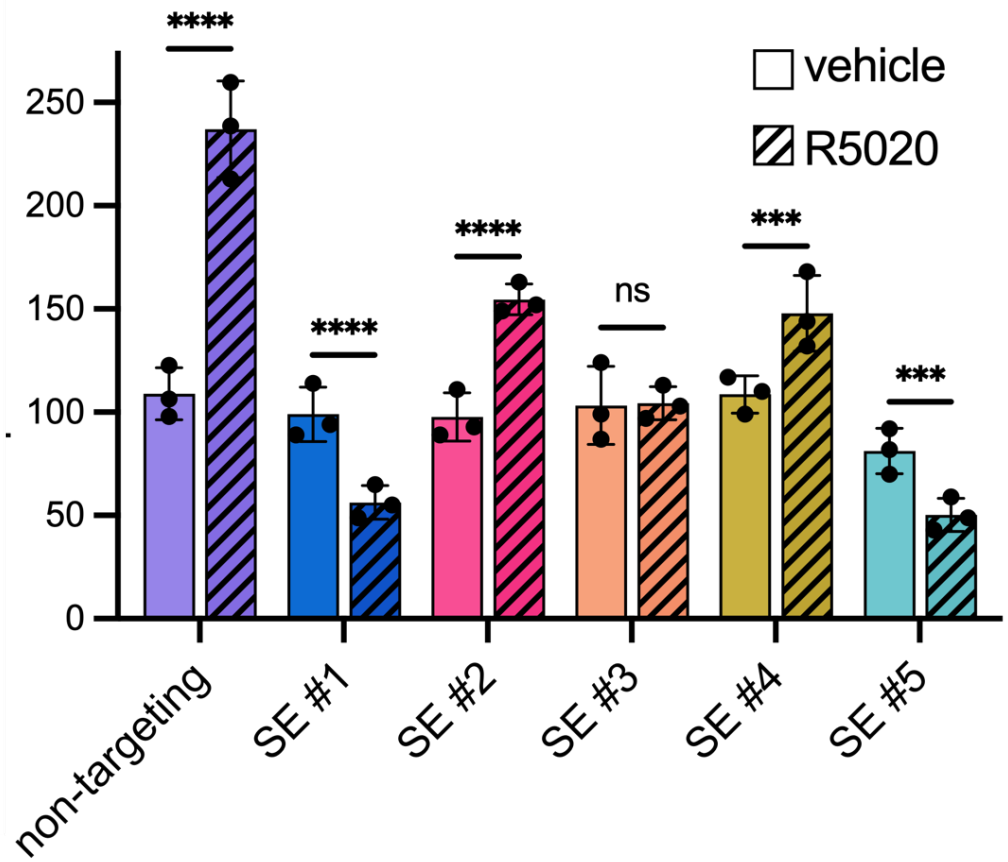
Noelle Gillis, unpublished, please do not post

Blocking PR-A binding to Super Enhancers inhibits sphere formation

CRISPRi Enhancer Targeting System



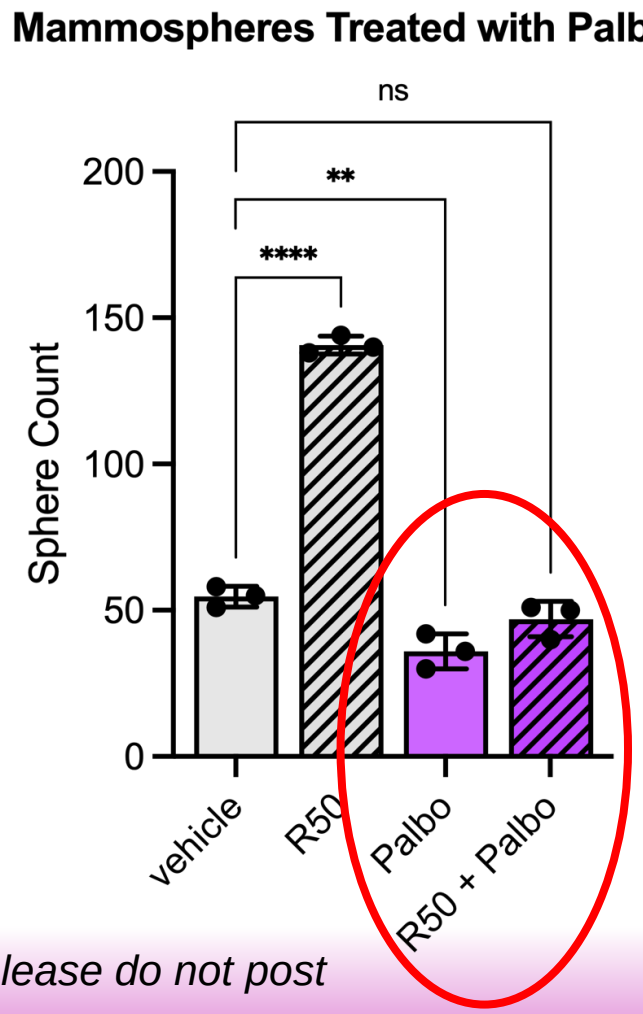
T47D PR-A Sphere Growth

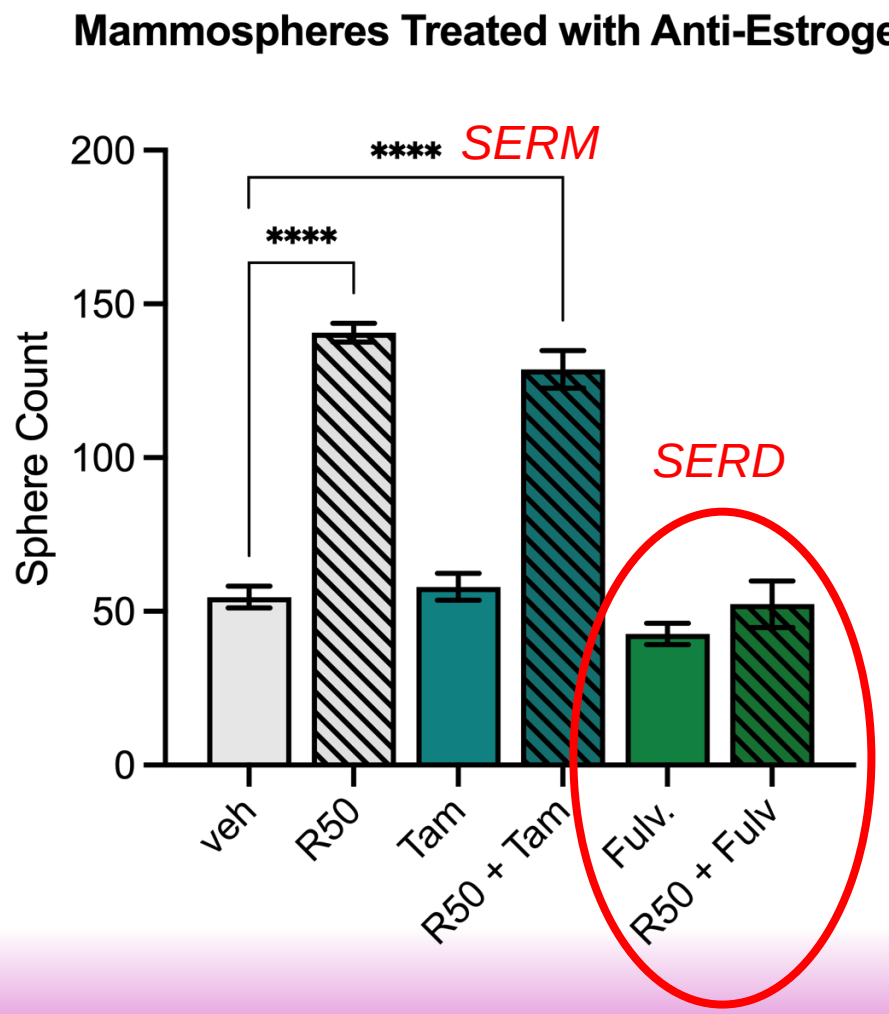


unpublished, please do not post

Stemness phenotype requires CDK4/6 and *ER scaffolding*

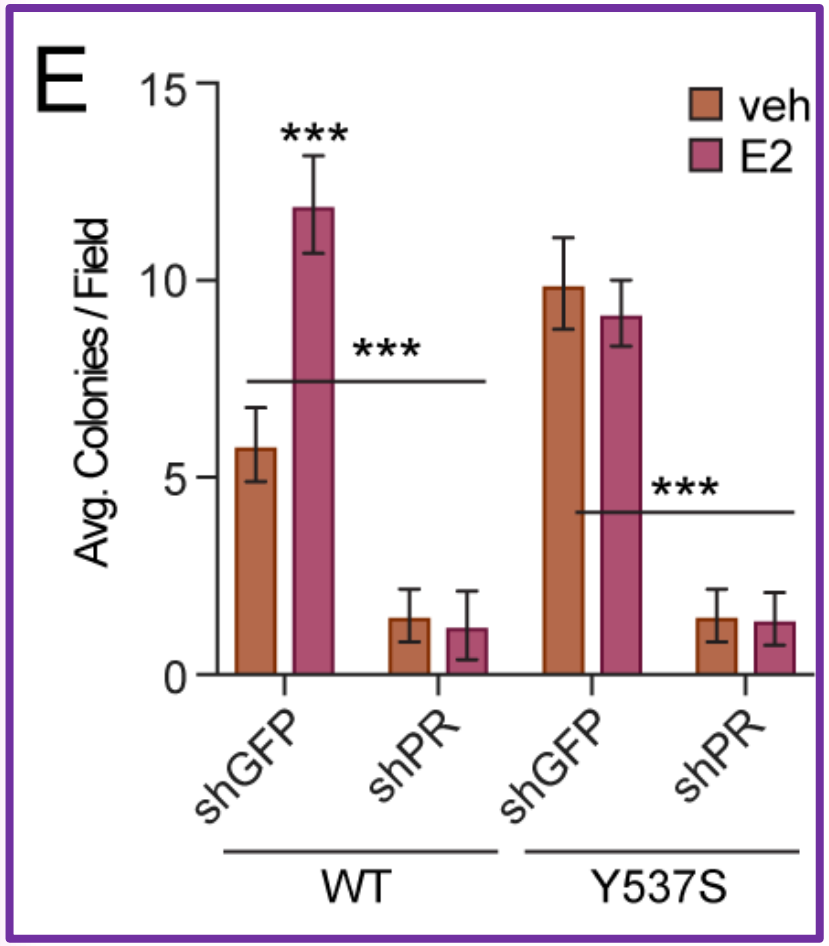
Mammosphere Data (unpublished)



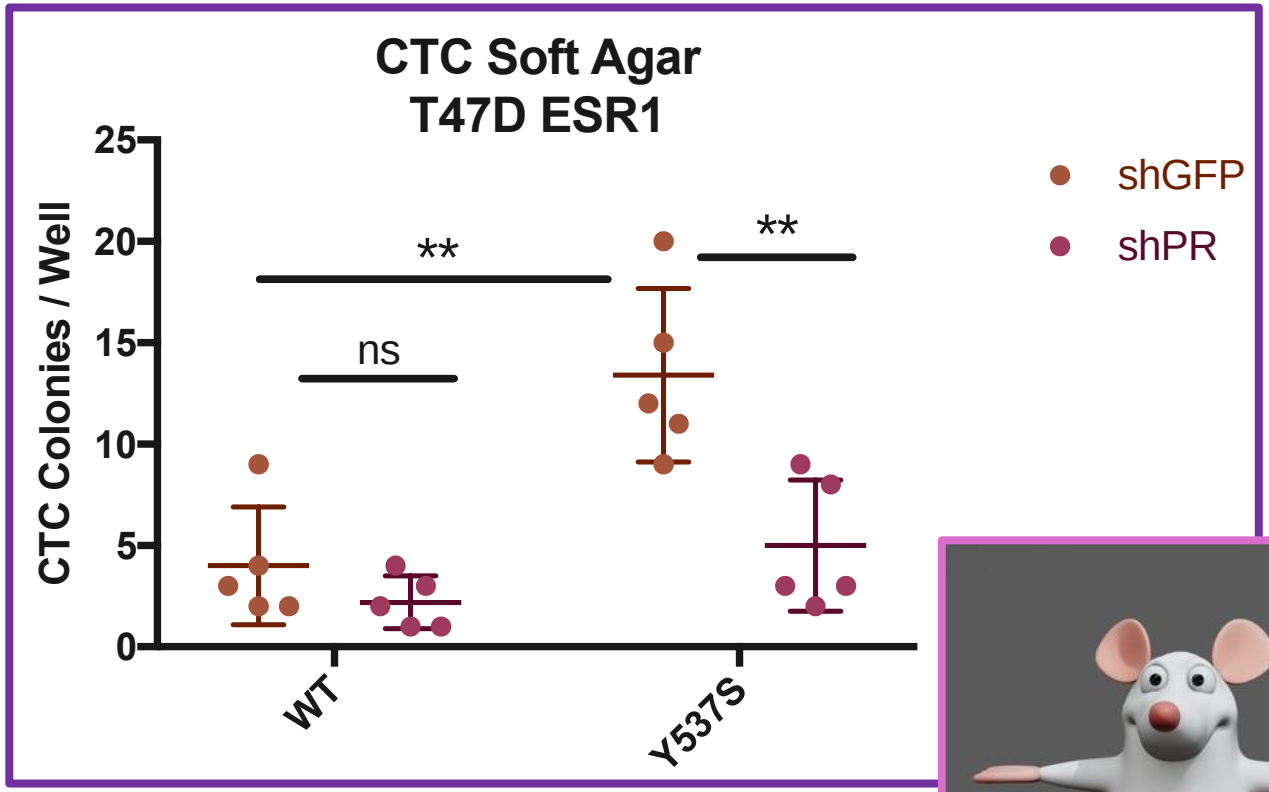


unpublished, please do not post

ESR1 mutant models require PR for circulating tumor cell viability



*In vitro (*Anchorage-Independent Growth)



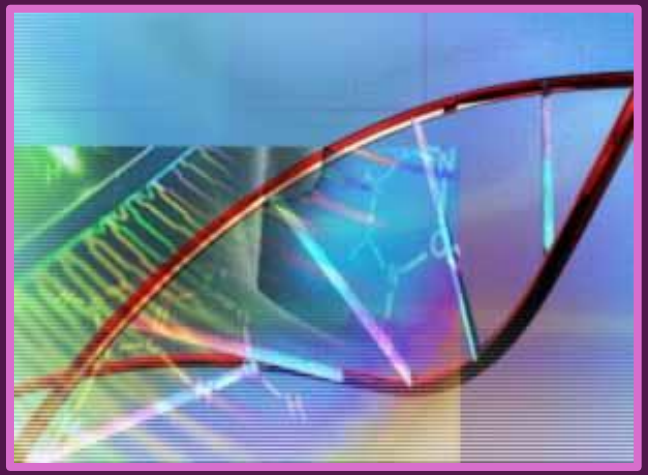
In vivo (MIND model)

Steroid hormone receptors impact all aspects of cancer biology

- SRs may exhibit opposing proliferative and stemness capacity *in vivo*
- Inhibition of proliferation without cell killing enables alternate cancer cell fates
  - EMT
  - Quiescence / Dormancy
  - Stemness
  - Metabolic Plasticity / Pro-survival
  - Dissemination / Metastasis

Understanding mechanisms of cell fate decision (DREAM states) will pave the way for new targeted therapies that kill non-proliferating or dormant circulating tumor cells (CTCs) and cancer stem cells (CSCs)

Prevention strategies may include periodic deletion or “culling” of MaSCs or pre-cancerous populations in high-risk groups



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Ostander Lab (UMN):
Julie Ostrander, PhD

Sartorius Lab (CU Anschutz):
Carol Sartorius, PhD
Jess Finlay-Schutlz, PhD

University of Minnesota Genomics Core

Minnesota Supercomputing Institute

Masonic Cancer Center
University of Minnesota
Comprehensive Cancer Center designated by the National Cancer Institute

NIH NATIONAL CANCER INSTITUTE

Alien is a movie where nobody listens to the smart woman, and then they all die except for the smart woman and her cat. Four stars.

ARX788

THP

VOTE! US

This message was approved by the Childless Cat Lady Society of America

Beware of low dose hormone exposures…

Cancer risk in women using the levonorgestrel-releasing intrauterine system in Finland. T Soini et. al Obset Gynecol 2014

↑ E2
↓ LNG

(premenopausal women being treated for menorrhagia)

Standardized incidence ratio (observed-to-expected ratio)

- 855,324 women-years with 2,781 cancer cases (ages 30-49)

- Endometrial adenocarcinoma 0.50 (following one purchase)
- Endometrial adenocarcinoma 0.25 (following two purchases)
- Ovarian cancer 0.60
- Pancreatic cancer 0.50
- Lung cancer 0.68

- Breast cancer 1.19 following one purchase
- Breast cancer 1.40 following two purchases

} *PR or AR?*

Beware of low dose hormone exposures…(postmenopausal women)

Trabert B, Bauer DC, Buist DSM, Cauley JA, Falk RT, Geczik AM, Gierach GL, Hada M, Hue TF, Lacey JV Jr, LaCroix AZ, Tice JA, Xu X, Dallal CM, Brinton LA. **Association of Circulating Progesterone With Breast Cancer Risk Among Postmenopausal Women.** JAMA Netw Open. 2020 Apr 1;3(4):e203645. doi: 10.1001/jamanetworkopen.2020.3645. PMID: 32329771; PMCID: PMC7182797.

↑ E2 – high circulating progesterone was associated with increased risk

↓ E2 – high circulating progesterone was associated with decreased risk