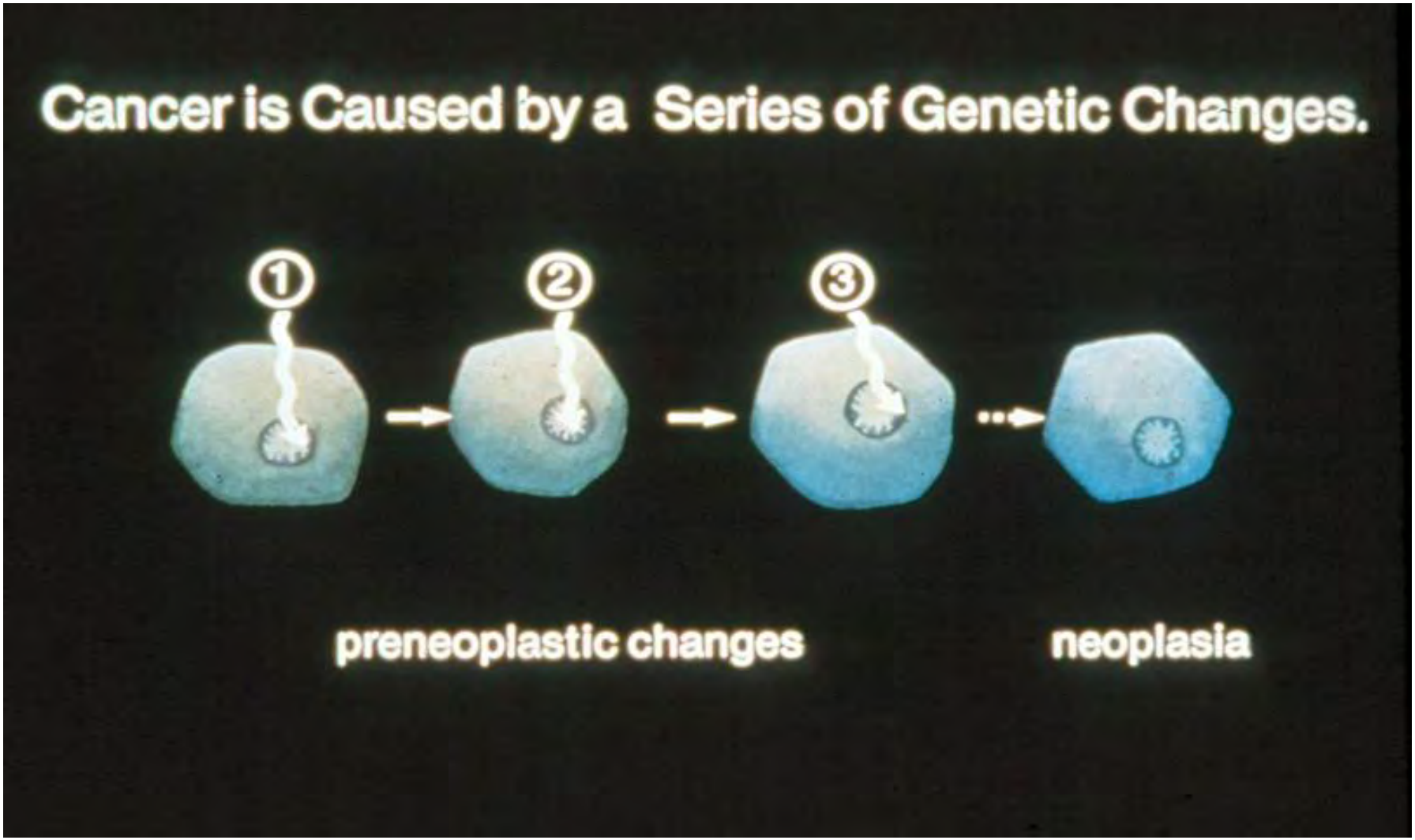
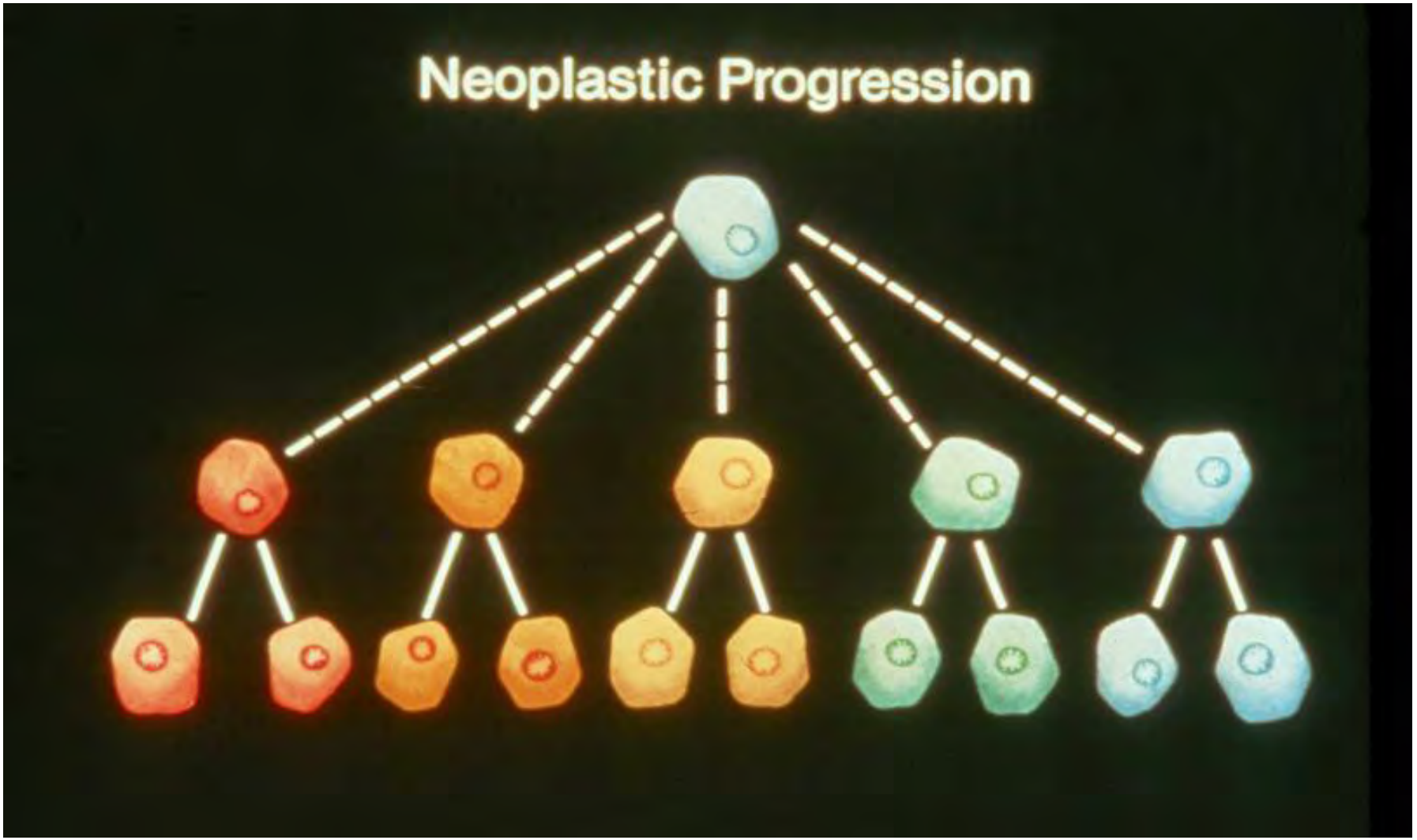
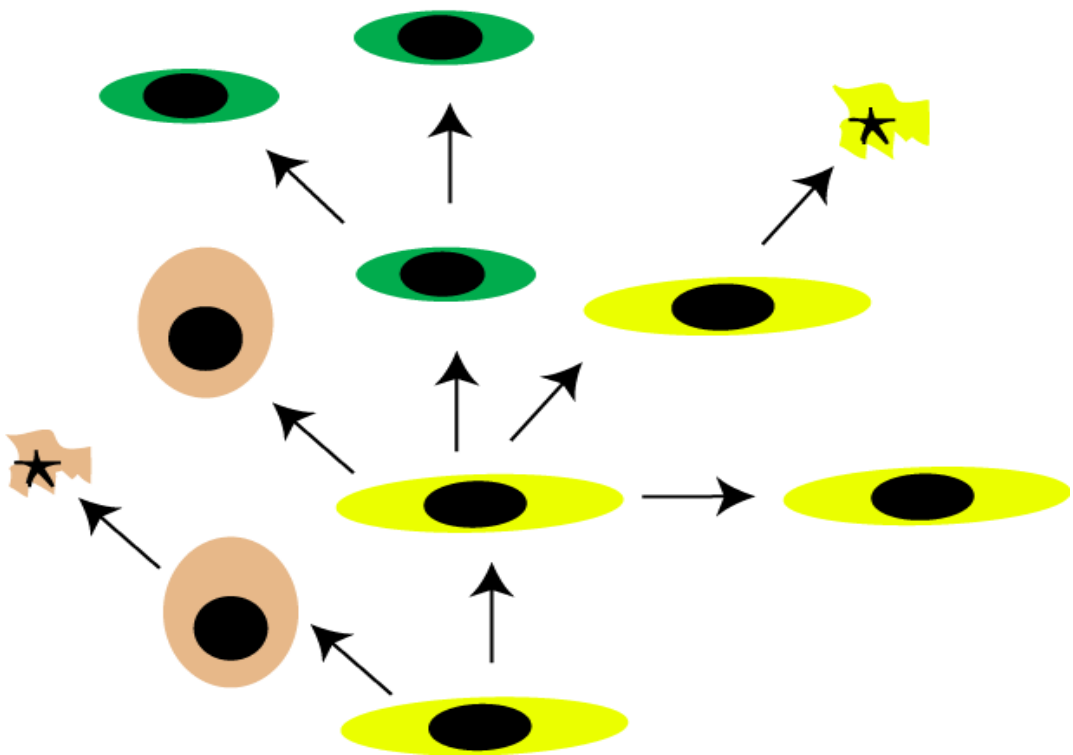

Cancer is Caused by a Series of Genetic Changes.
1
2
3
preneoplastic changes
neoplasia

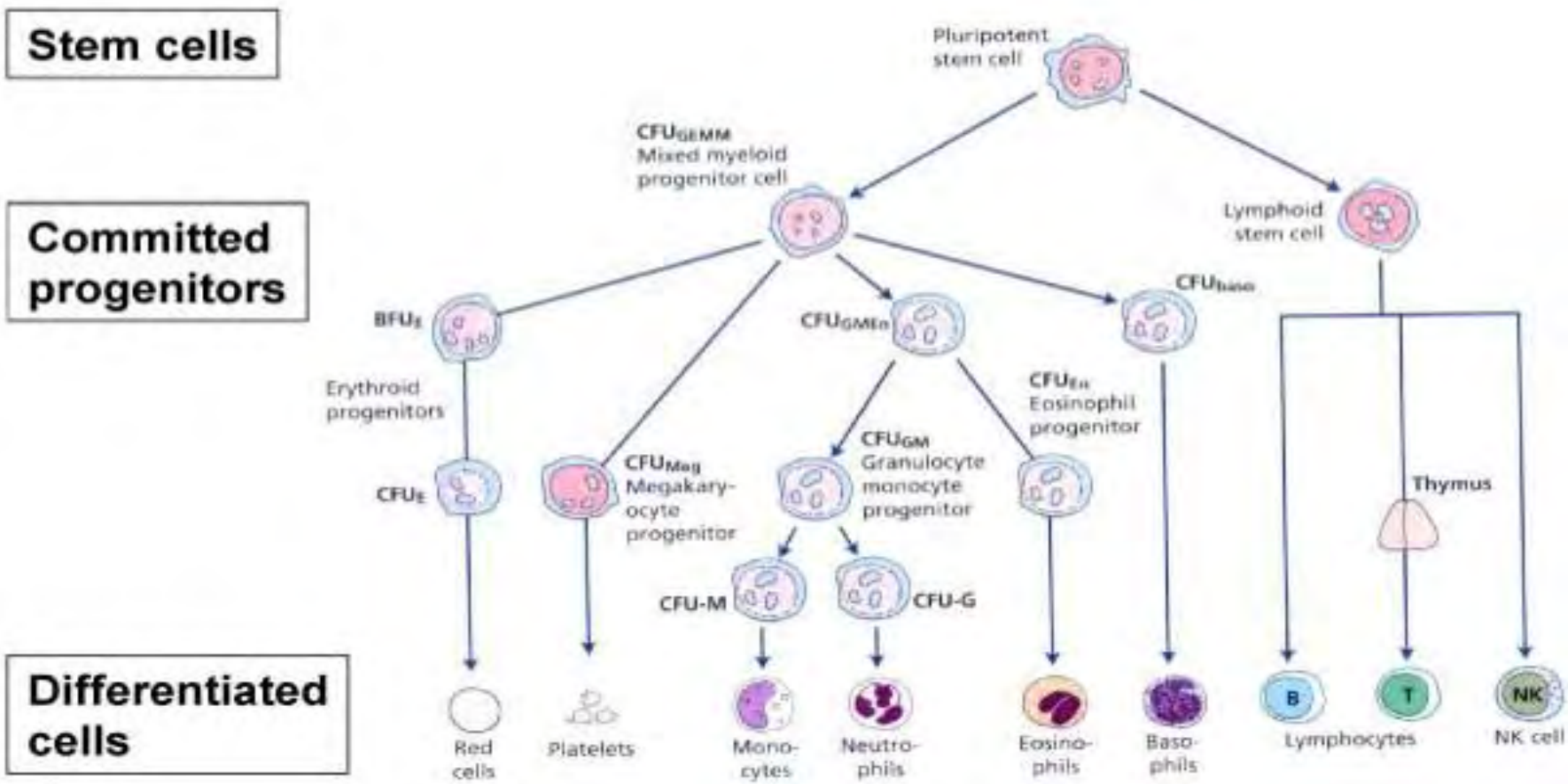

Neoplastic Progression

Tumor heterogeneity = Incomprehensible chaos

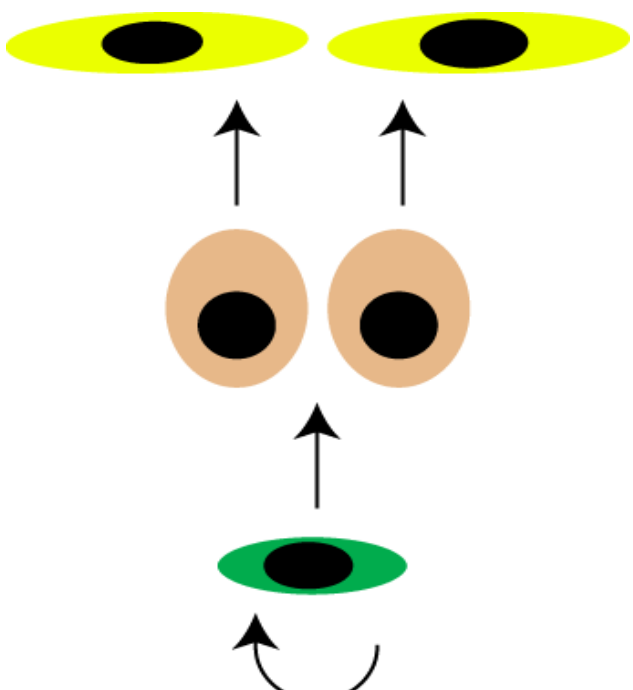


ADAPTED FROM REYA ET AL. NATURE (2001) 414:105

Lineage commitment in Hematopoeisis



Perhaps cancer growth is hierarchical and orderly



If organogenesis ~ carcinogenesis, cancers have stem cells

REYA ET AL. NATURE (2001) 414:105

Organogenesis vs. Cancer

- Organogenesis
  - Proliferation
  - Invasion
  - Motility
  - Angiogenesis
  - Differentiation
  - Terminates upon completion

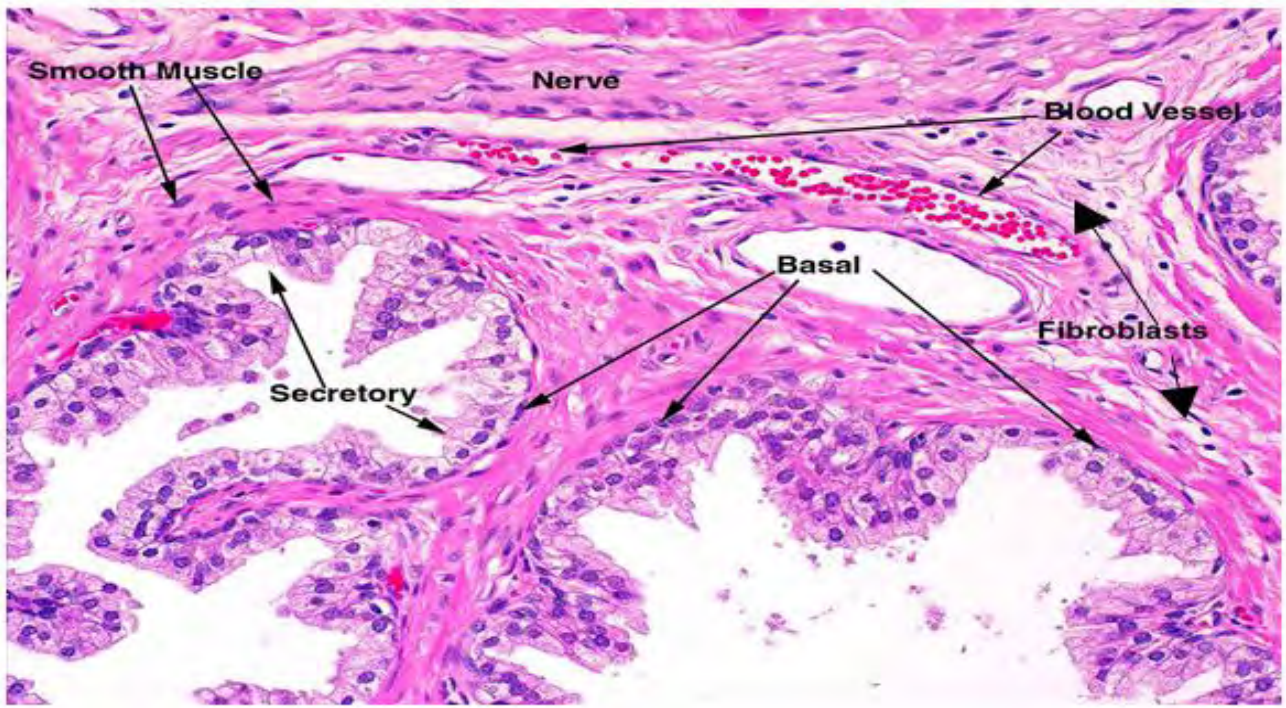
- Carcinogenesis
  - Proliferation
  - Invasion
  - Motility
  - Angiogenesis
  - Differentiation
  - Escapes termination signals

Origin of Cancer Stem Cell

Malignantly Transformed Normal Stem Cell

OR

Malignantly Transformed Normal Cell which Acquires “Stem-Cell” like Activities


Smooth Muscle
Nerve
Blood Vessel
Basal
Fibroblasts
Secretory

Normal Prostate Stem Cells Are Not Dependent Upon Androgen For Their Survival

J Isaacs and D Coffey

THE PROSTATE Supplement 2:33-50, 1988

Rodent Studies

Lynette Wilson' Group at NYU

Owen Witte's Group at UCLA

Human Studies

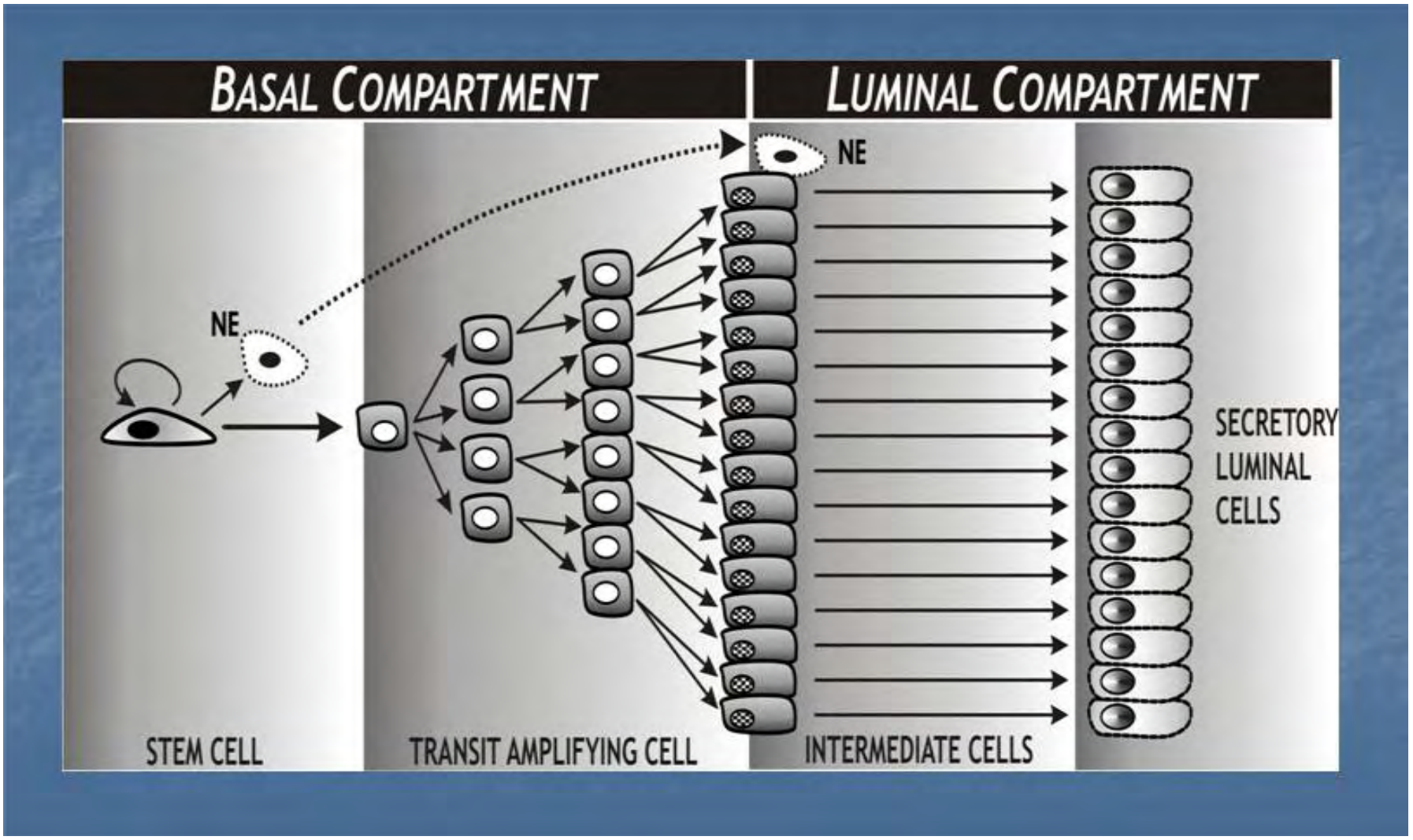
Anne Collins/Norman Maitland's Group at York, UK

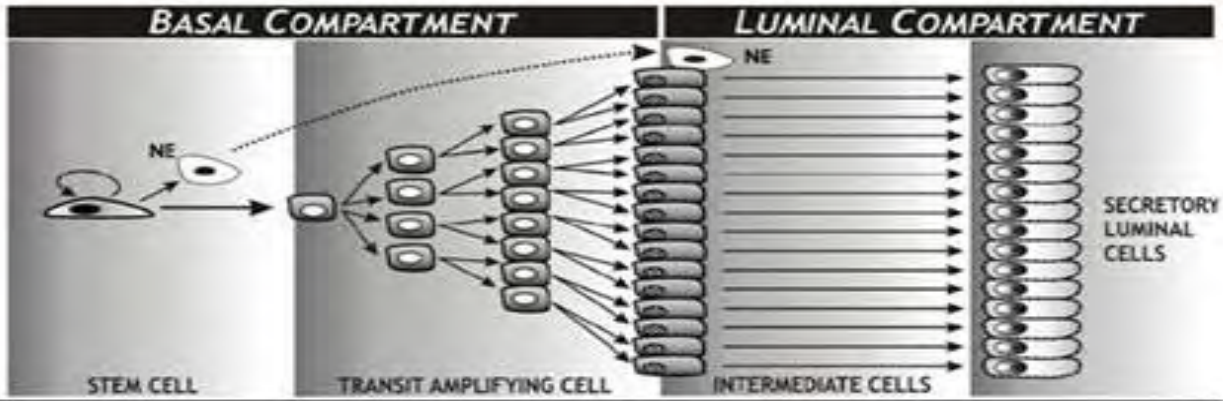
John Isaacs' Group at JHU

Max Loda's Group at Harvard

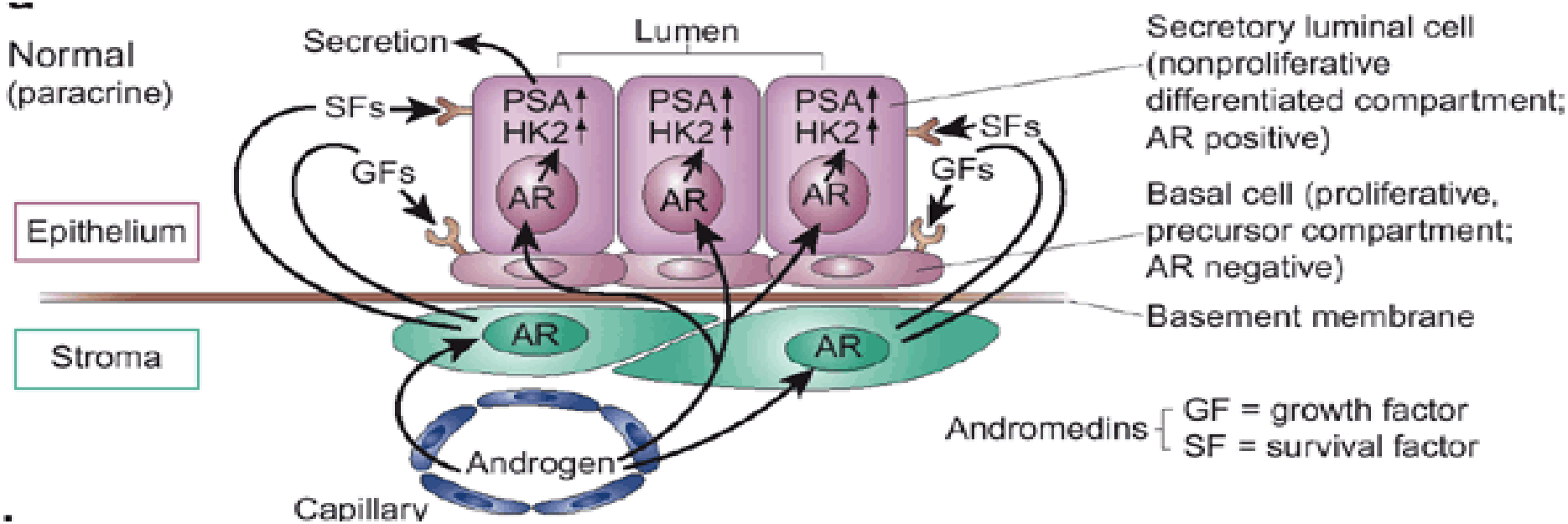
Jack Schalken's Group at Nijmegen in Netherlands

Gary Smith' Group at RPCI


BASAL COMPARTMENT
LUMINAL COMPARTMENT
NE
NE
SECRETORY LUMINAL CELLS
STEM CELL
TRANSIT AMPLIFYING CELL
INTERMEDIATE CELLS



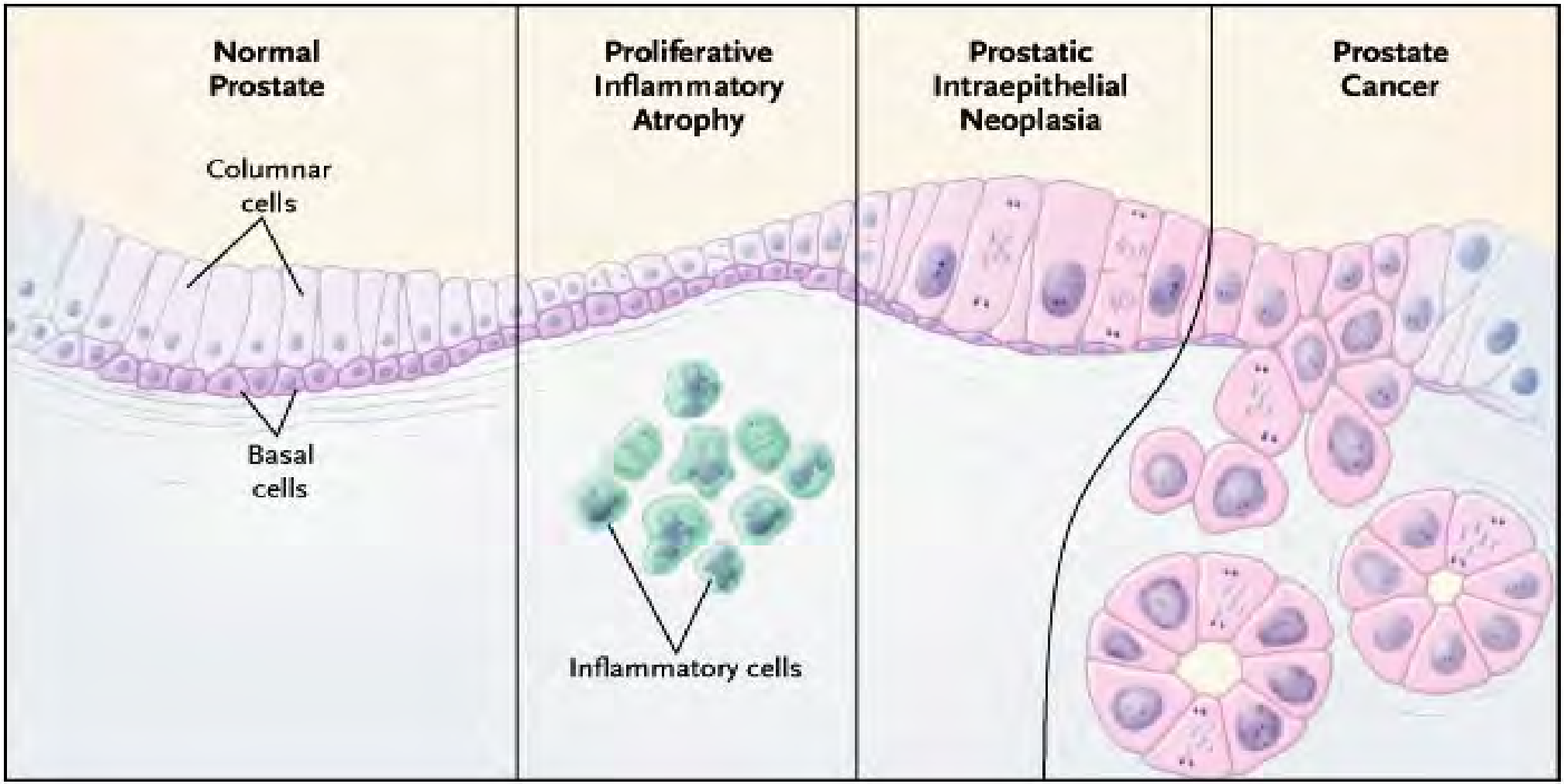
Response to Andromedins:					
-Survival		-	-	+	+++
-Proliferation		-	+++	+	-
Renewal Capacity		High	Limited	Very Limited	None
Proliferative Index		Low	1.1%	<0.3%	<0.1%
CD133	protein	++	-	-	-
ABC-G2	protein	++	-	-	-
$\alpha_2\beta_1$ Integrin	protein	+++	+++	++	-
Keratin 5	protein	+++	+++	+	-
ΔN p63	protein	-	+++	+	-
PSCA	protein	-	-	+++	-
Keratin 18	protein	-	-	+	+++
AR	mRNA	-	-	+	+++
	protein	-	-	-	+++
PSA	mRNA	-	-	+	+++
	protein	-	-	-	+++


Normal
(paracrine)
Secretion
Lumen
SFs
PSA↑
HK2↑
AR
GFs
Epithelium
Stroma
Androgen
Capillary
Secretory luminal cell
(nonproliferative
differentiated compartment;
AR positive)
Basal cell (proliferative,
precursor compartment;
AR negative)
Basement membrane
Andromedins
GF = growth factor
SF = survival factor

Ivan Litvinov

Donald Vander Griend

The Androgen Receptor is a Growth Suppressor Gene for Normal Prostatic Epithelial Cells

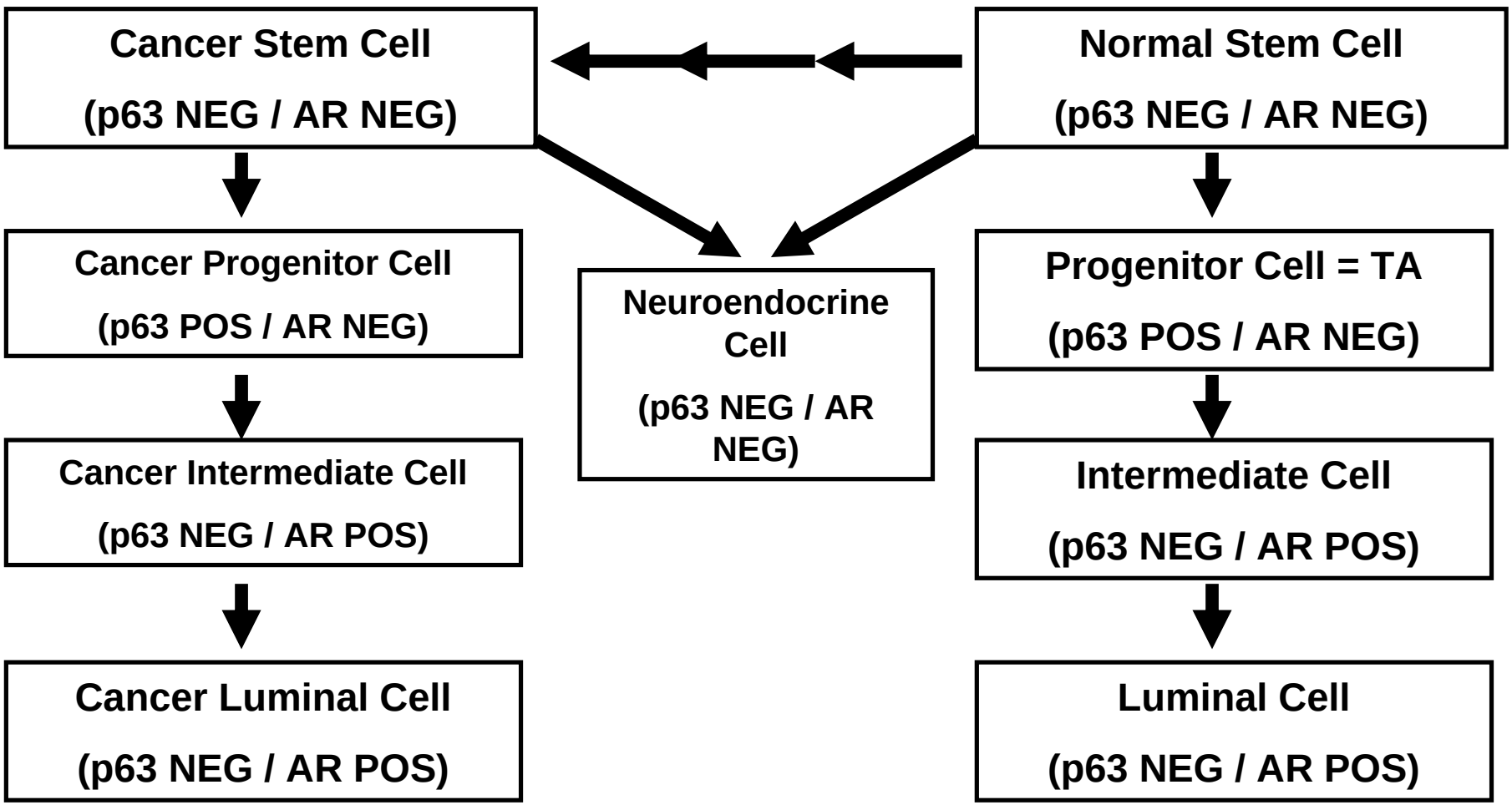


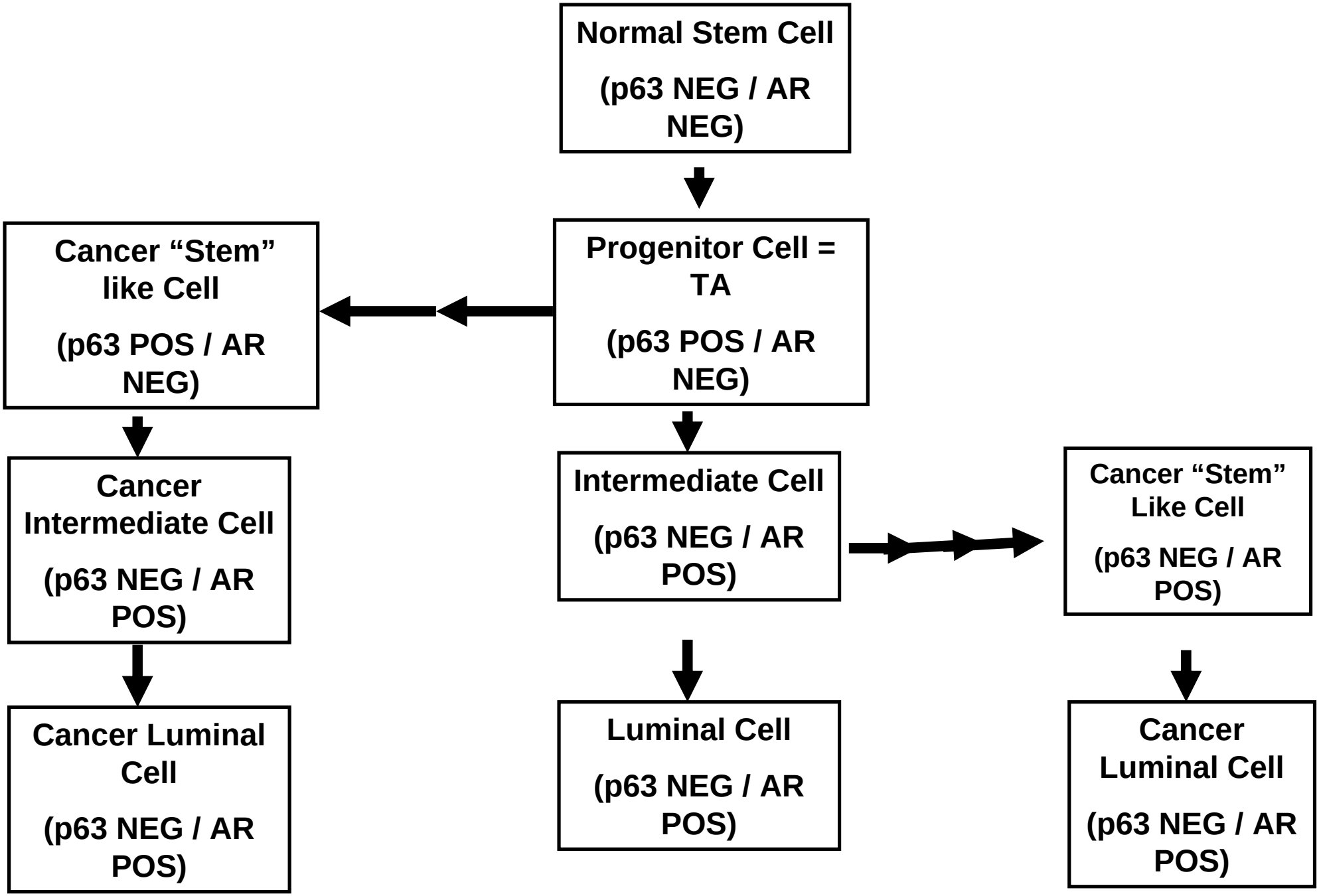
Nelson, W.G. *et al.* New Engl. J. Med. *349:* 366-381, 2003

The Androgen Receptor is a Growth Suppressor Gene for Normal Prostatic Epithelial Cells but an Oncogene for Prostate Cancer Cells.

Litvinov IV, Vander Griend DJ, Antony L, Dalrymple S, De Marzo AM, Drake CG, Isaacs JT.

Androgen receptor as a licensing factor for DNA replication in androgen-sensitive prostate cancer cells.
Proc Natl Acad Sci 103:15085-90, 2006.

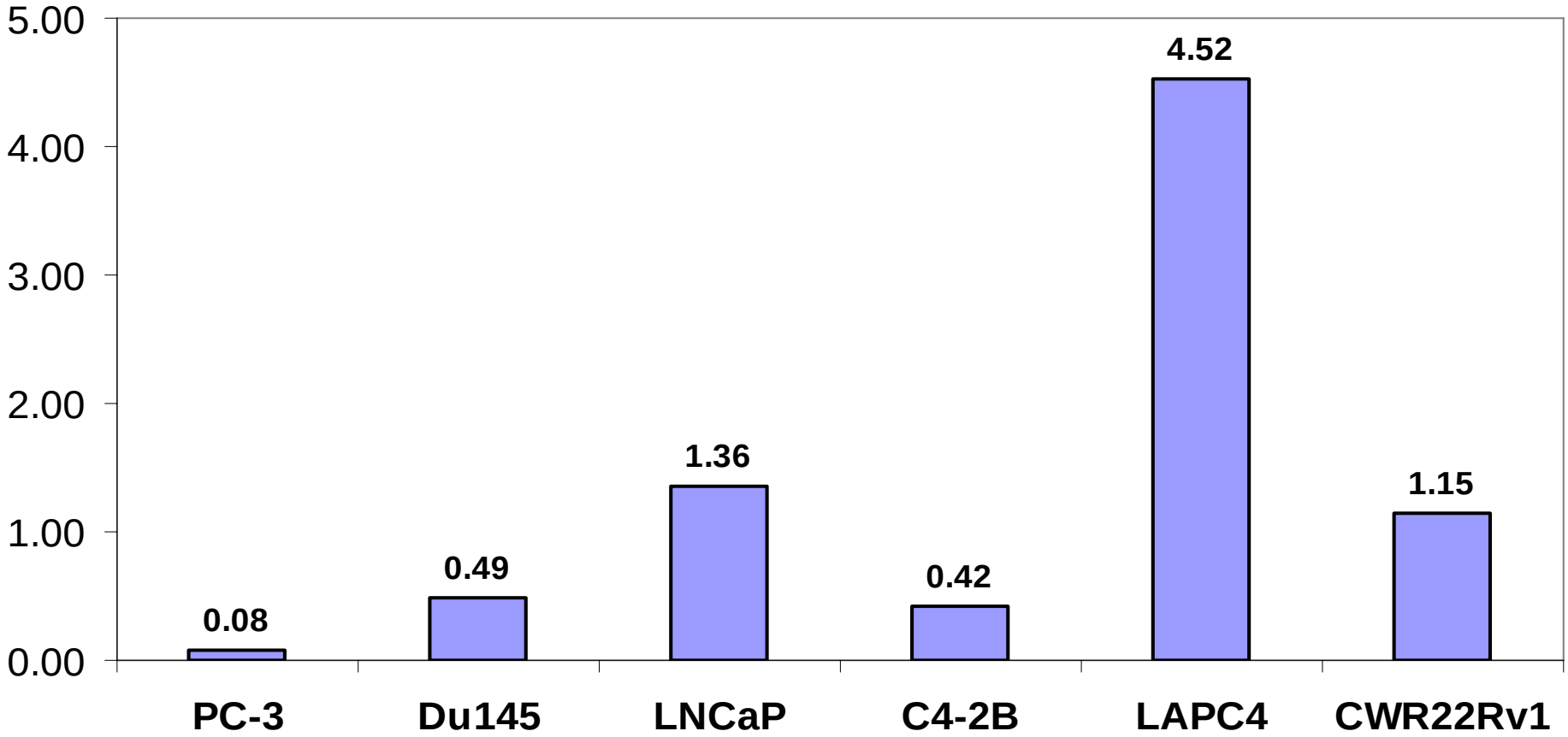

Cancer Stem Cell
(p63 NEG / AR NEG)
Normal Stem Cell
(p63 NEG / AR NEG)
Cancer Progenitor Cell
(p63 POS / AR NEG)
Neuroendocrine Cell
(p63 NEG / AR NEG)
Progenitor Cell = TA
(p63 POS / AR NEG)
Cancer Intermediate Cell
(p63 NEG / AR POS)
Intermediate Cell
(p63 NEG / AR POS)
Cancer Luminal Cell
(p63 NEG / AR POS)
Luminal Cell
(p63 NEG / AR POS)

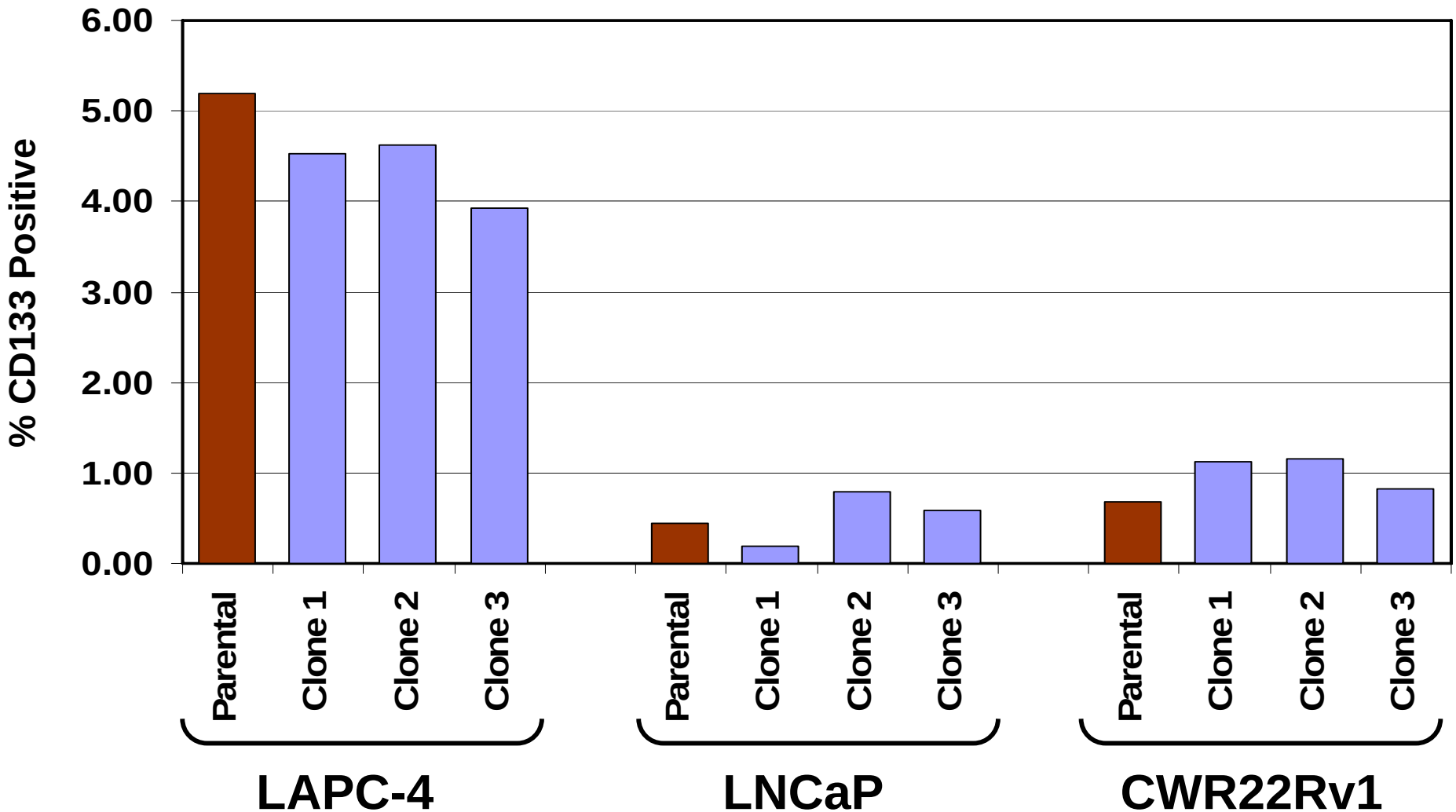

Normal Stem Cell
(p63 NEG / AR NEG)
Progenitor Cell = TA
(p63 POS / AR NEG)
Cancer "Stem" like Cell
(p63 POS / AR NEG)
Cancer Intermediate Cell
(p63 NEG / AR POS)
Cancer Luminal Cell
(p63 NEG / AR POS)
Intermediate Cell
(p63 NEG / AR POS)
Luminal Cell
(p63 NEG / AR POS)
Cancer "Stem" Like Cell
(p63 NEG / AR POS)
Cancer Luminal Cell
(p63 NEG / AR POS)

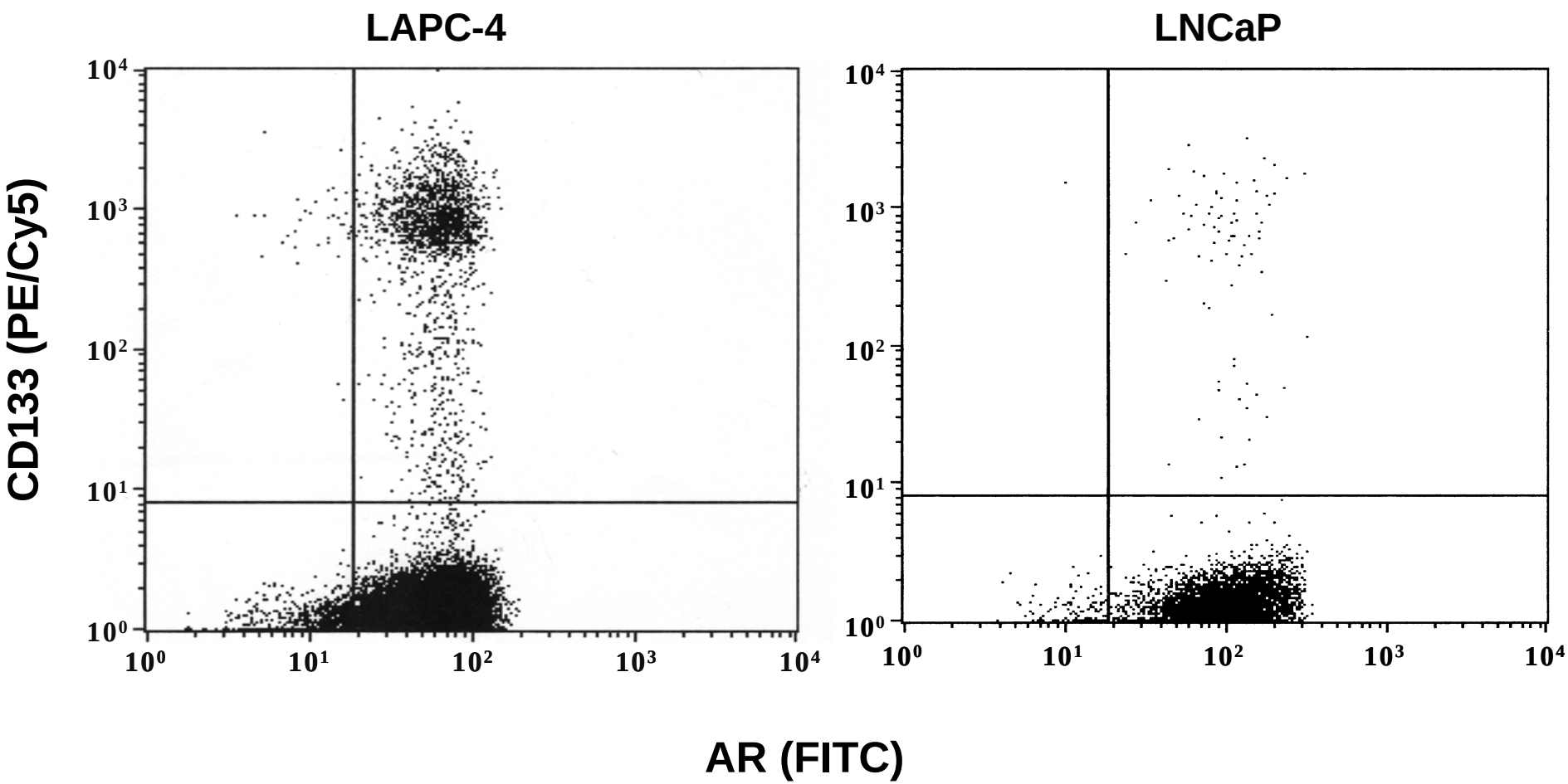
Donald
Vander Griend

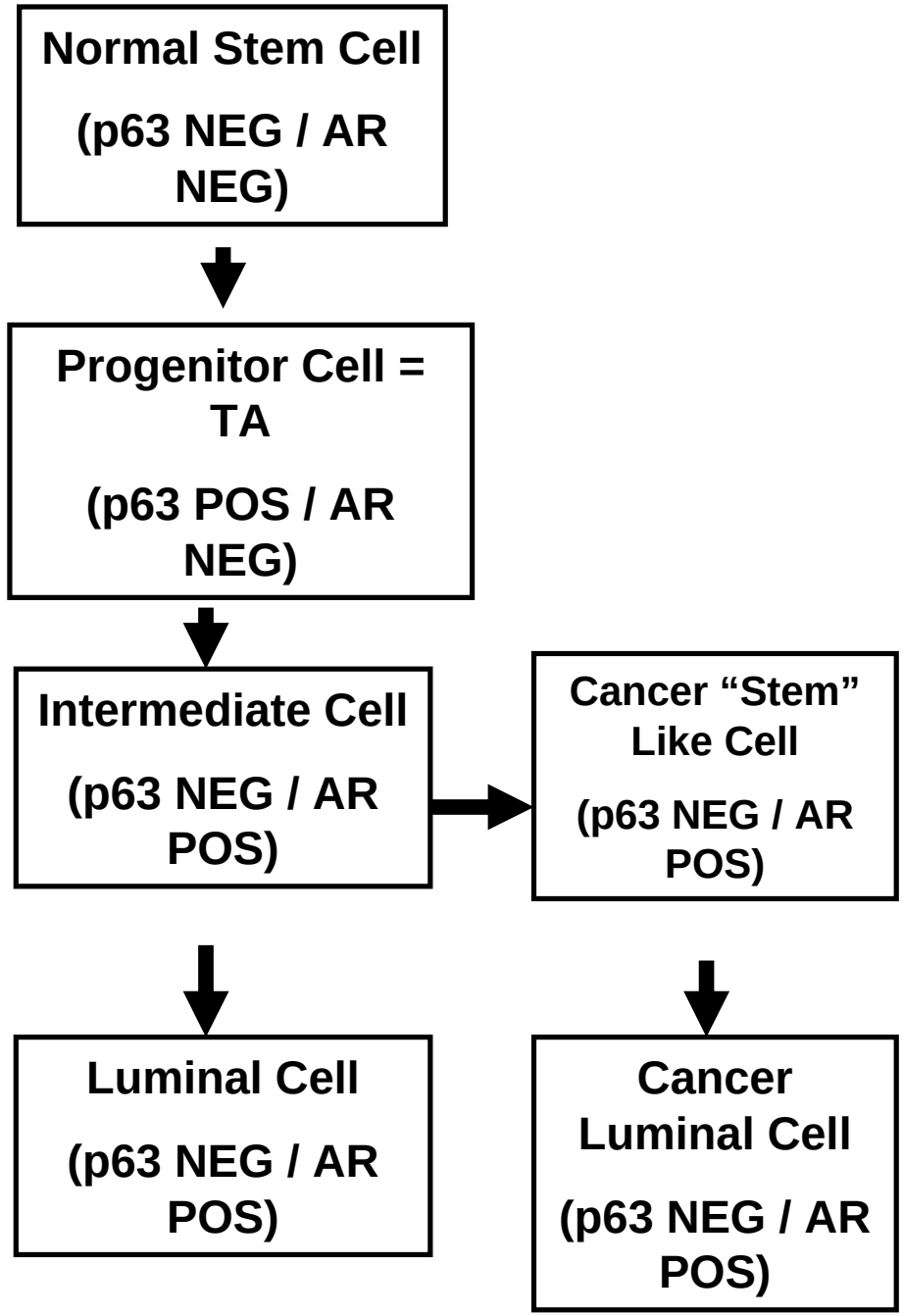
ΔNp63
PREC
957e/hTERT
PC-3
Du145
E006AA
DuCAP
VCAP
MDA PCa 2b
LNCaP
C4-2B
LAPC-4
CWR-R1
CWR-22Rv1
α
β
γ

% CD133-Positive Cells in Prostate Cancer Cell Lines




% CD133 Positive
6.00
5.00
4.00
3.00
2.00
1.00
0.00
Parental
Clone 1
Clone 2
Clone 3
Parental
Clone 1
Clone 2
Clone 3
Parental
Clone 1
Clone 2
Clone 3
LAPC-4
LNCaP
CWR22Rv1


LAPC-4
LNCaP
CD133 (PE/Cy5)
AR (FITC)
10^0
10^1
10^2
10^3
10^4


Normal Stem Cell
(p63 NEG / AR NEG)
Progenitor Cell = TA
(p63 POS / AR NEG)
Intermediate Cell
(p63 NEG / AR POS)
Cancer “Stem” Like Cell
(p63 NEG / AR POS)
Luminal Cell
(p63 NEG / AR POS)
Cancer Luminal Cell
(p63 NEG / AR POS)