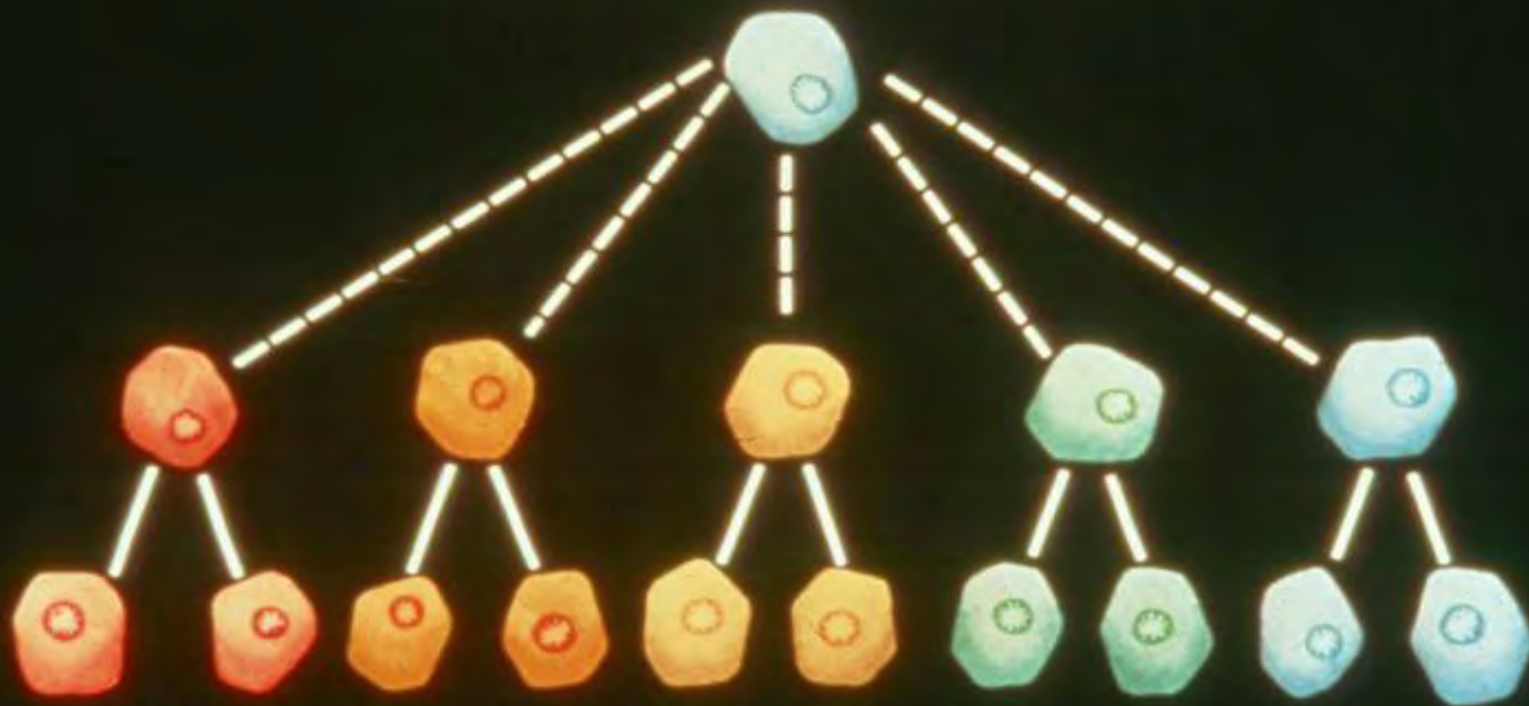


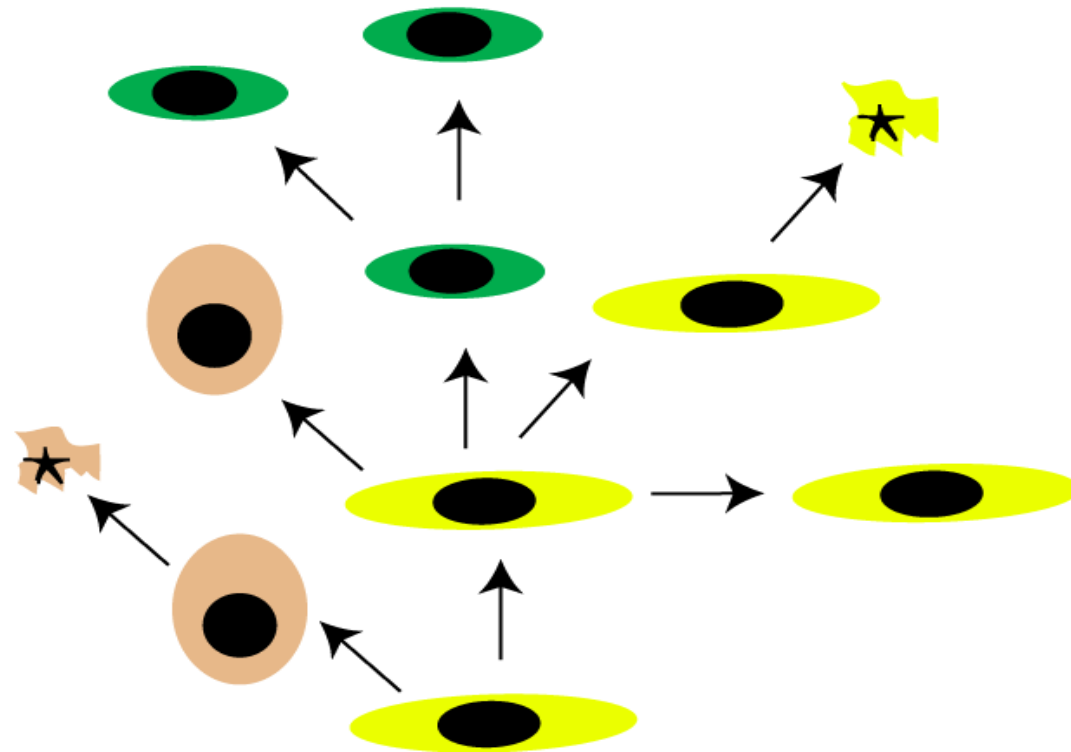
Cancer is Caused by a Series of Genetic Changes.



Neoplastic Progression



Tumor heterogeneity = Incomprehensible chaos

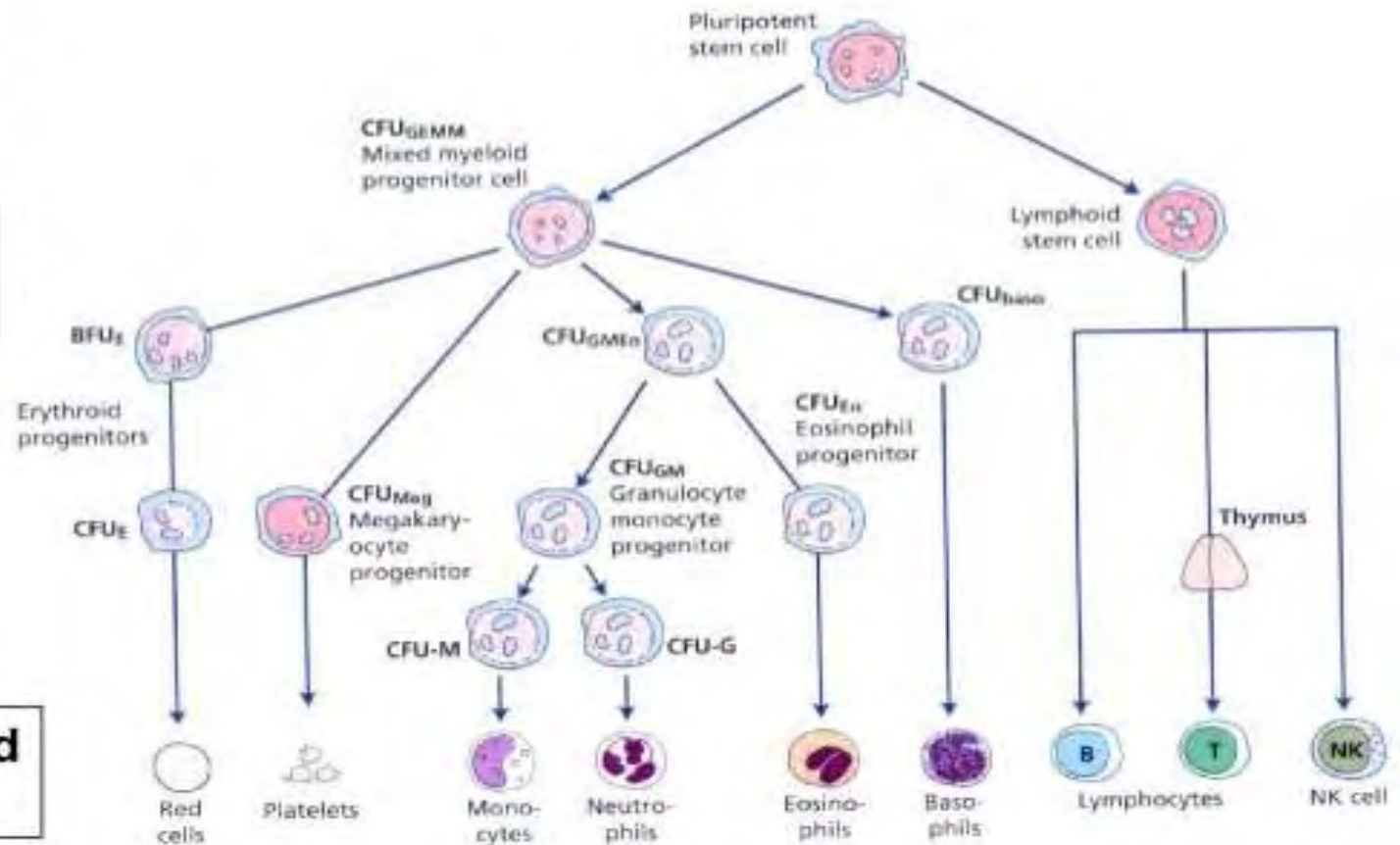


Lineage commitment in Hematopoiesis

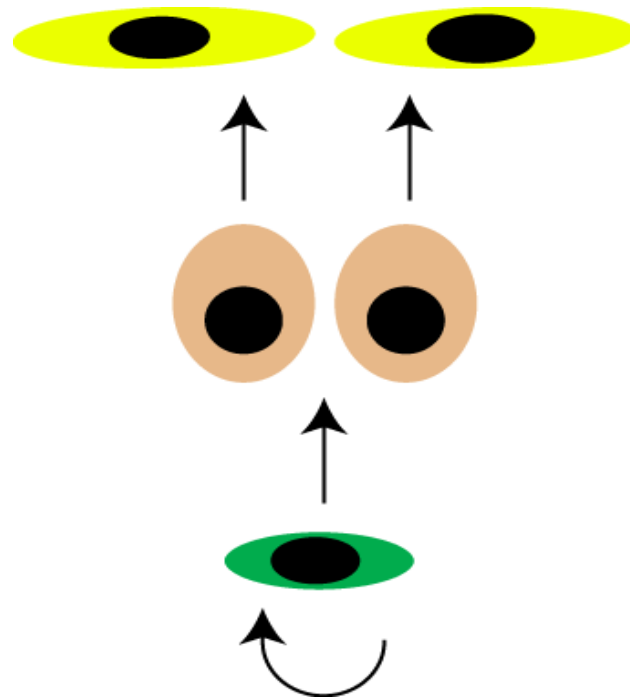
Stem cells

Committed progenitors

Differentiated cells



Perhaps cancer growth is hierarchical and orderly



If organogenesis \simeq carcinogenesis,
cancers have stem cells

Organogenesis vs. Cancer

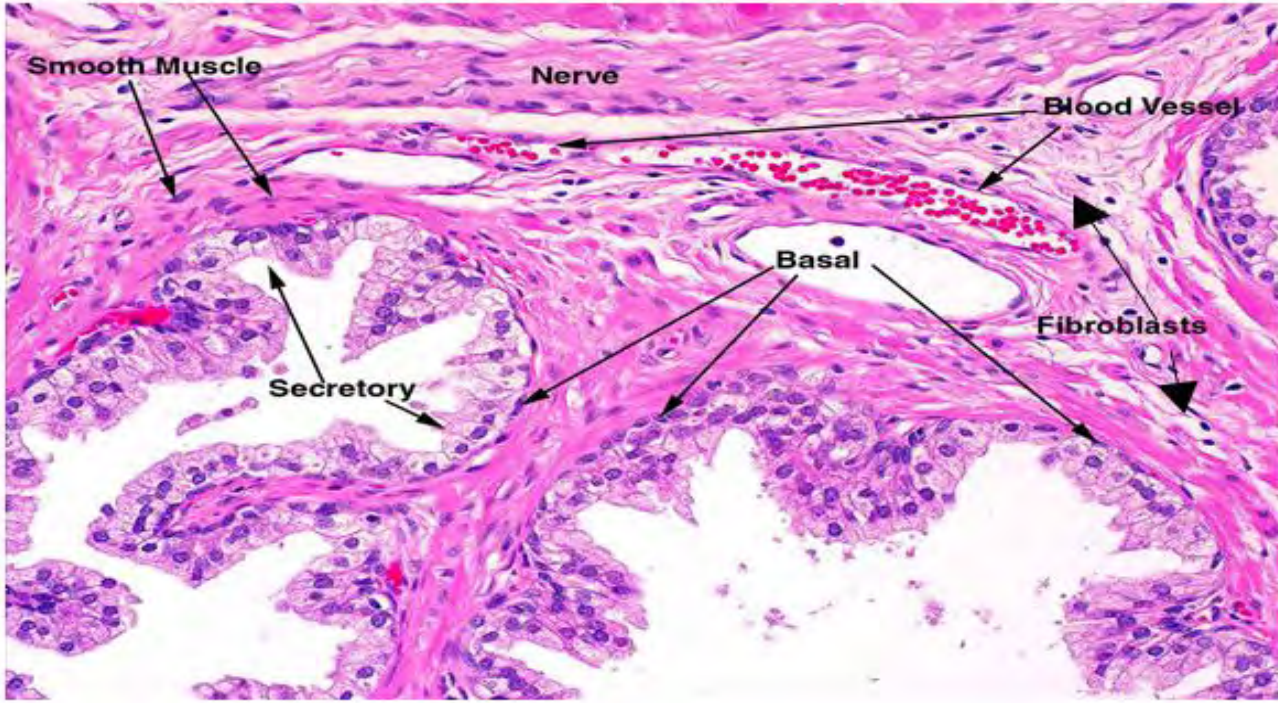
- Organogenesis
 - Proliferation
 - Invasion
 - Motility
 - Angiogenesis
 - Differentiation
 - Terminates upon completion
- Carcinogenesis
 - Proliferation
 - Invasion
 - Motility
 - Angiogenesis
 - Differentiation
 - Escapes termination signals

Origin of Cancer Stem Cell

Malignantly Transformed Normal Stem Cell

OR

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



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

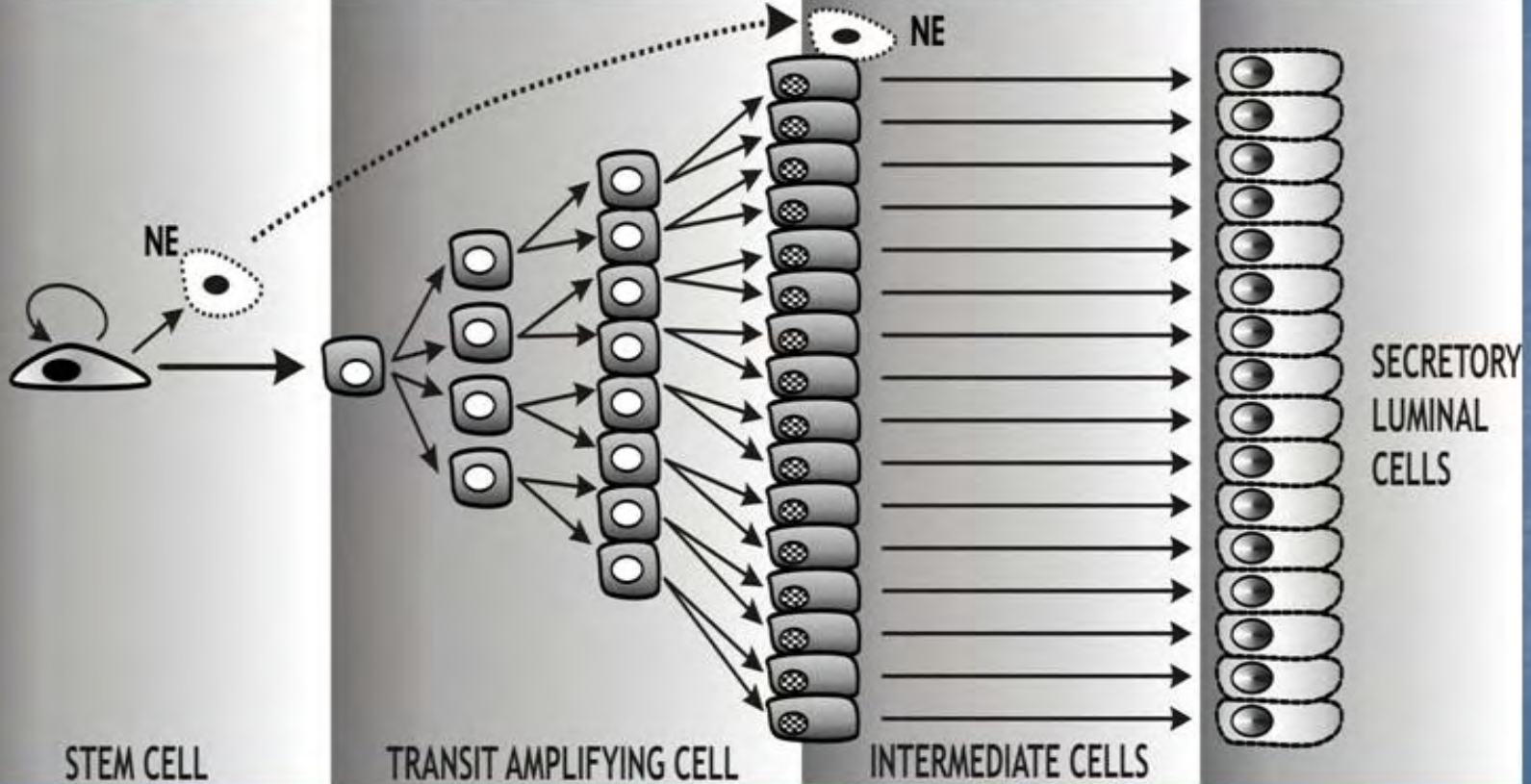
Max Loda's Group at Harvard

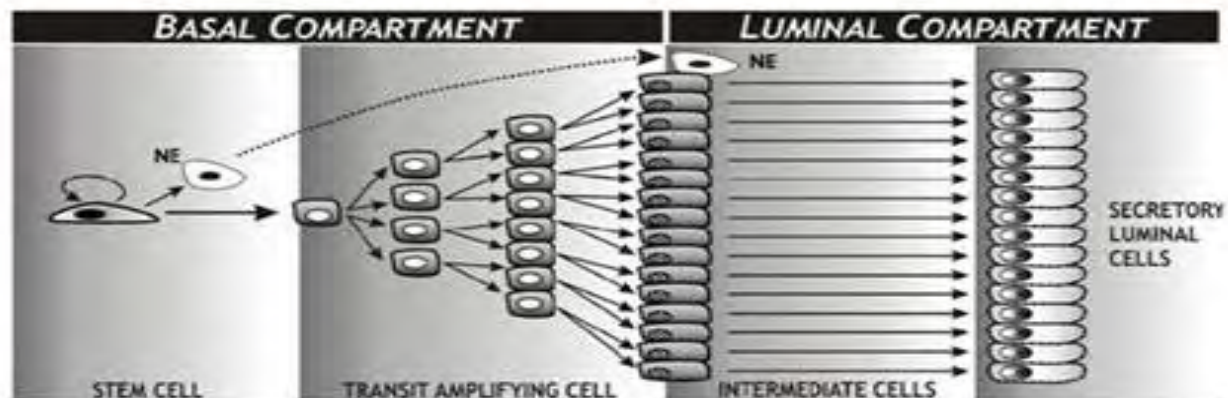
Jack Schalken's Group at Nijmegen in
Netherlands

Gary Smith' Group at RPCI

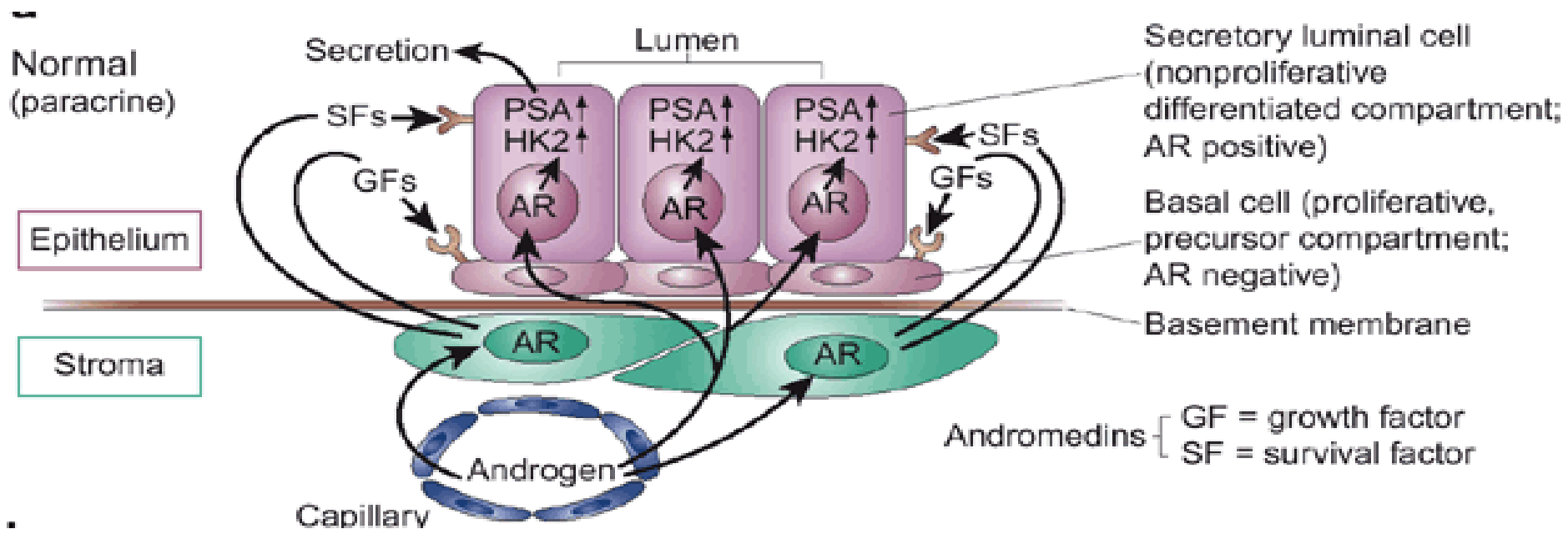
BASAL COMPARTMENT

LUMINAL COMPARTMENT





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)

Epithelium

Stroma

Secretory luminal cell (nonproliferative differentiated compartment; AR positive)

Basal cell (proliferative, precursor compartment; AR negative)

Basement membrane

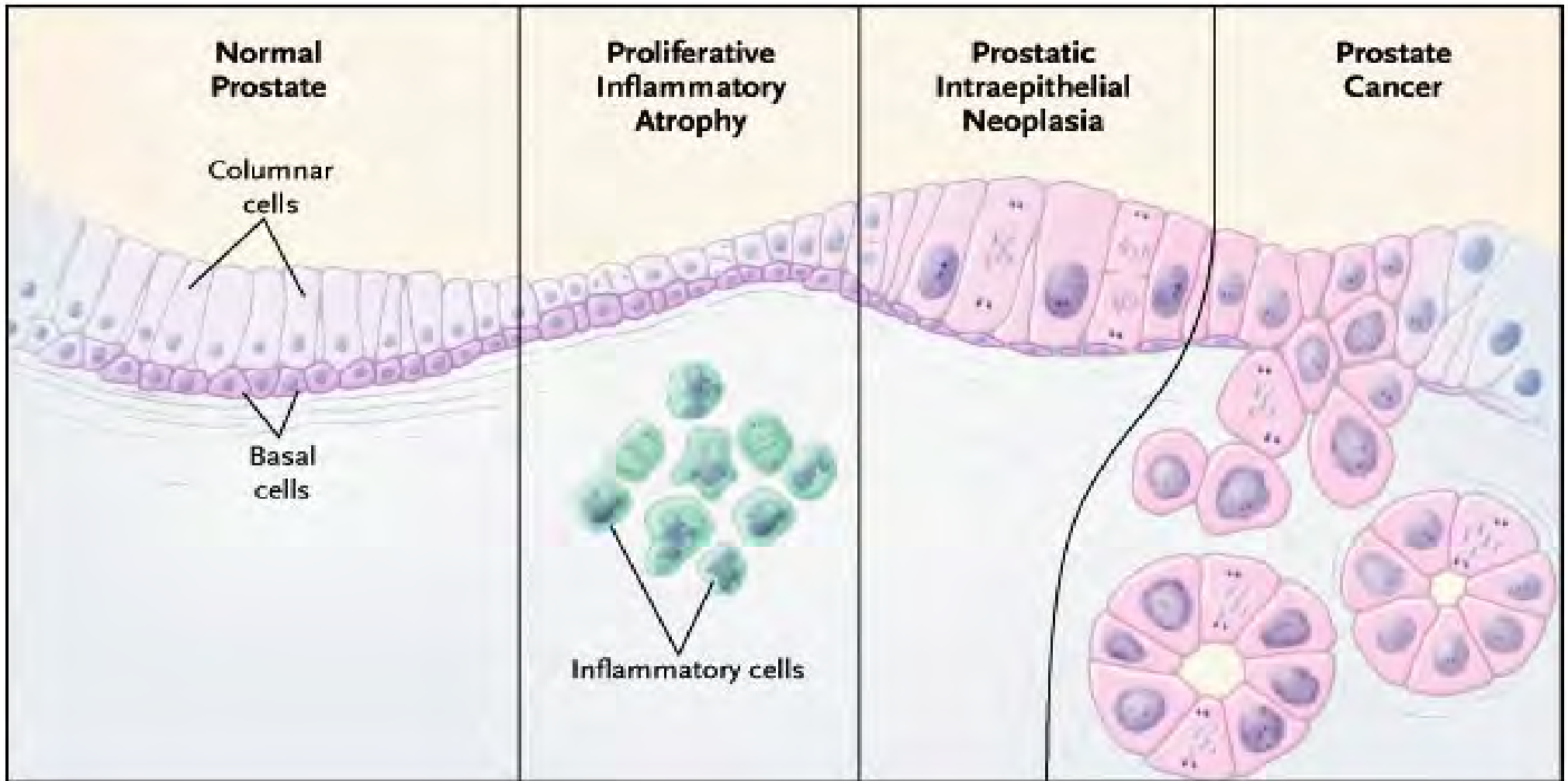
Andromedins { GF = growth factor
SF = survival factor

Capillary

Ivan Litvinov

Donald Vander Griend

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



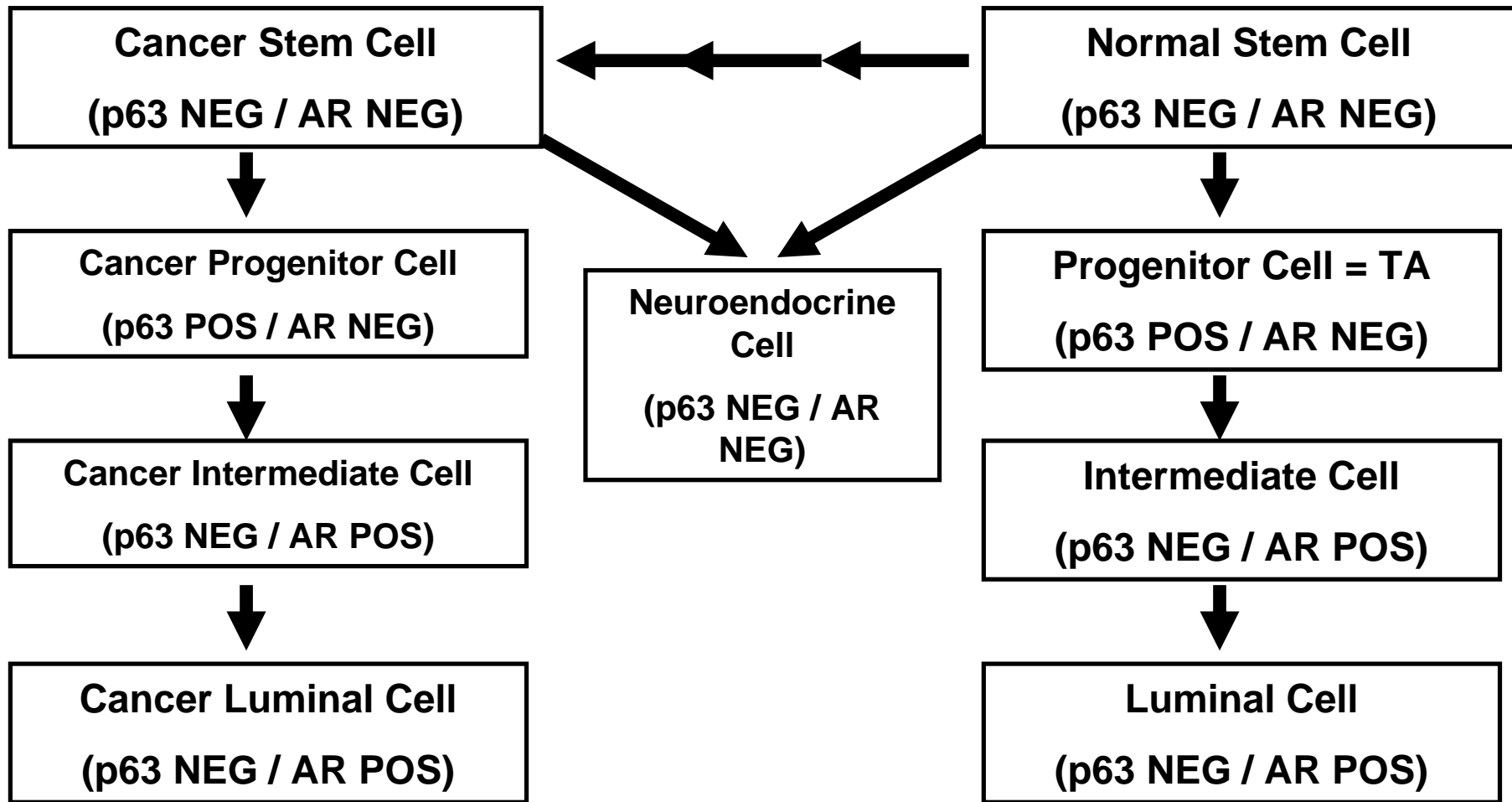
Nelson, W.G. *et al.* New Engl. J. Med. 349: 366-381, 2003

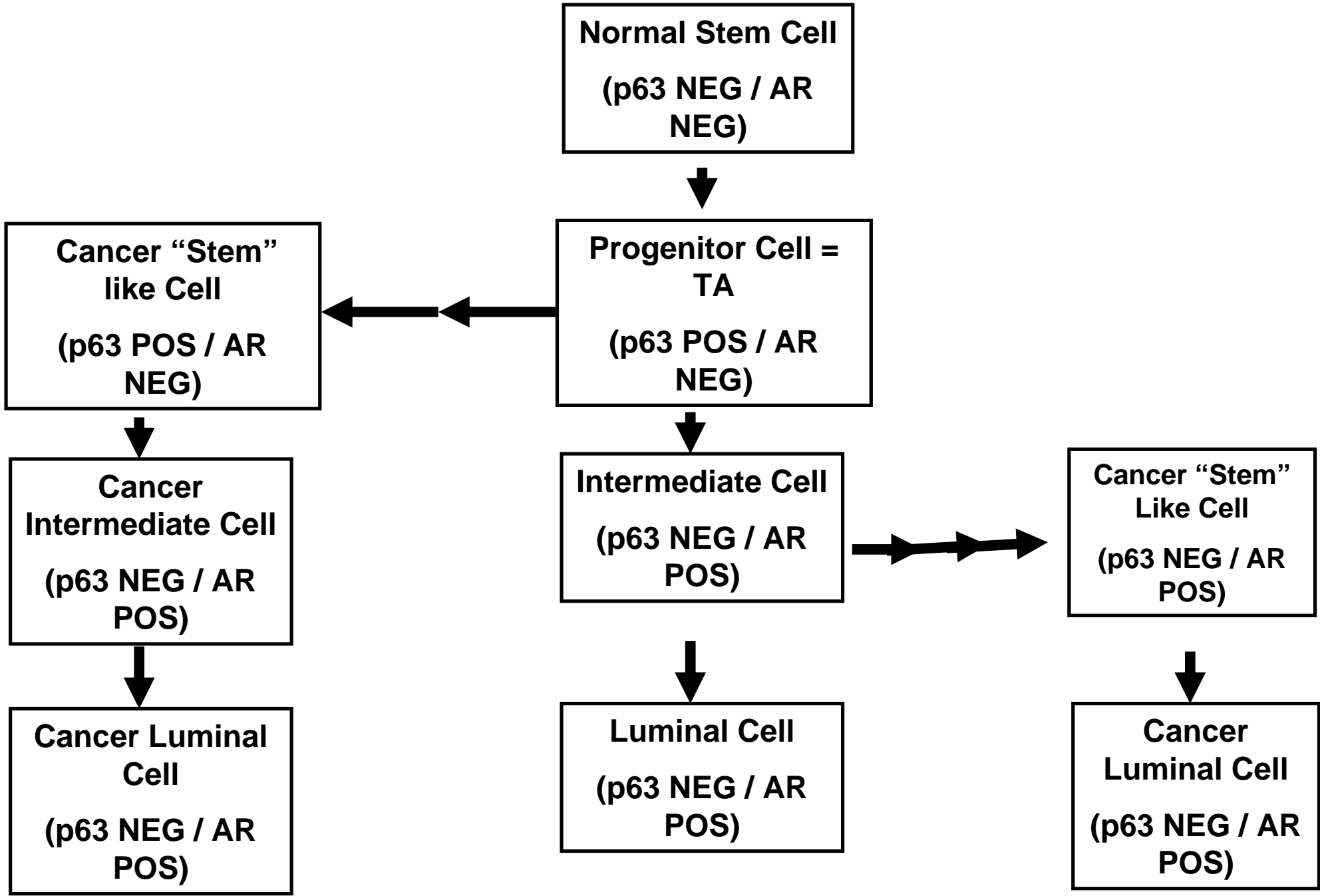
The Androgen Receptor is a Growth
Suppressor Gene for Normal Prostatic
Epithelial Cells but an Oncogene for
Prostate Cancer Cells.

**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.**

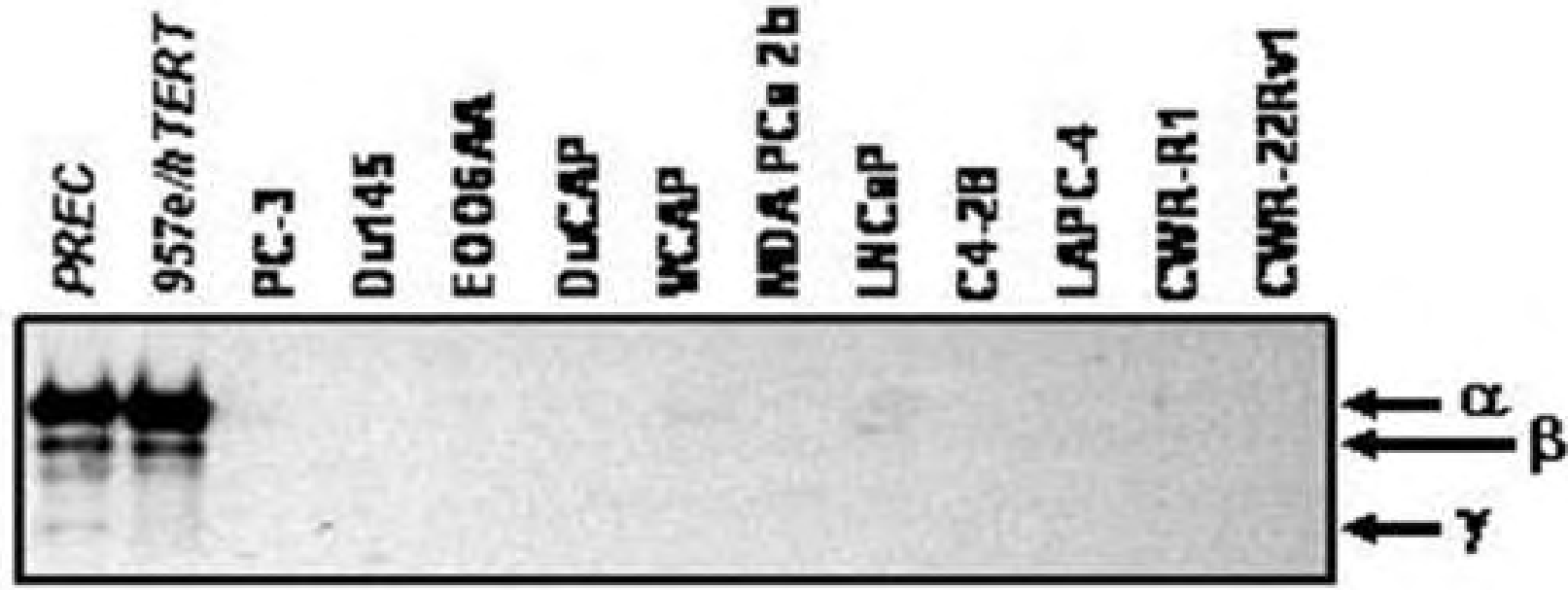
Proc Natl Acad Sci 103:15085-90, 2006.



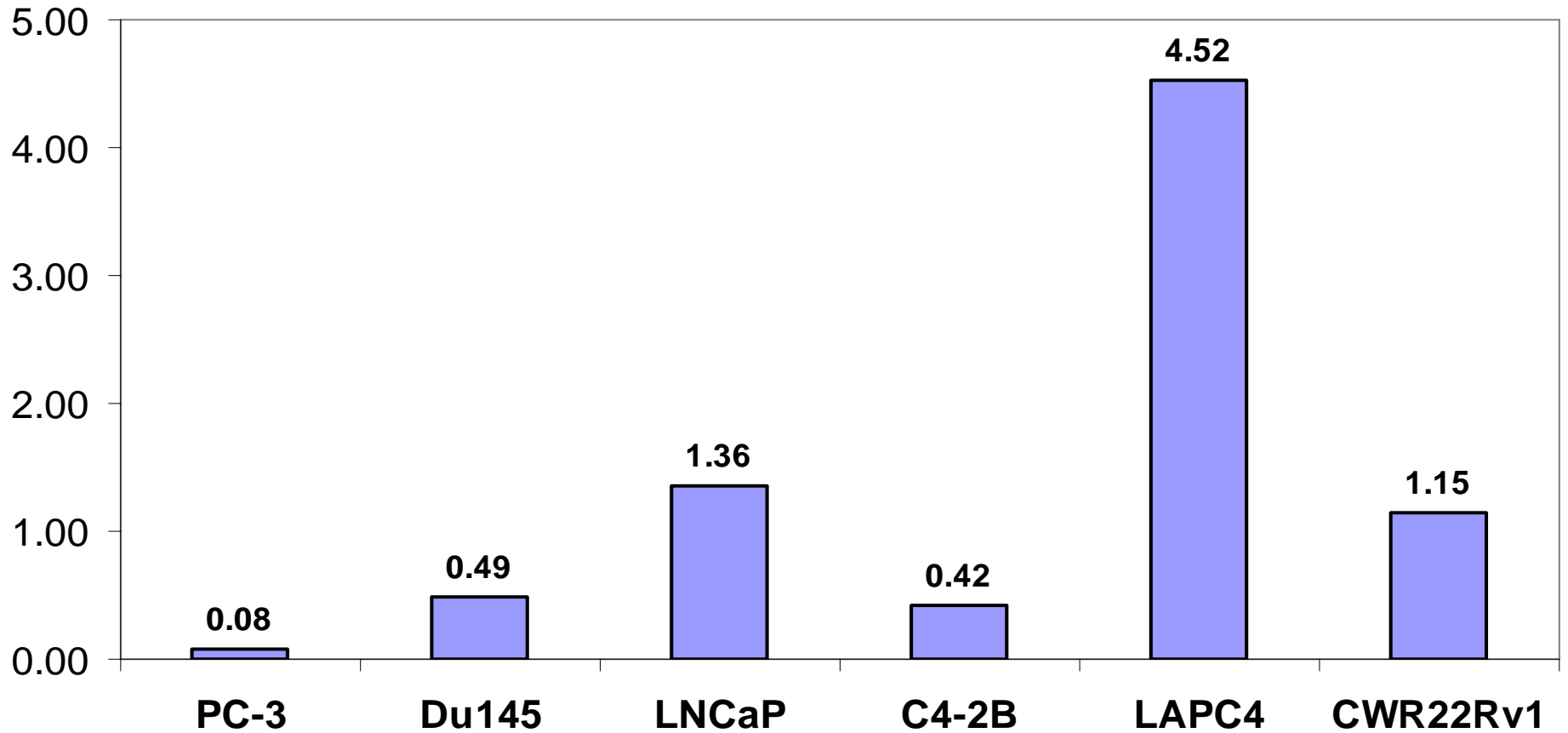


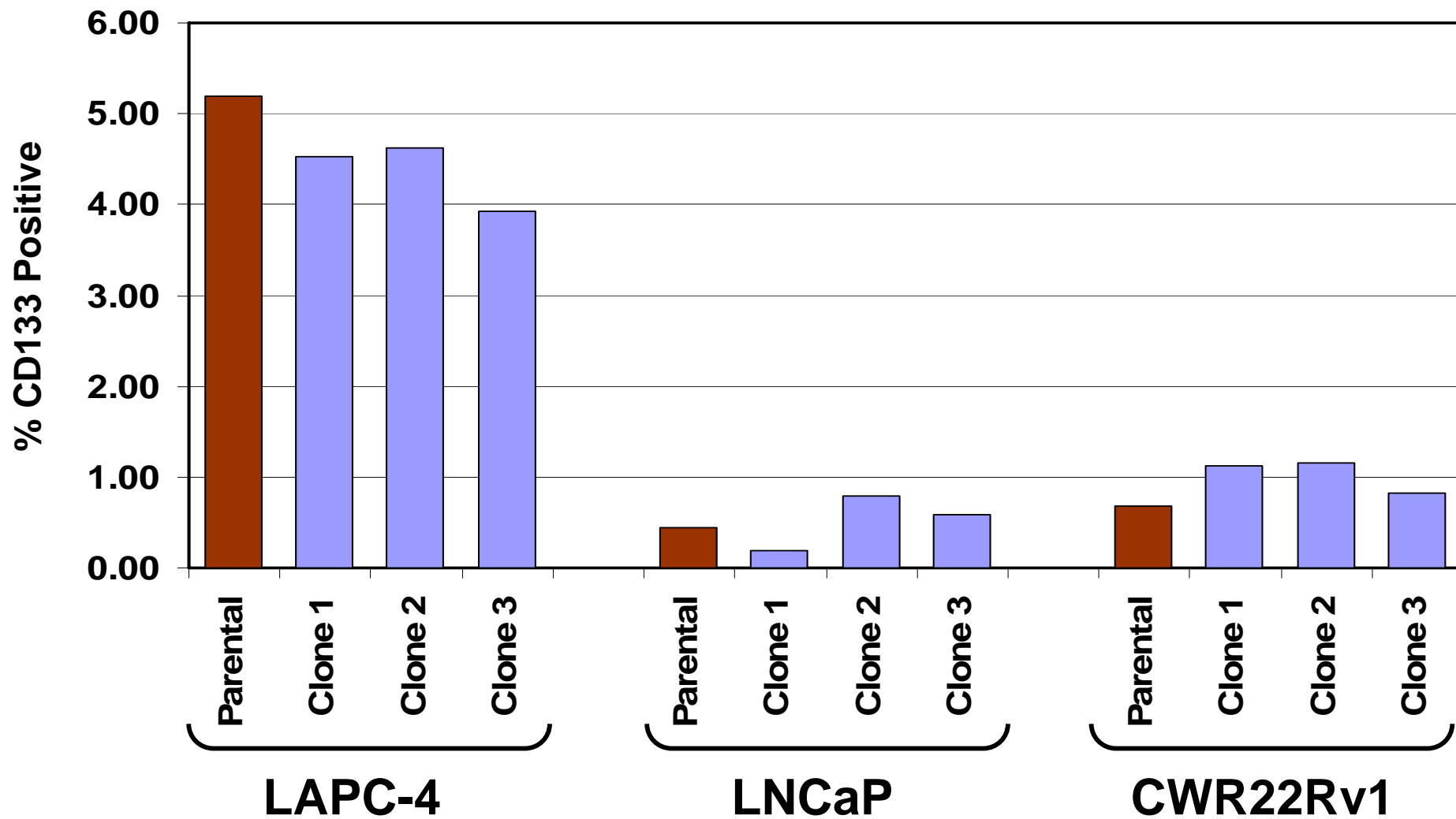
**Donald
Vander Griend**

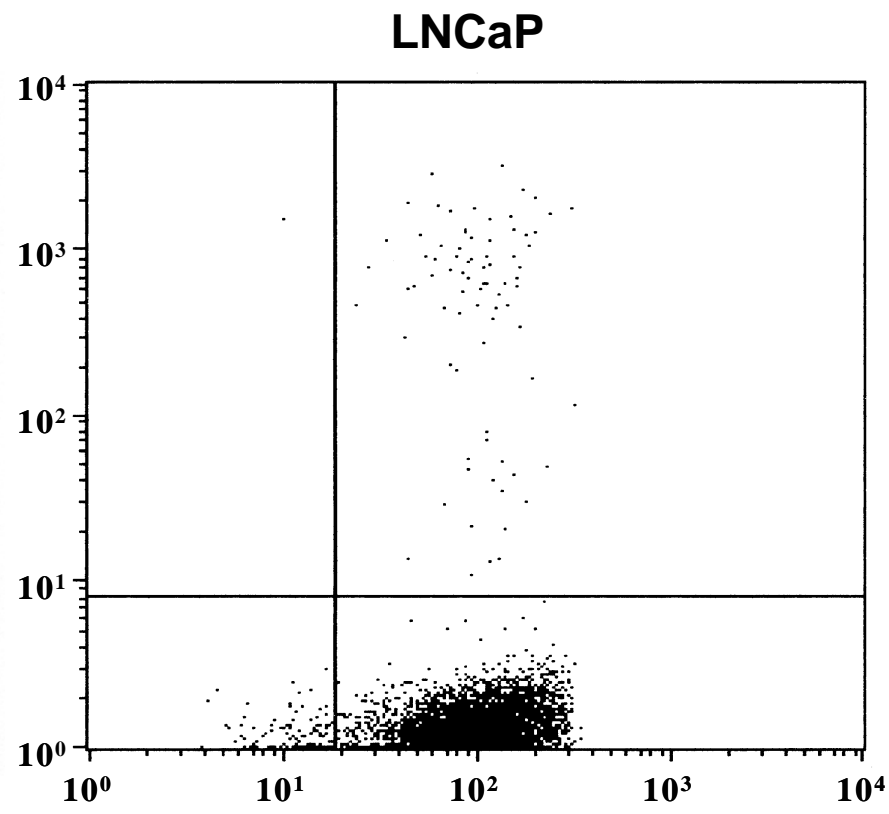
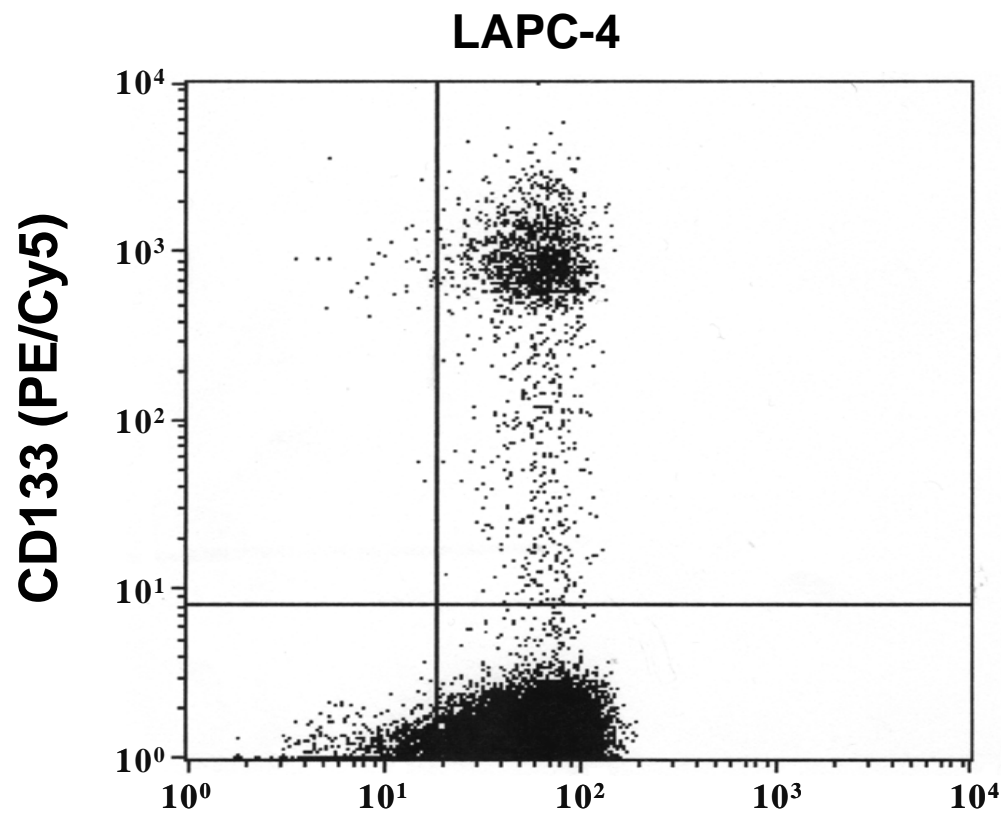
$\Delta Np83$



% CD133-Positive Cells in Prostate Cancer Cell Lines







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)