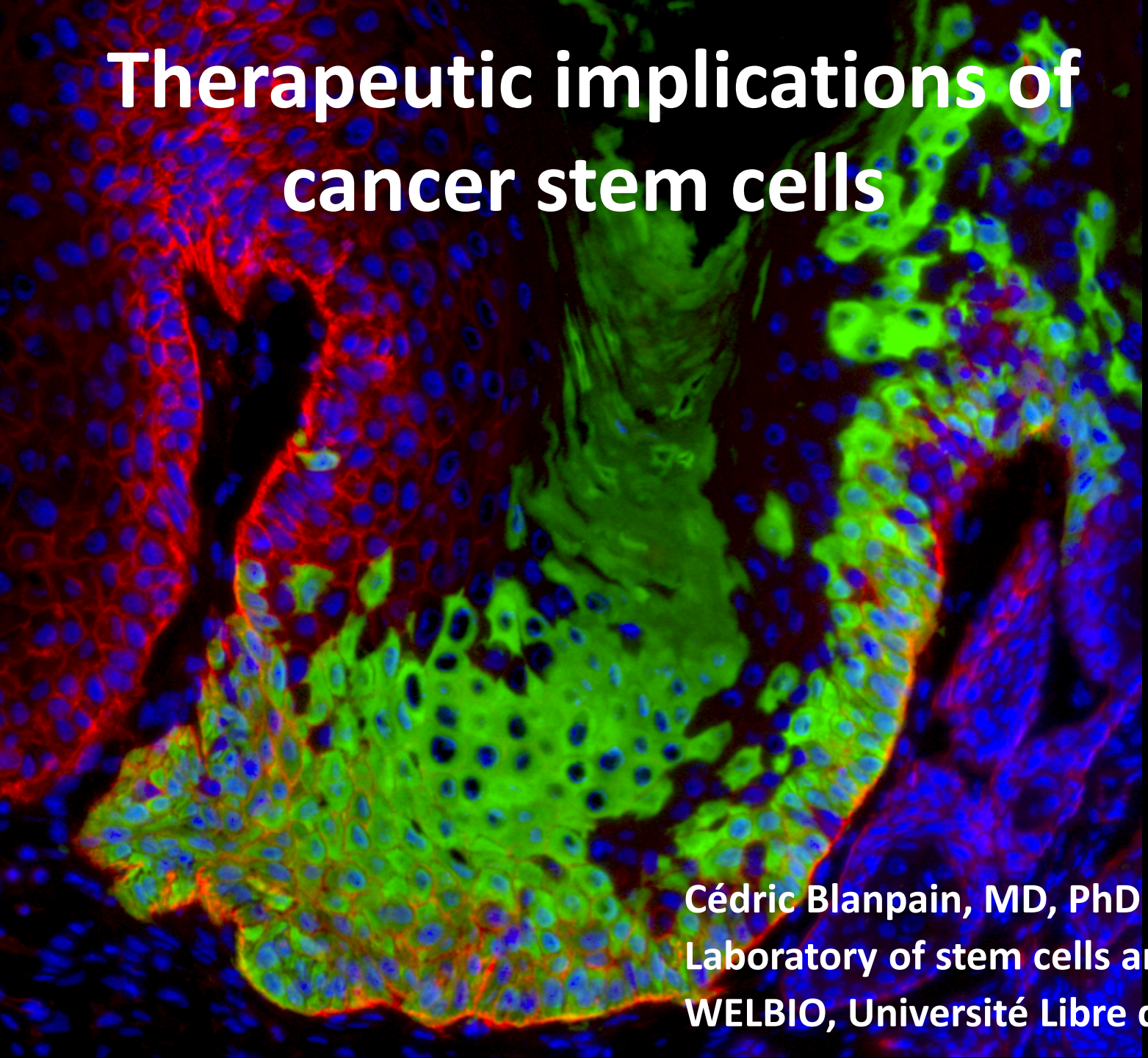
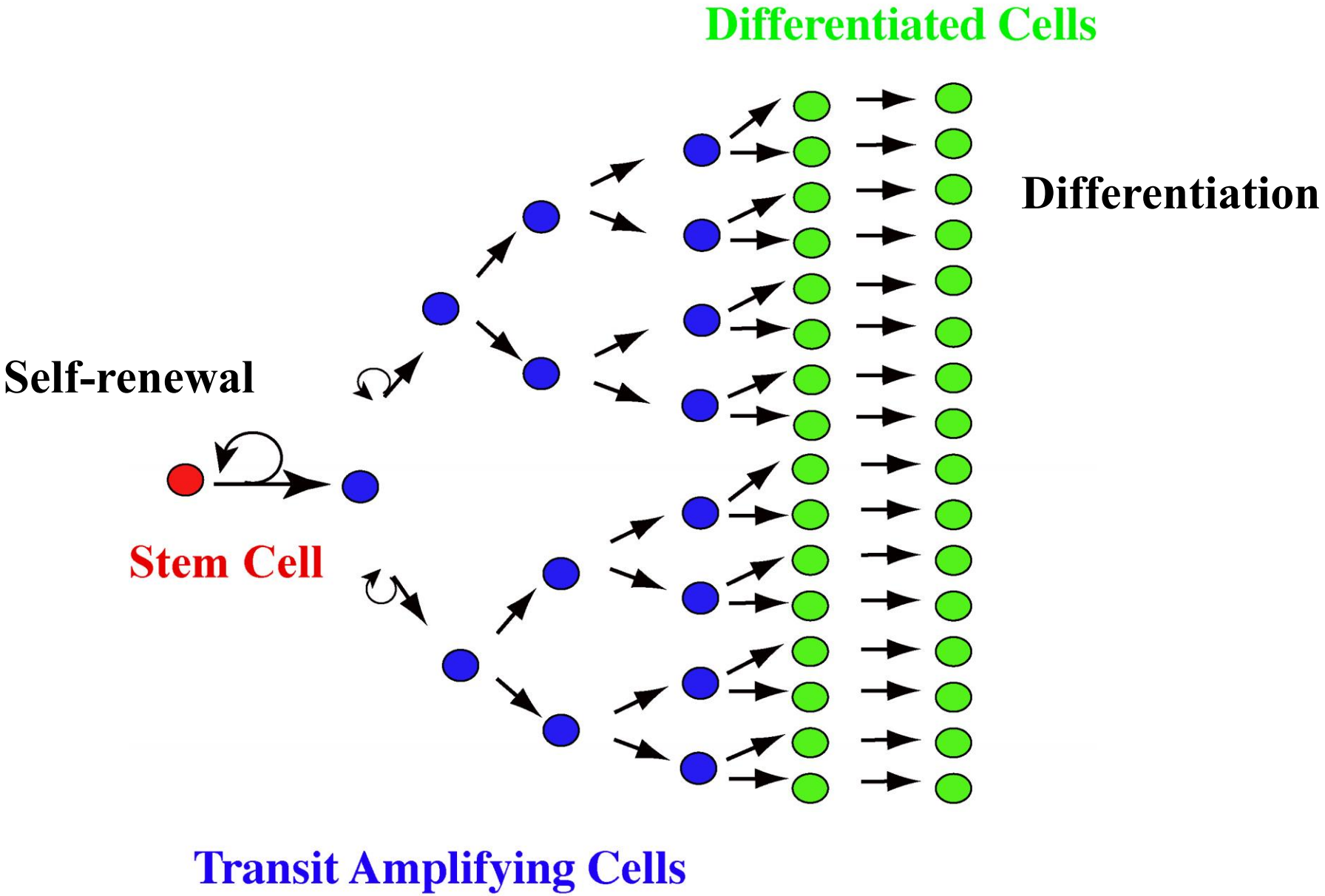
Therapeutic implications of cancer stem cells

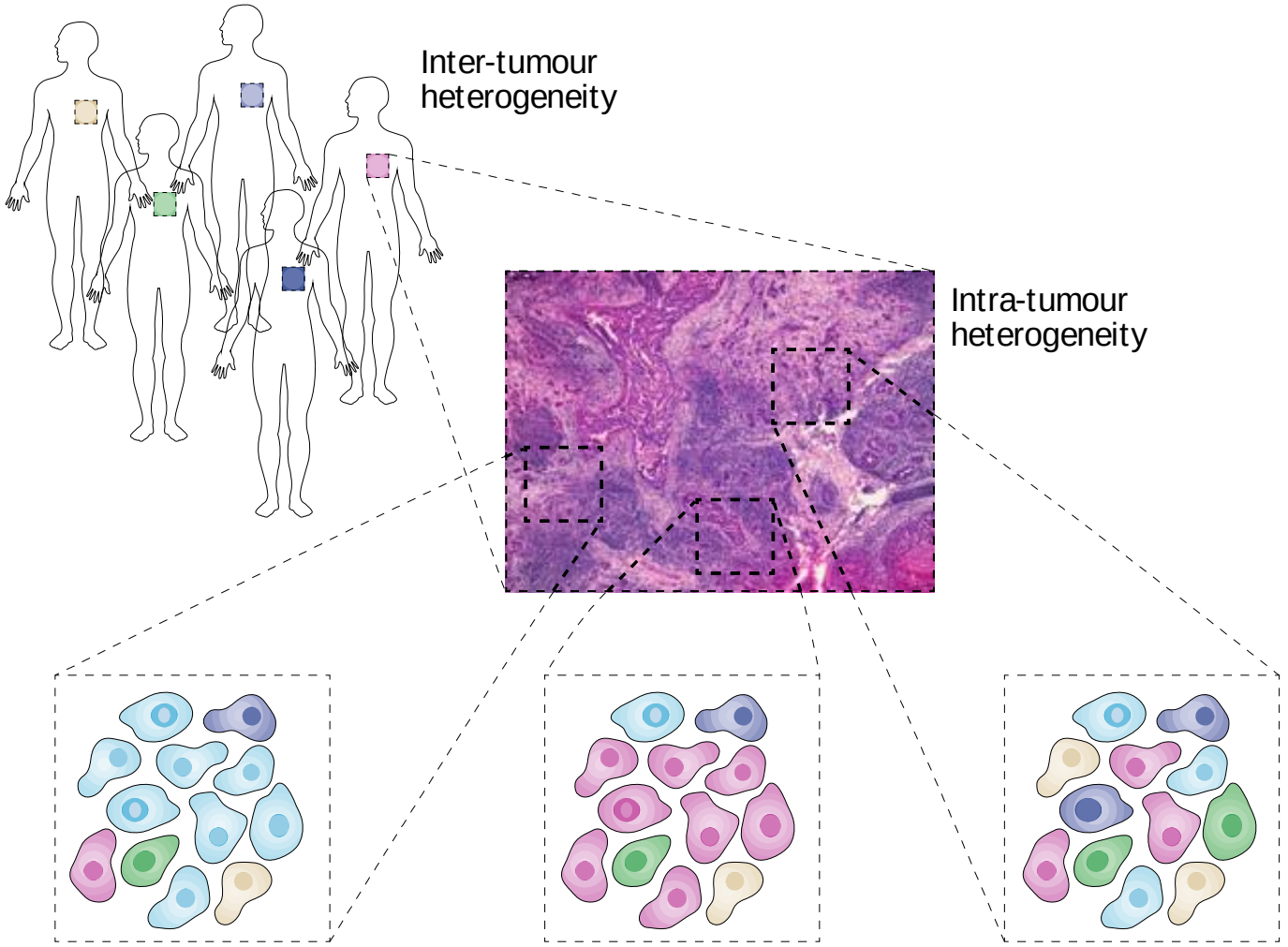


Cédric Blanpain, MD, PhD
Laboratory of stem cells and cancer
WELBIO, Université Libre de Bruxelles

Stem cell properties

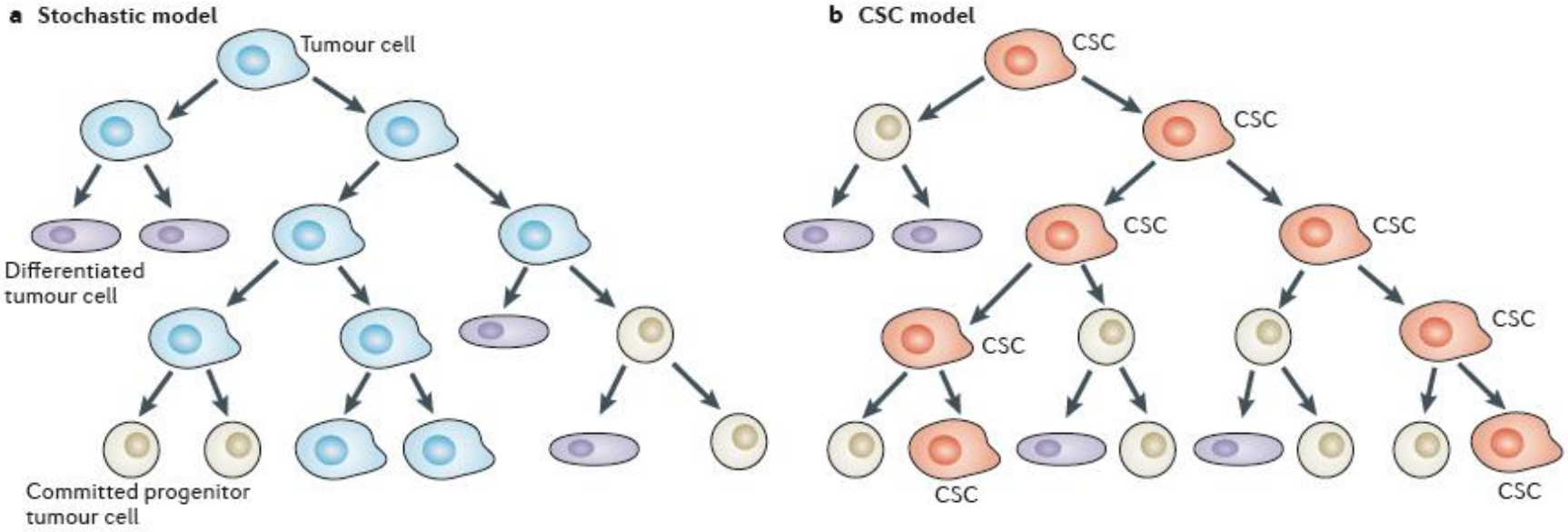


Tumor heterogeneity



Marusyk A et al. Nat Rev Cancer 2012

Stochastic cancer evolution versus cancer stem cells?

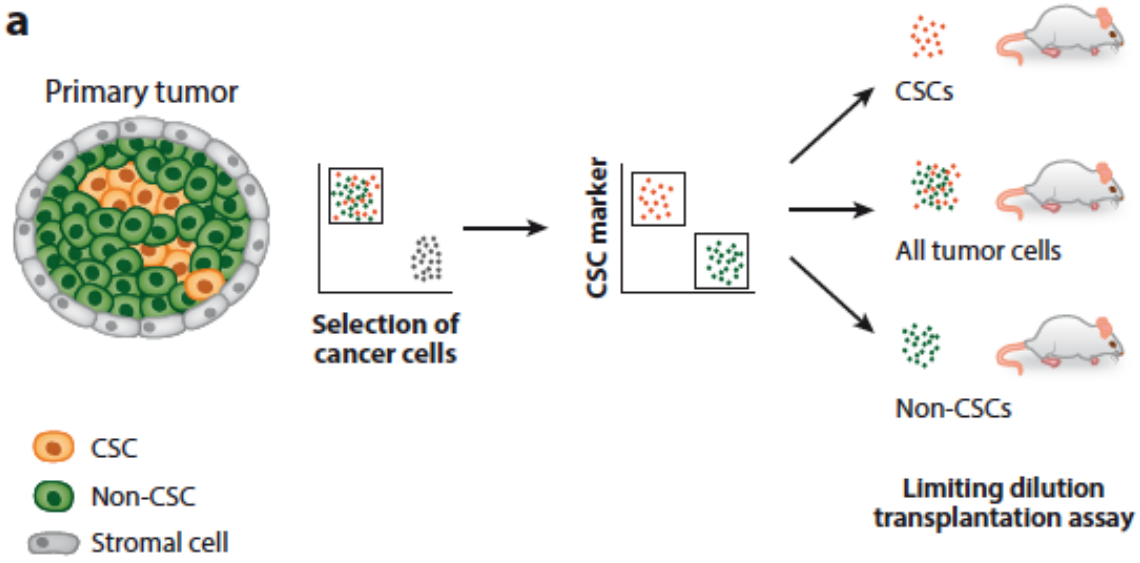


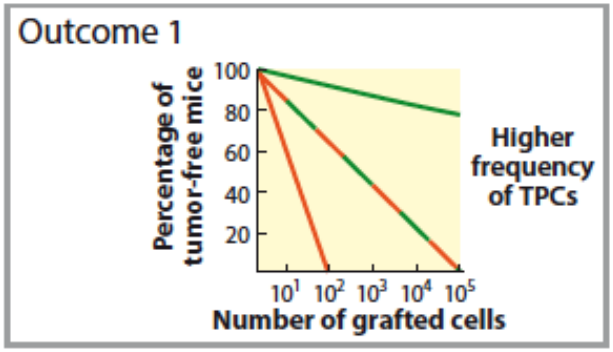
Beck & Blanpain Nature Reviews Cancer 2013

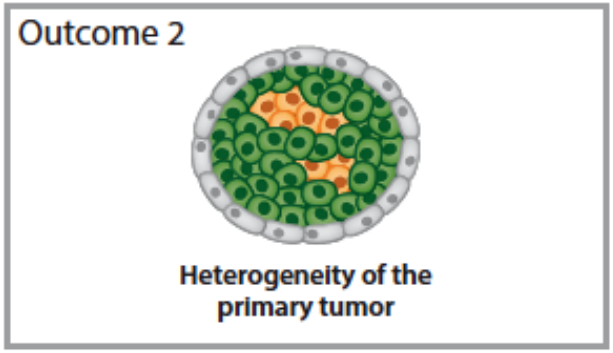
Cancer stem cells

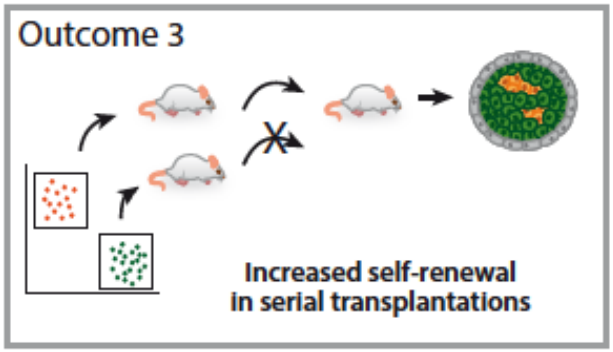
- Defining cancer stem cell by transplantation assays to and its limitation
- Studying cancer stem cells within their native environment and defining their clonal dynamic by lineage tracing experiments
- Uncovering the essential role and plasticity of cancer stem cell by lineage ablation

Assessing cancer stem cell potential by transplantation assays









Nassar & Blanpain Annual Reviews of Pathology 2016

A cell initiating human acute myeloid leukaemia after transplantation into SCID mice

Tsvee Lapidot, John E. Dick et al. **Nature** 367, 645-648 1994

Limiting dilution analysis showed that the frequency of these leukaemia-initiating cells in the peripheral blood of AML patients was **one engraftment unit in 250,000 cells**. We fractionated AML cells on the basis of cell-surface-marker expression and found that the leukaemia-initiating cells that could engraft SCID mice to produce **large numbers of colony-forming progenitors were $CD34^+CD38^-$; however, the $CD34^+CD38^+$ and $CD34^-$ fractions contained no cells with these properties**.

Human acute myeloid leukemia is organized as a hierarchy that originates from a primitive hematopoietic cell

DOMINIQUE BONNET & JOHN E. DICK

Department of Genetics, Research Institute, Hospital for Sick Children and Department of Molecular and Medical Genetics, University of Toronto, 555 University Avenue, Toronto, Ontario M5G IX8, Canada
Correspondence should be addressed to J.E.D.
Department of Genetics, Research Institute, Hospital for Sick Children, 555 University Avenue, Toronto, Ontario, Canada M5G 1X8

Prospective identification of tumorigenic breast cancer cells

Muhammad Al-Hajj*, Max S. Wicha*, Adalberto Benito-Hernandez†, Sean J. Morrison*‡§, and Michael F. Clarke*‡¶

Departments of *Internal Medicine and †Pathology, Comprehensive Cancer Center, ‡Department of Developmental Biology, and §Howard Hughes Medical Institute, University of Michigan Medical School, Ann Arbor, MI 48109

Communicated by Jack E. Dixon, University of Michigan Medical School, Ann Arbor, MI, January 16, 2003 (received for review December 18, 2002)

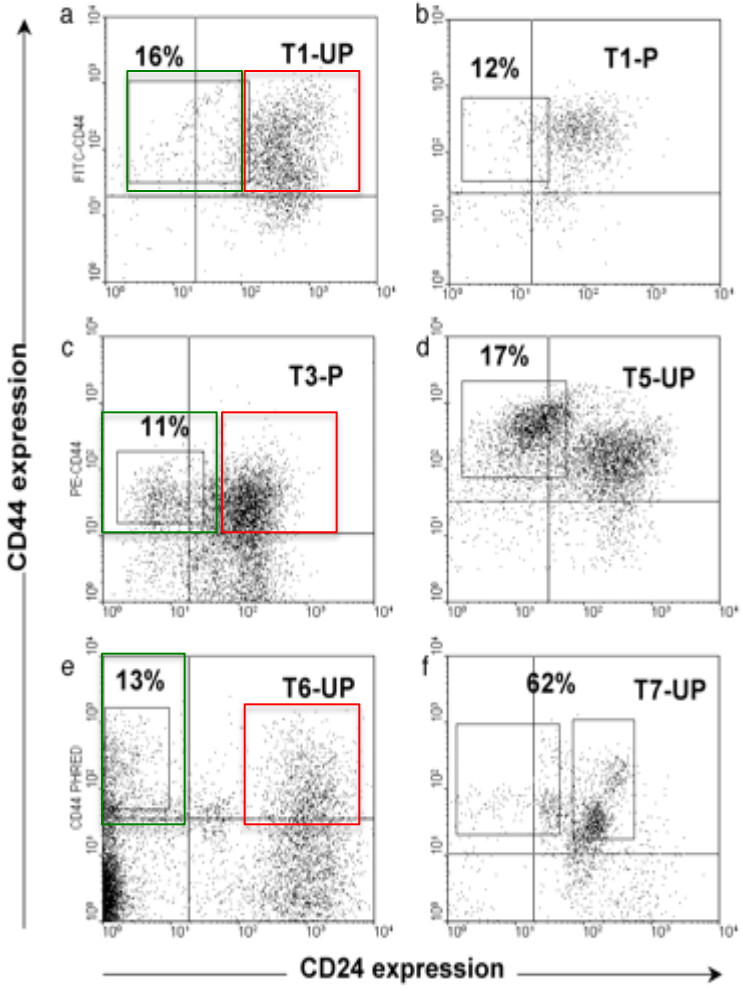


Table 2. Tumor formation ability of sorted cells

	Tumors/injections		
	8×10^5	5×10^5	2×10^5
Passaged T1			
CD44⁻	0/2	0/2	—
CD44⁺	2/2	2/2	—
B38.1⁻	0/2	0/2	—
B38.1⁺	2/2	2/2	—
CD24⁺	—	—	1/6
CD24⁻	—	—	6/6
Passaged T2			
CD44⁻	0/2	0/2	—
CD44⁺	2/2	2/2	—
B38.1⁻	0/2	0/2	—
B38.1⁺	2/2	2/2	—
CD24⁺	—	—	1/6
CD24⁻	—	—	6/6

The Epithelial-Mesenchymal Transition Generates Cells with Properties of Stem Cells

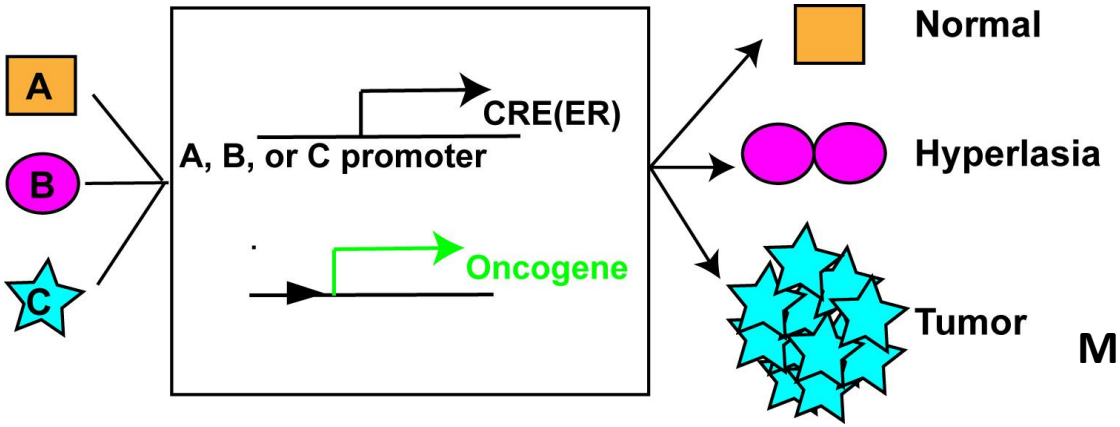
Sendurai A. Mani,[1,3,10,*] Wenjun Guo,[1,10] Mai-Jing Liao,[1,10] Elinor Ng. Eaton,[1] Ayyakkannu Ayyanan,[4] Alicia Y. Zhou,[1,2] Mary Brooks,[1] Ferenc Reinhard,[1] Cheng Cheng Zhang,[1] Michail Shipitsin,[5,6] Lauren L. Campbell,[5,7] Kornelia Polyak,[5,6,7] Cathrin Brisken,[4] Jing Yang,[8] and Robert A. Weinberg[1,2,9,*]

Cell *133*, 704–715, May 16, 2008 ©2008 Elsevier Inc.

Table 2. Tumor Incidence of Transformed HMLEs Induced to Undergo EMT by Ectopic Expression of Snail or Twist and Then Injected into Host Mice in Limiting Dilutions

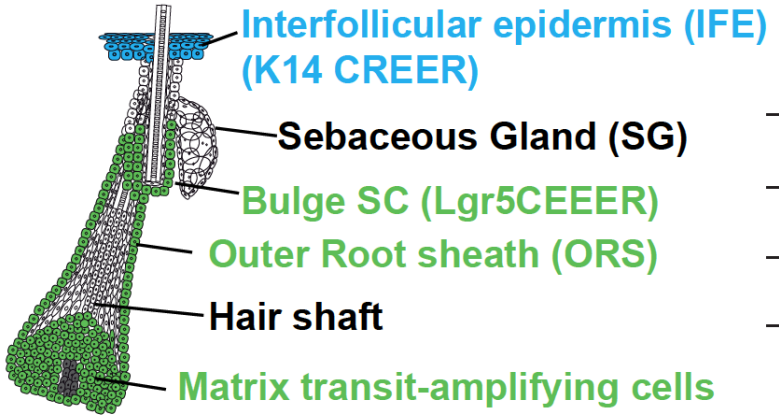
	Tumors Incidence/Number of Injections			
Cells Injected	1×10^6	1×10^5	1×10^4	1×10^3
HMLE-Vector-Ras	2/6	3/9	0/9	0/9
HMLE-Snail-Ras	6/6	9/9	9/9	6/9
HMLE-Twist-Ras	6/6	9/9	9/9	7/9

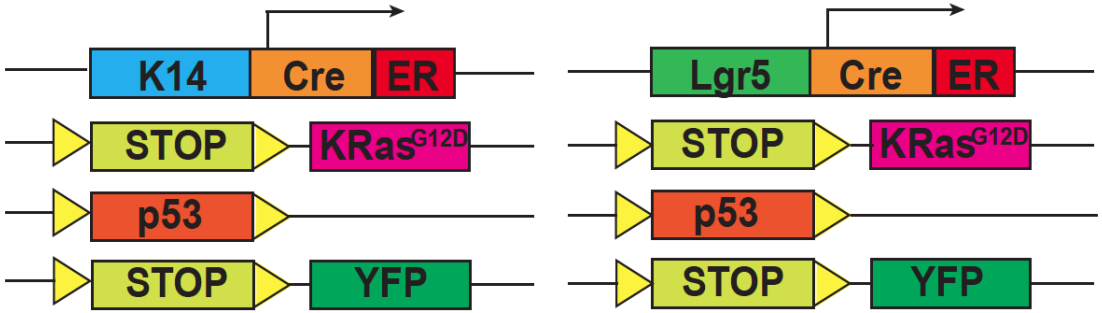
Do tumor heterogeneity in skin SCCs arise from the cancer cell of origin?



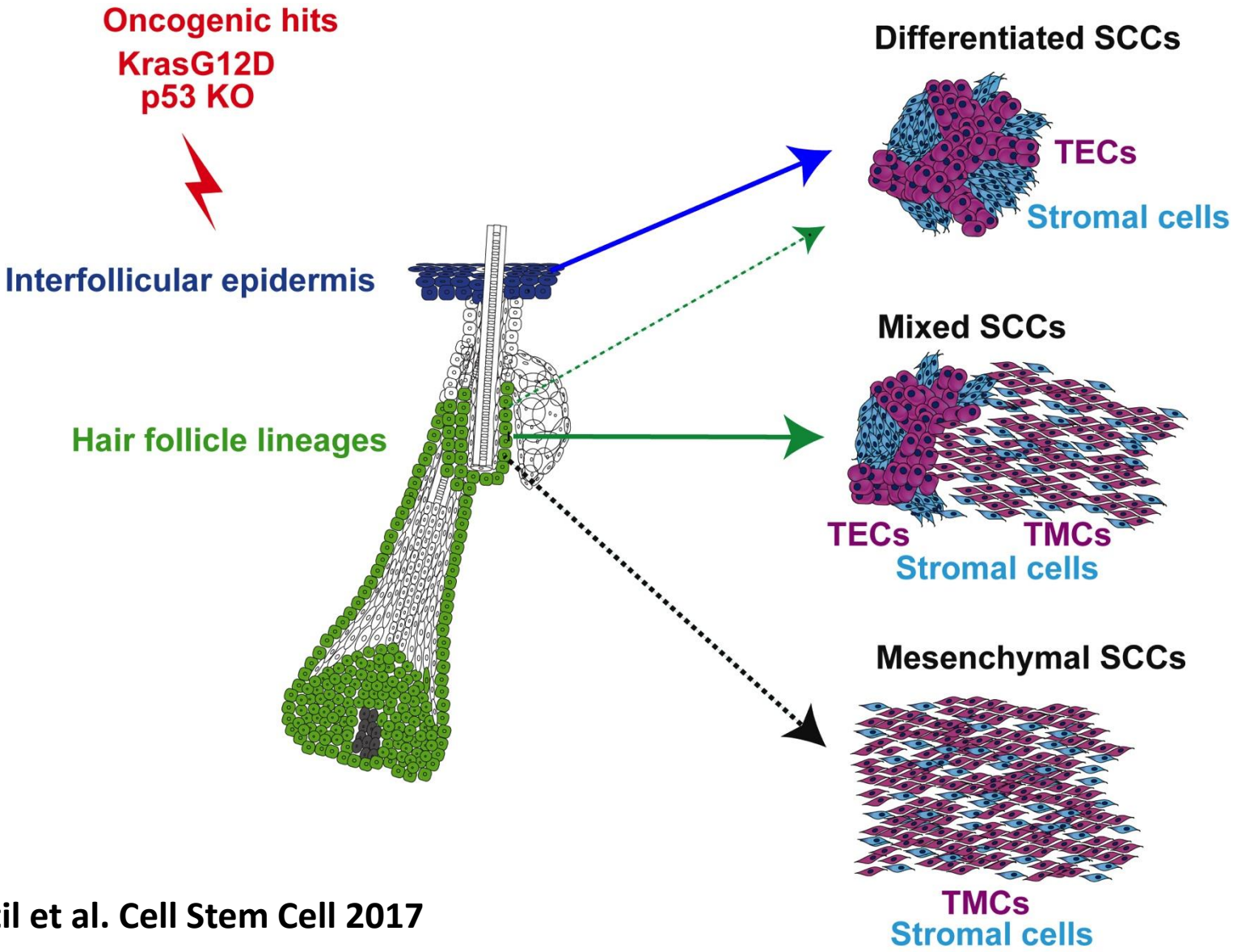
Mathilde Latil, PhD Dany Nassar, PhD

Tumor A = Tumor B?



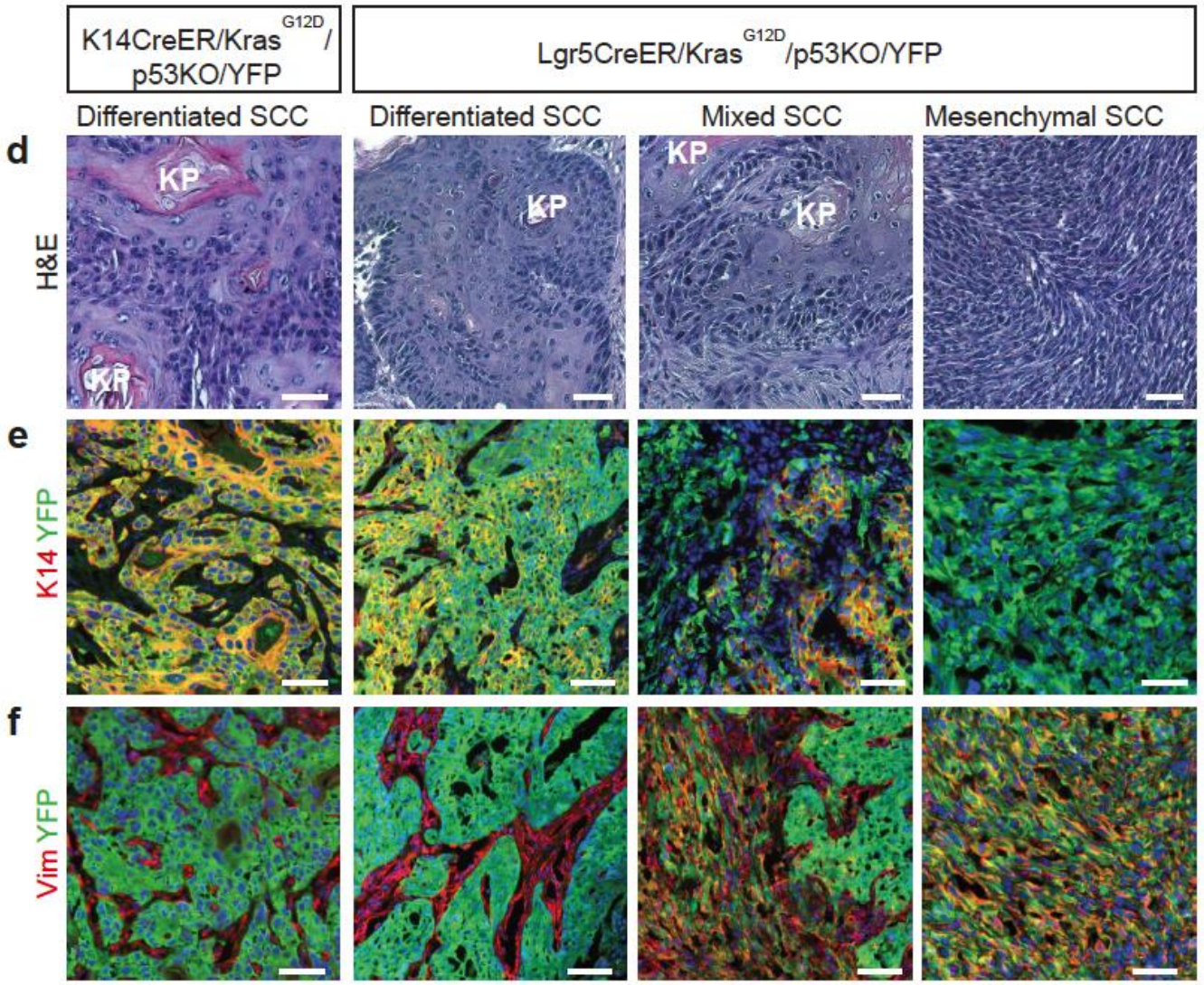


The cellular origin of skin SCC controls EMT related tumour heterogeneity



Latil et al. Cell Stem Cell 2017

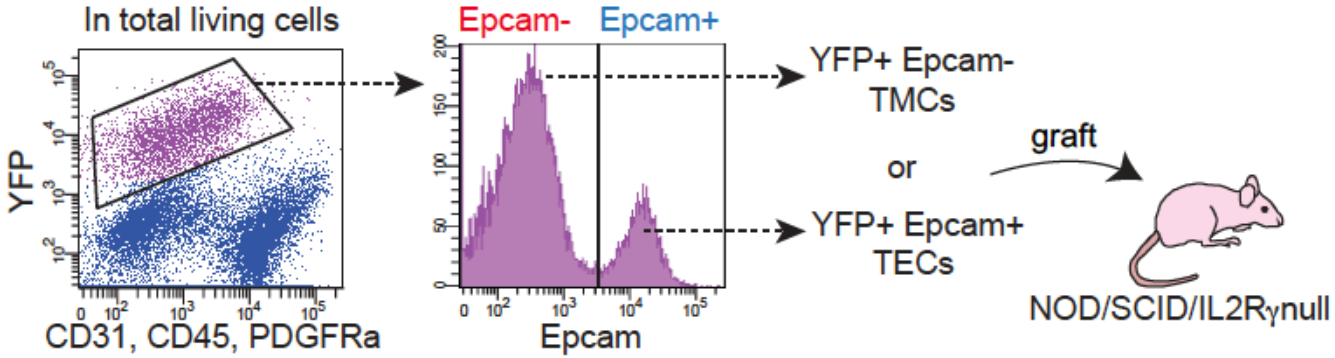
IFE and hair follicle stem cells give rise to distinct tumor phenotypes upon KRasG12D/p53KO



Epithelial features

Mesenchymal features

Increased tumor propagation during EMT



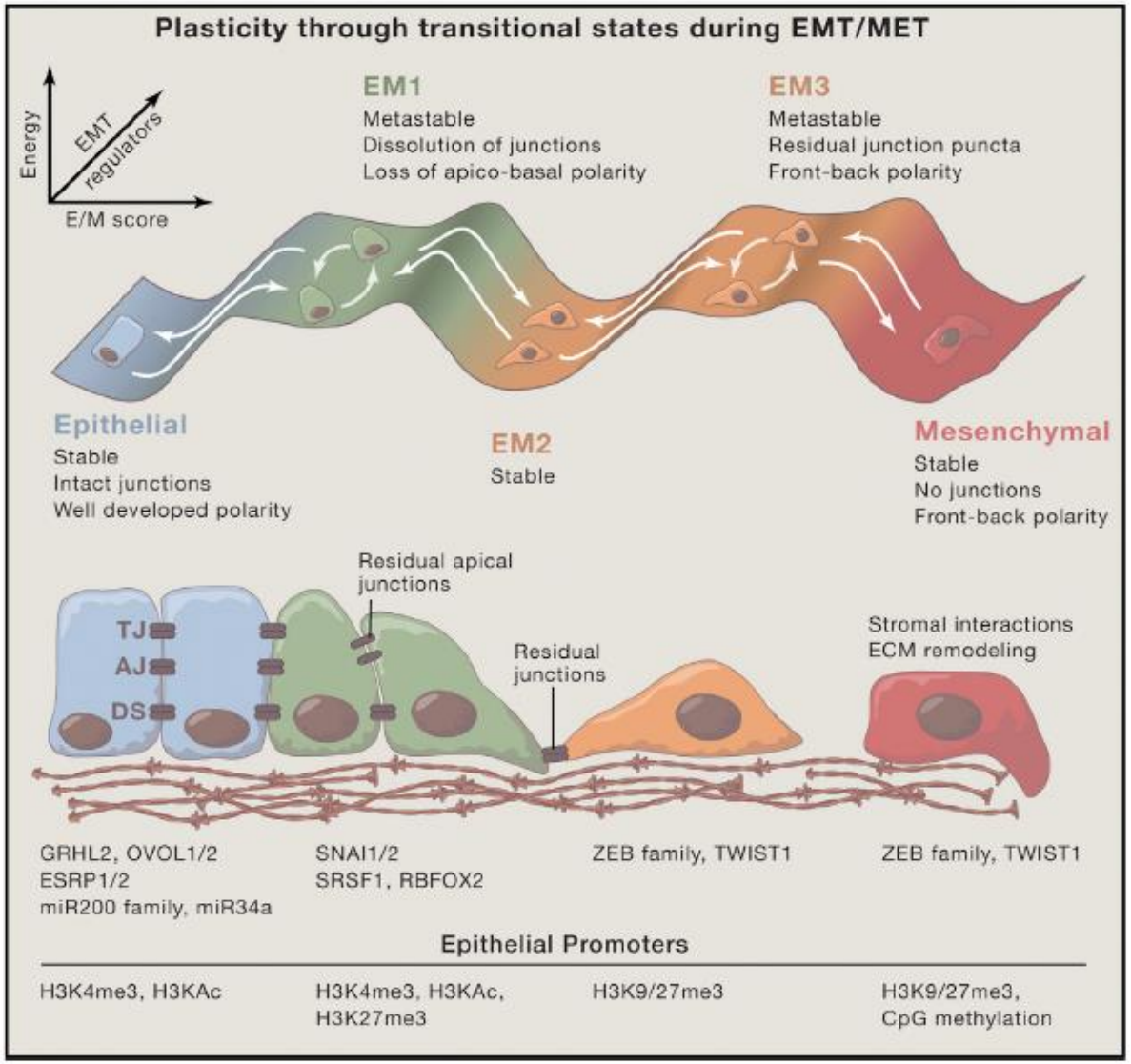
	K14CreER/Kras^{G12D}/ p53KO/YFP	Lgr5CreER/Kras^{G12D}/p53KO/YFP		
Number of grafted cells	**YFP+ Epcam+**	**YFP+ Epcam+**	**YFP+ Epcam-**	**YFP+ Total**
1000	28/33 (n=11)	31/36 (n=12)	29/30 (n=10)	22/24 (n=8)
100	19/30 (n=10)	6/21 (n=7)	20/24 (n=8)	9/12 (n=4)
10	5/24 (n=8)	4/21 (n=7)	12/15 (n=5)	3/18 (n=6)
TPC frequency	**1/271** (1/413-1/177)	**1/407** (1/600-1/276)	**1/71** (1/113-1/44)	**1/220** (1/404-1/120)

p=0,106 p=2,23.10^{-10}

p=3,86.10^{-7}

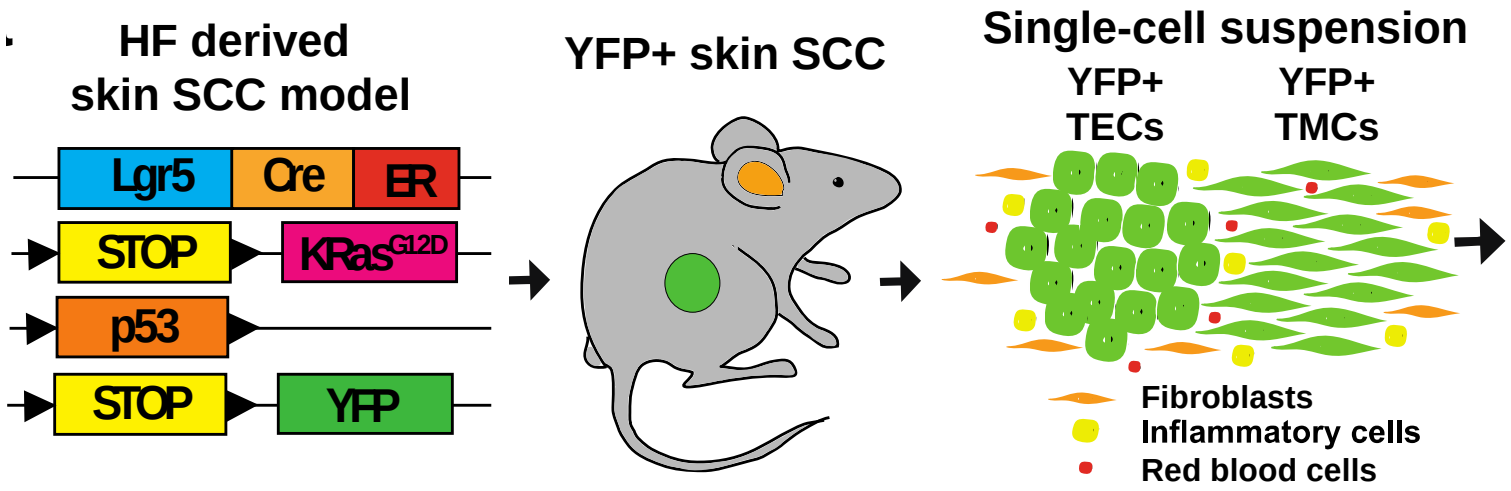
Latil et al. Cell Stem Cell 2017

Does EMT occur through distinct transitional states ?

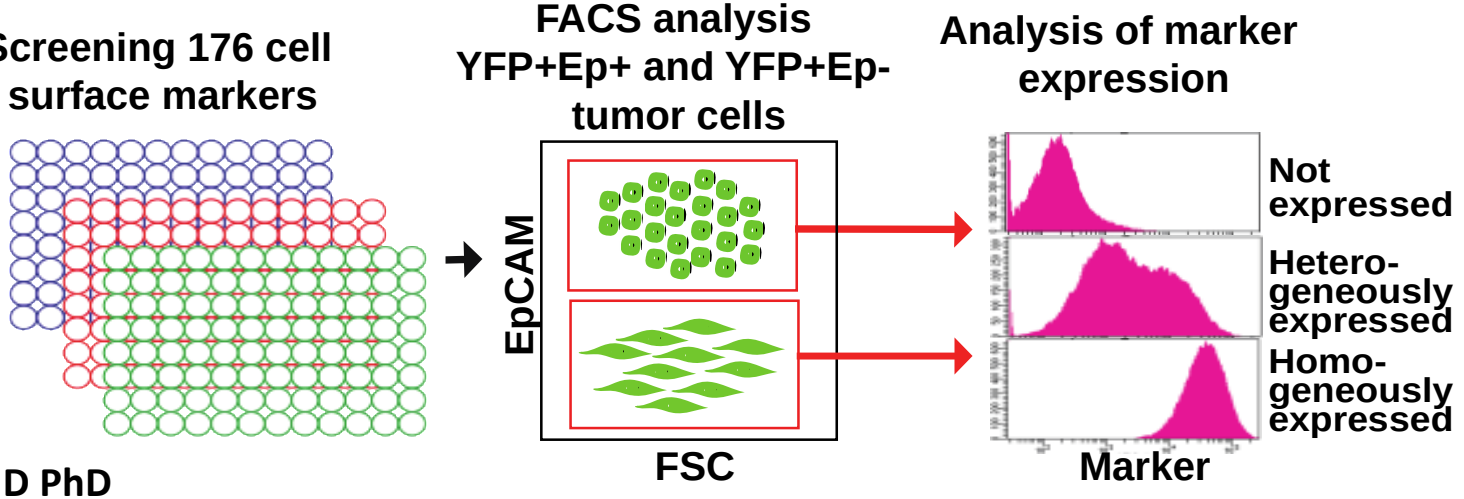


Nieto et al. Cell 2016

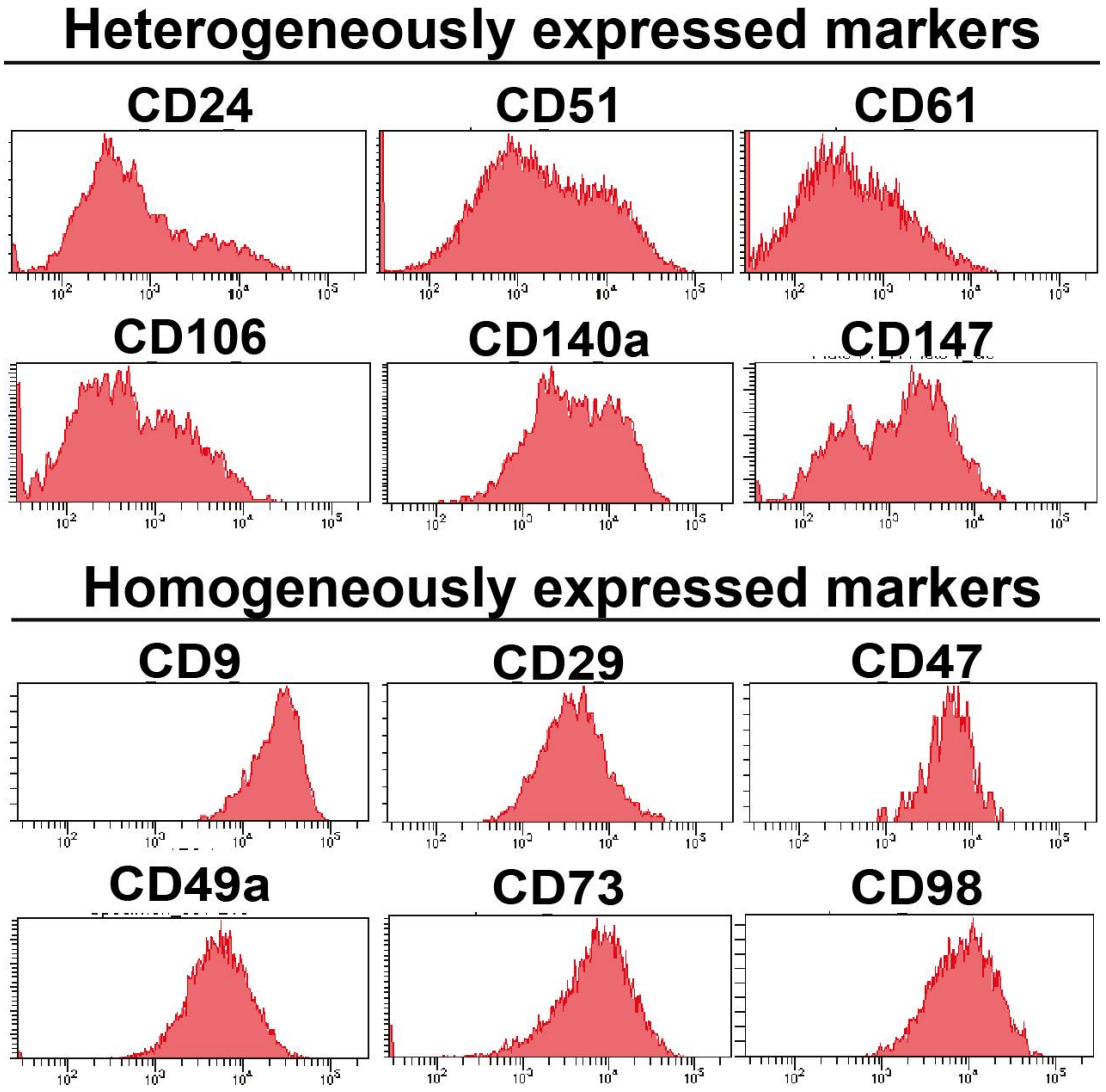
Identification of the tumor transition states occuring during EMT in vivo

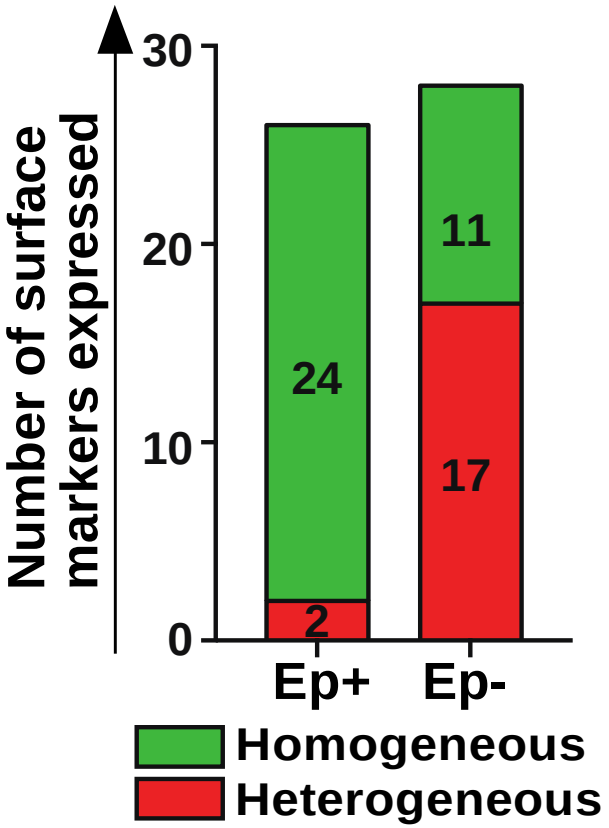


Eugenia Pastushenko, MD PhD

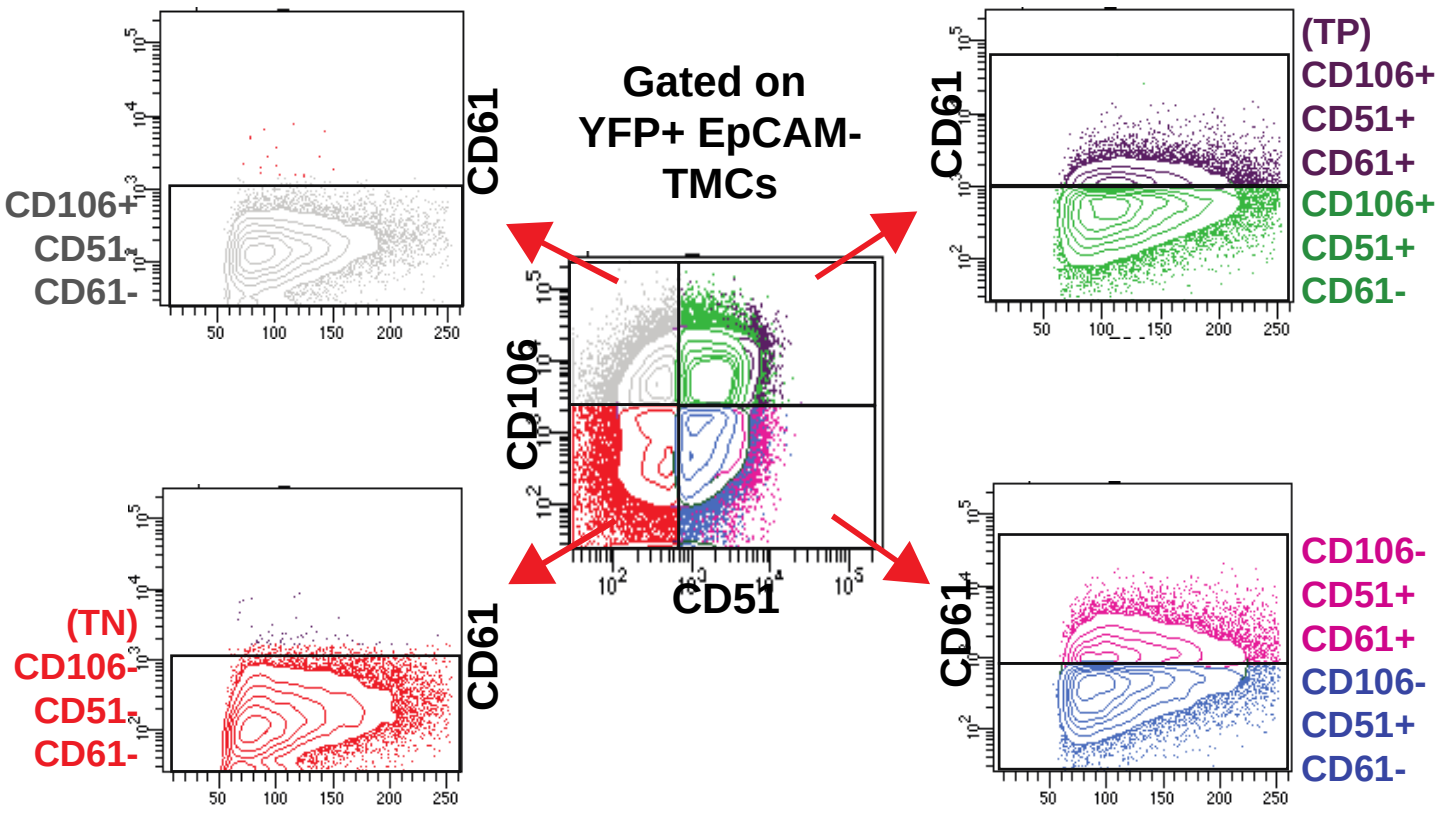


Identification of cell surface markers heterogenously expressed during EMT in vivo

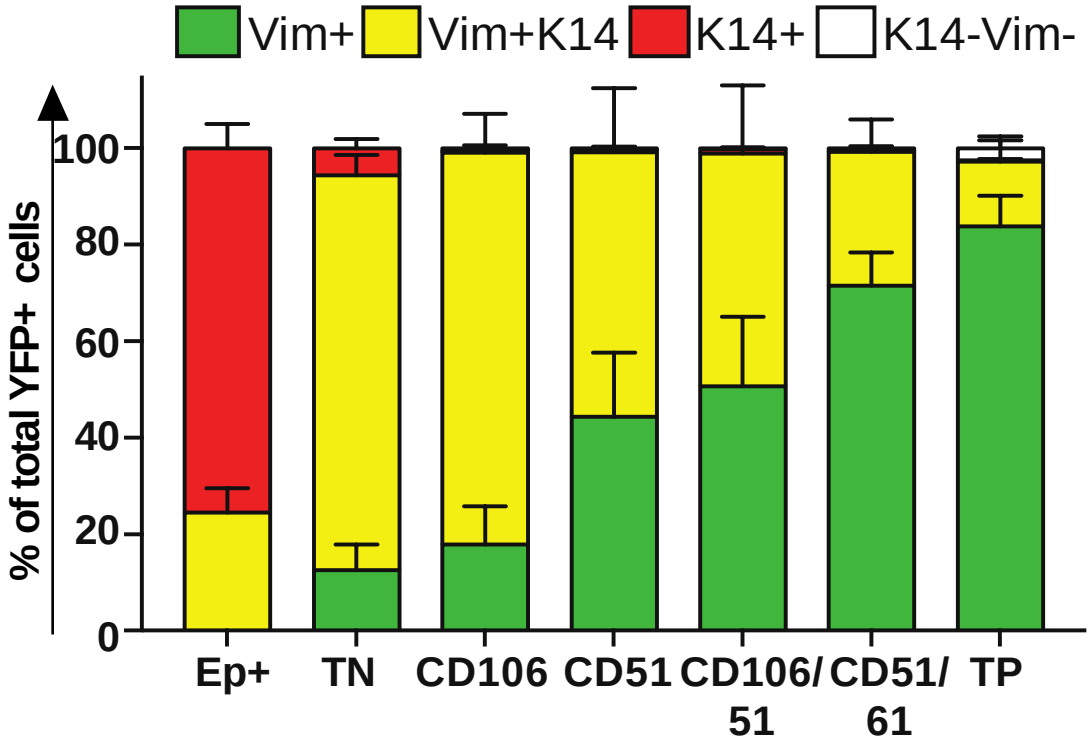


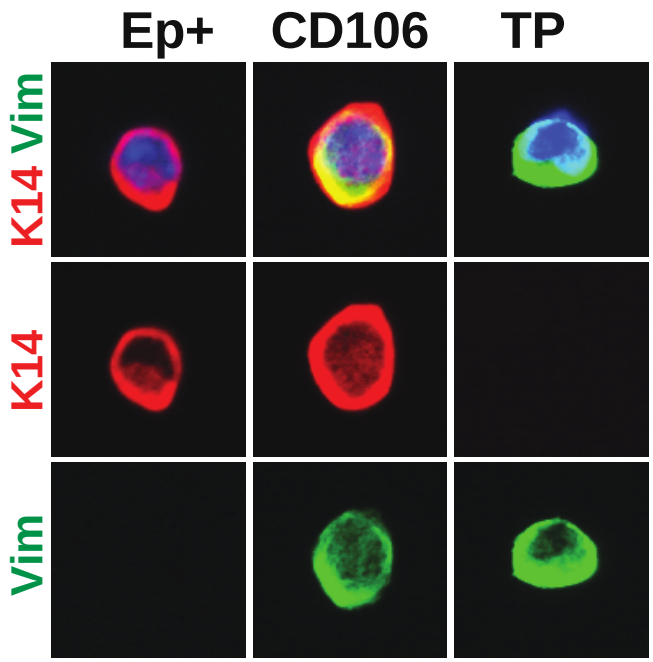


Identification of the tumor transition states occuring during EMT in vivo



Uncovering the order of transition during EMT





EMT transition states present similar TPC capacity but exhibit different plasticity

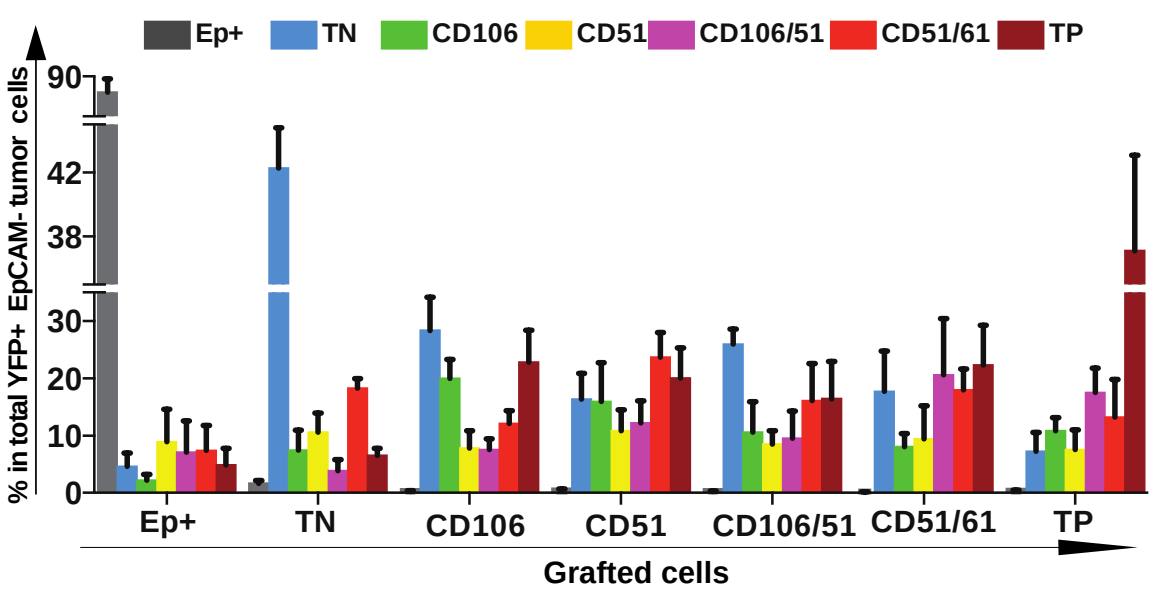
Number of grafted cells	Ep+	Ep-	TN	CD106	CD51	CD106/51	CD51/61	TP
1000	7/9 (n=3)	10/12 (n=3)	9/12 (n=2)	15/17 (n=2)	12/15 (n=3)	6/6 (n=2)	14/18 (n=3)	10/12 (n=2)
100	1/9 (n=3)	15/18 (n=4)	23/24 (n=4)	17/24 (n=4)	3/3 (n=3)	13/18 (n=3)	19/24 (n=3)	13/17 (n=4)
10	1/9 (n=3)	18/24 (n=3)	7/30 (n=4)	21/46 (n=4)	14/19 (n=3)	6/18 (n=3)	14/30 (n=3)	12/21 (n=3)
TPC frequency	**1/614** (1/1266-1/297)	**1/93** (1/159-1/54)	**1/146** (1/246-1/86)	**1/99** (1/156-1/63)	**1/130** (1/246-1/68)	**1/59** (1/99-1/35)	**1/168** (1/285-1/99)	**1/124** (1/226-1/69)

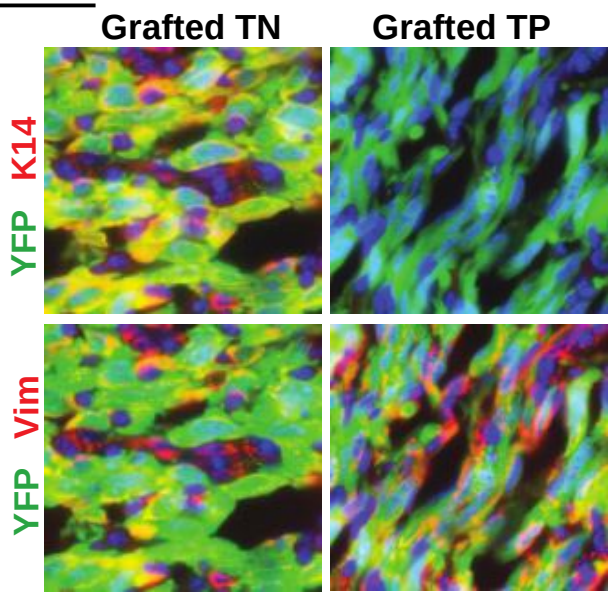
p= 0.004-3.35e-08

p=0.0049

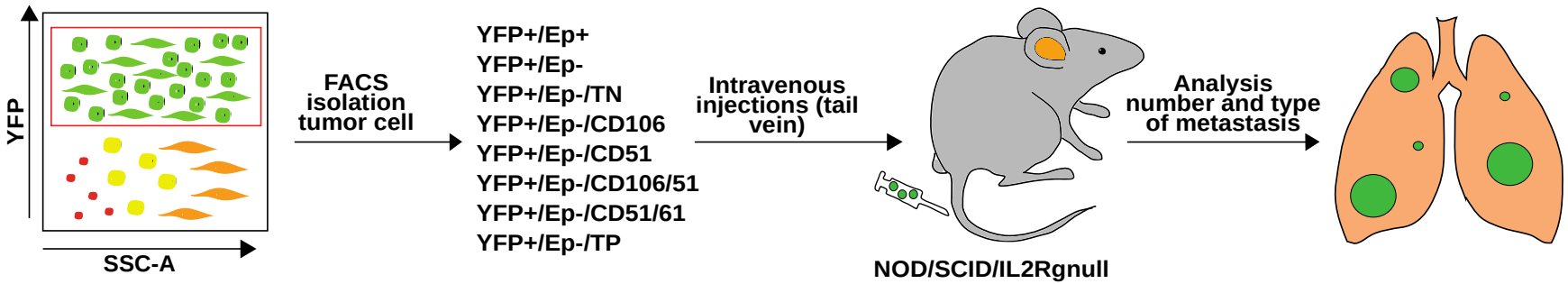
p=0.001

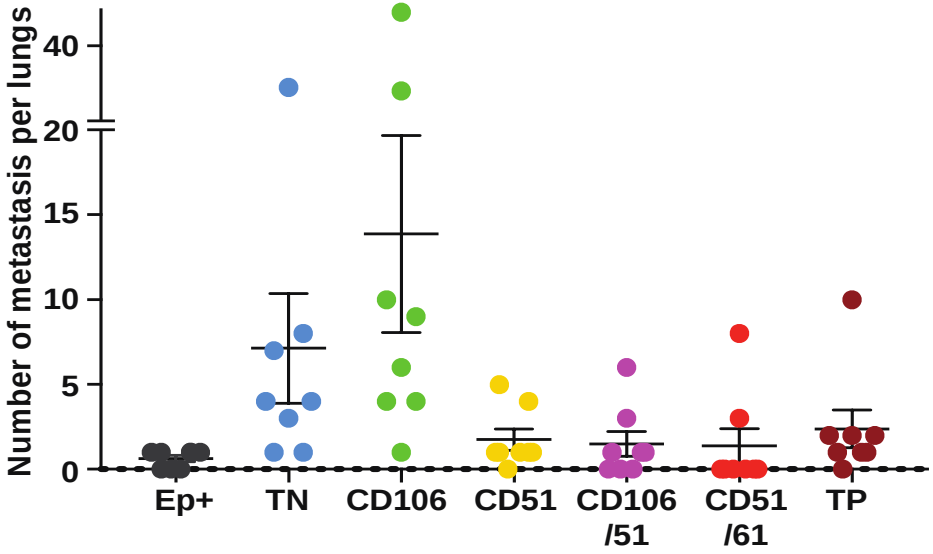
c

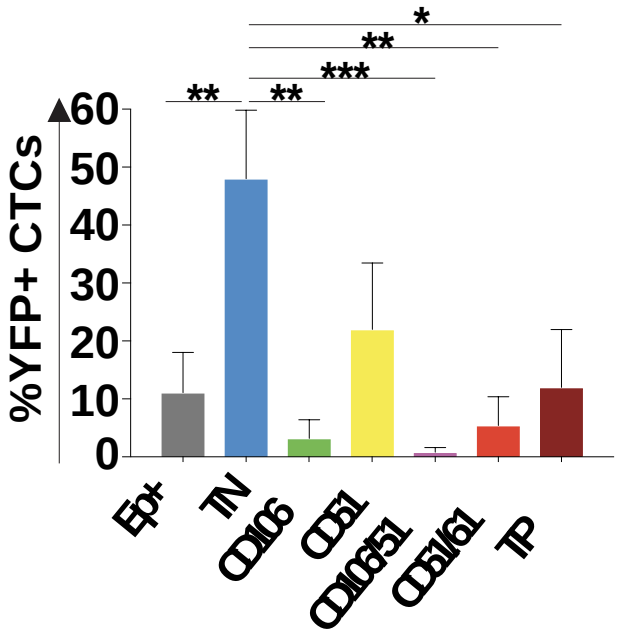




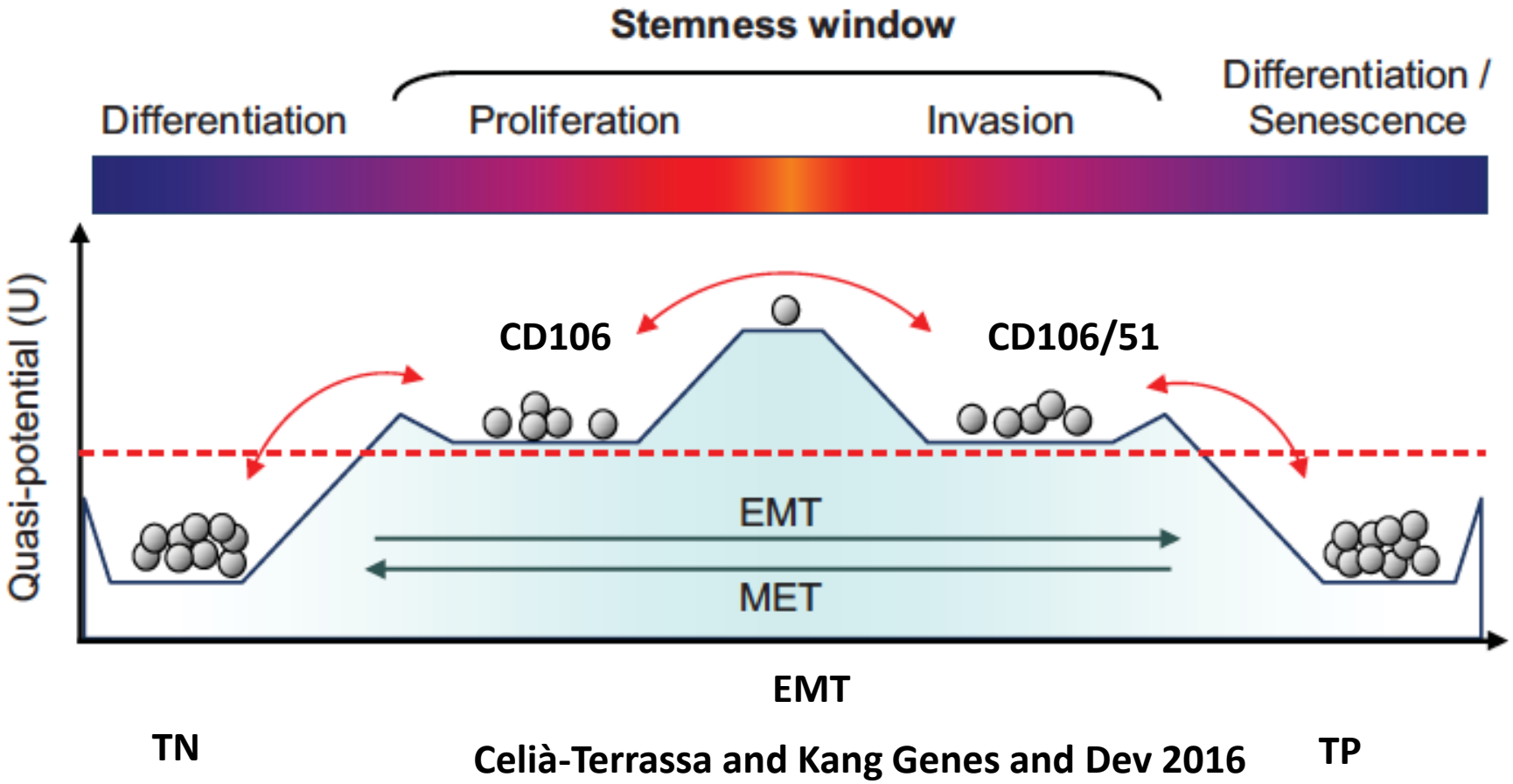
Different EMT transition states present different metastatic potential







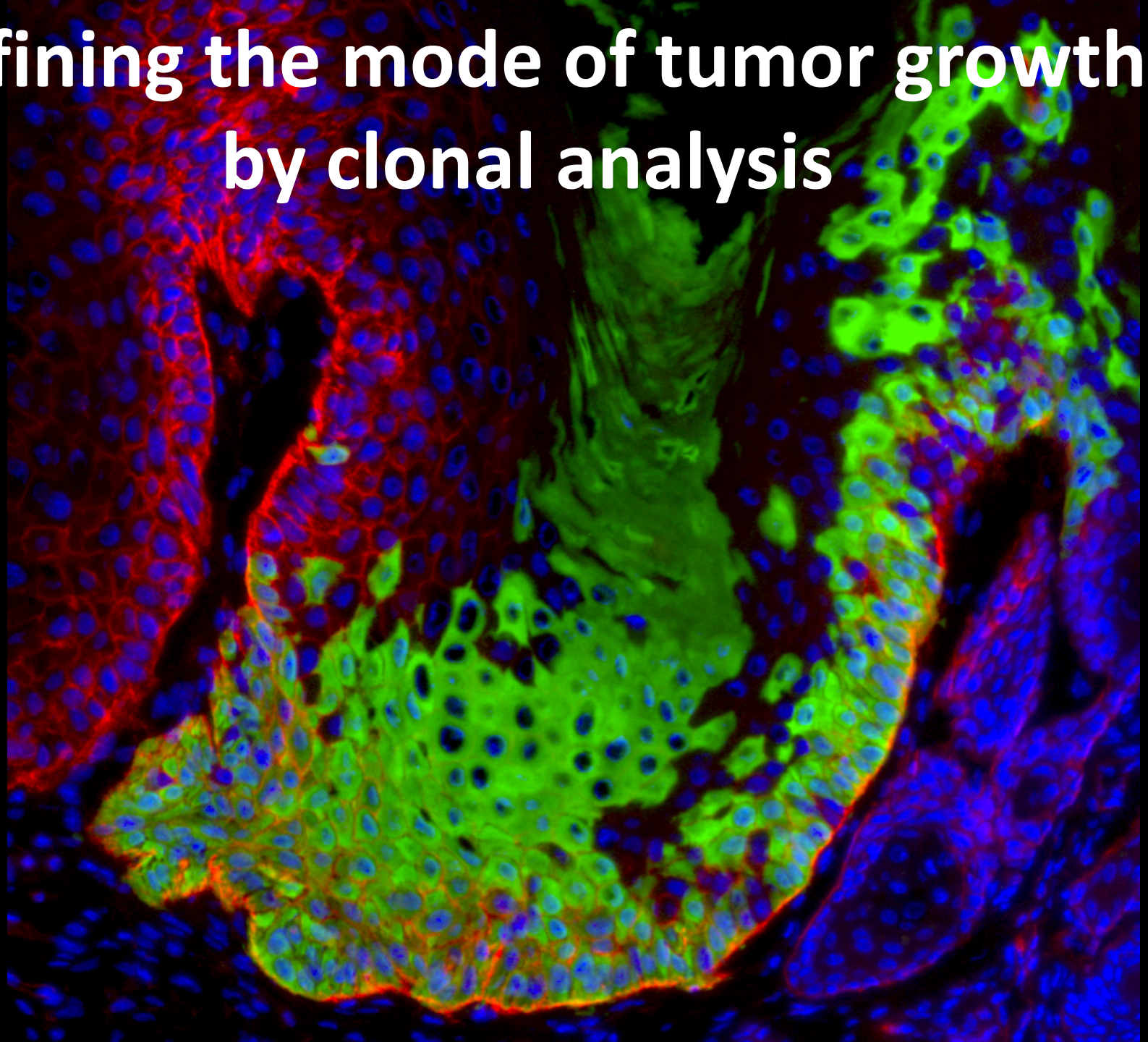
Transition through the different EMT states



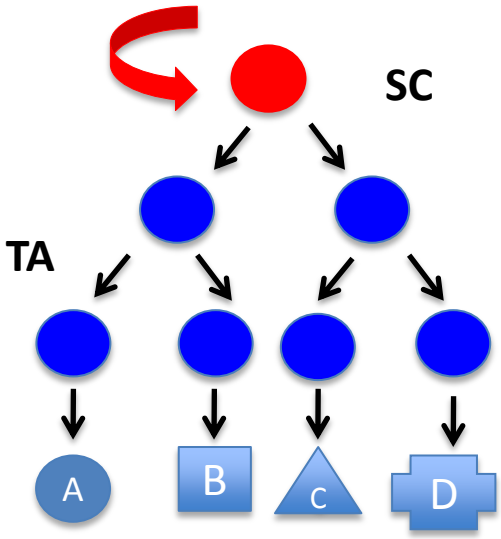
Celià-Terrassa and Kang Genes and Dev 2016

Pastushenko Nature 2018 in press

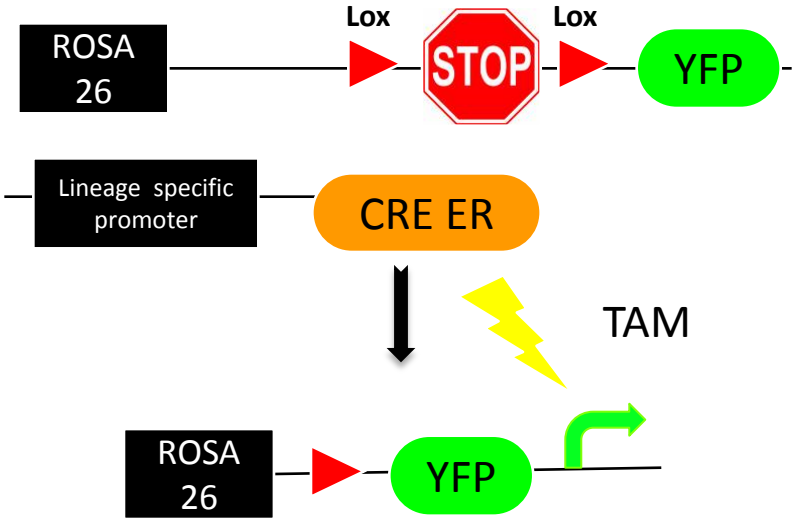
Defining the mode of tumor growth by clonal analysis



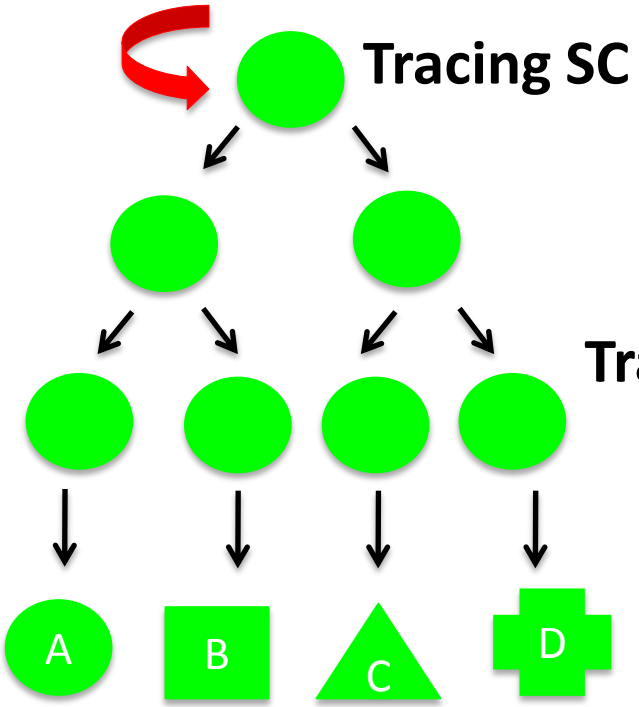
Lineage tracing SC and their progeny



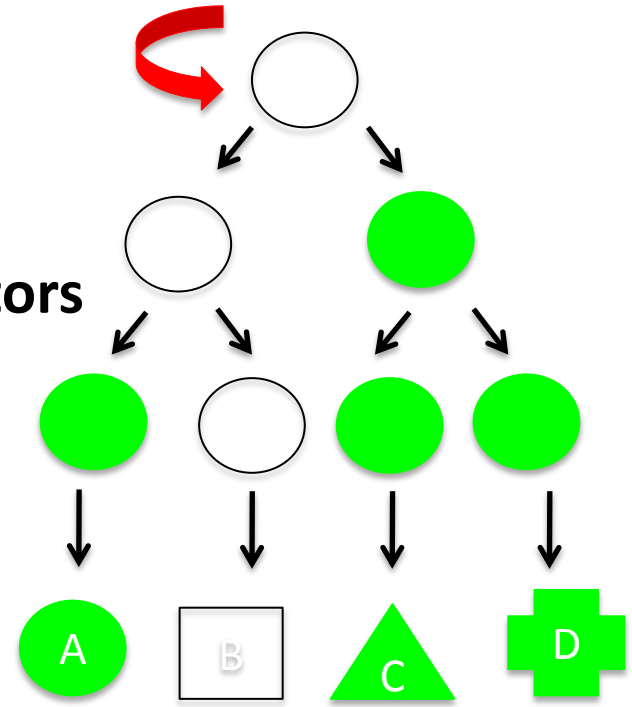
Differentiated cells



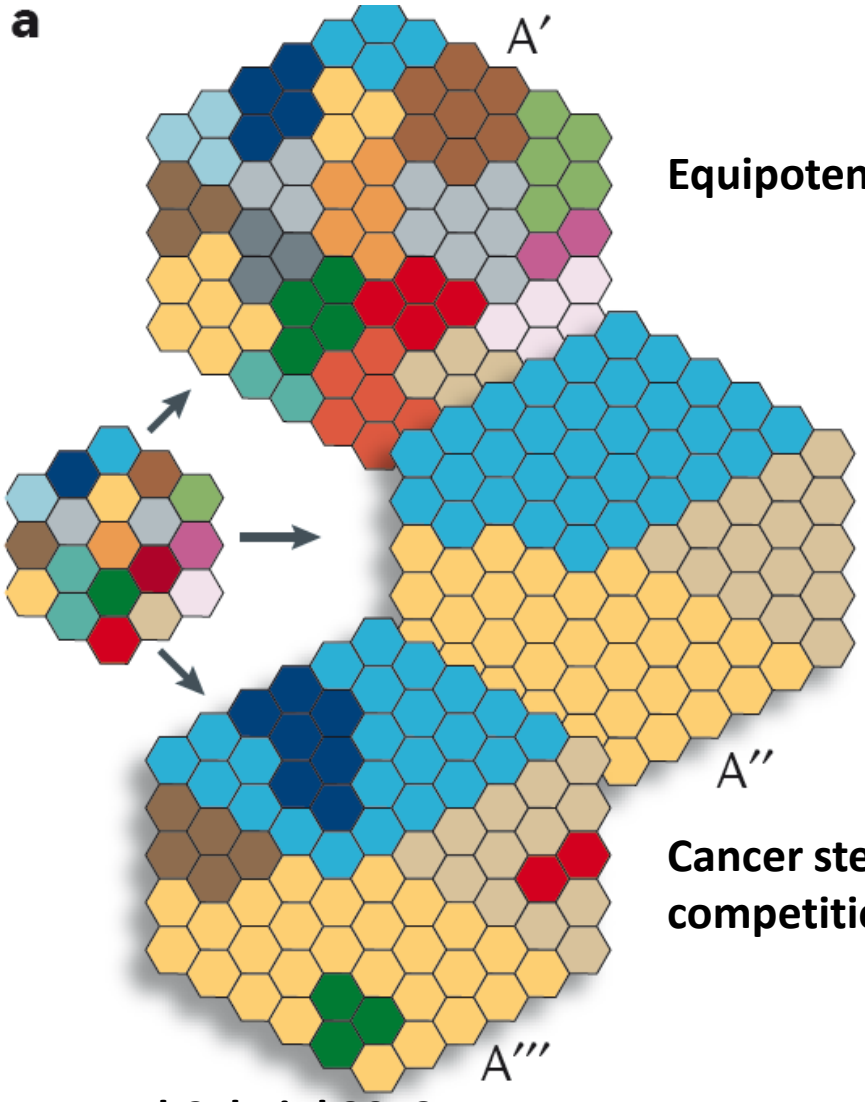
Tracing SC



Tracing progenitors



Clonal tracing to define the mode of tumor growth



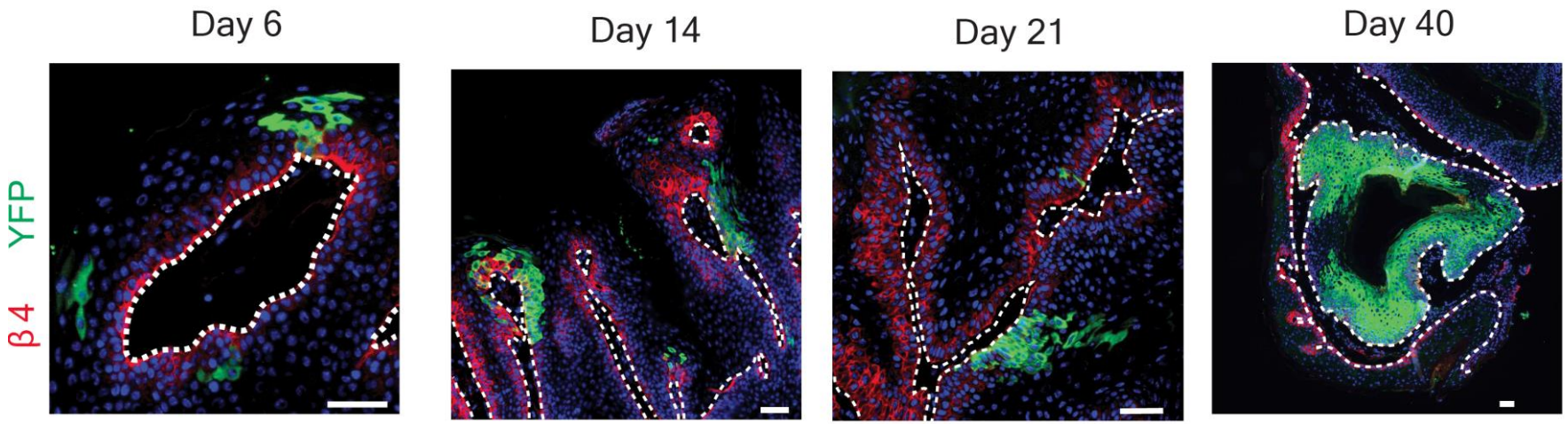
Equipotency

Cancer stem cell

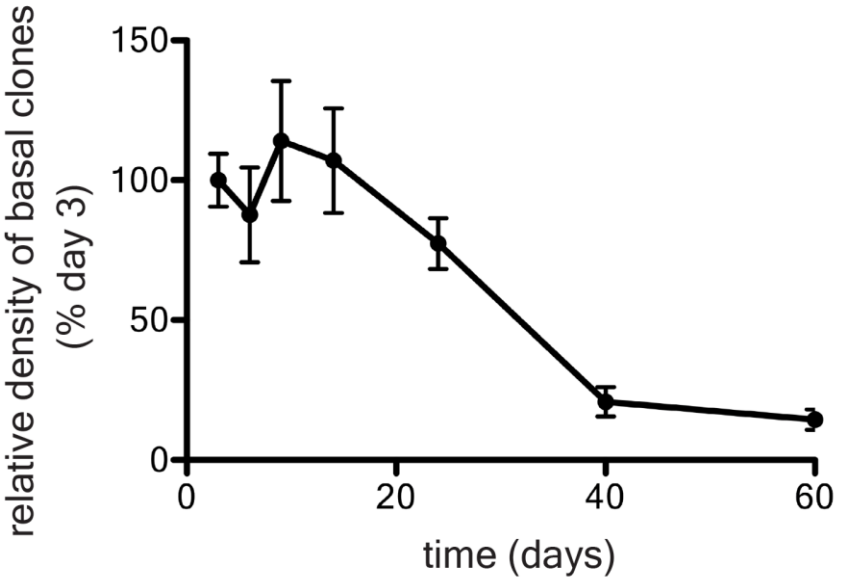
Cancer stem cell with neutral cell competition

Blanpain & Simons Nat Rev Mol Cel Biol 2013

Most tumor clones disappear over time together with the emergence of dominant clones

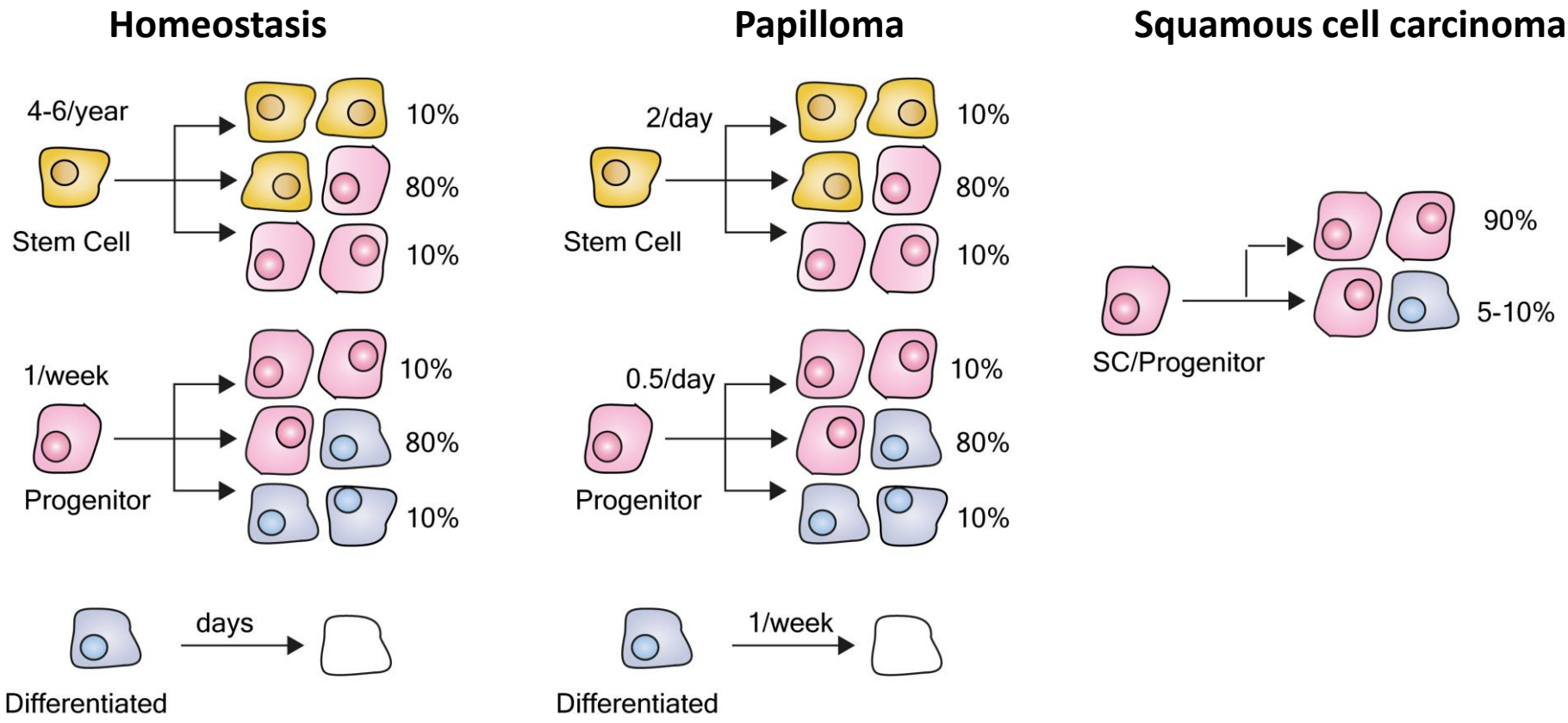


Gregory Driessens, PhD



Driessens et al. Nature 2012

Changes in the proliferation dynamics during skin tumor progression



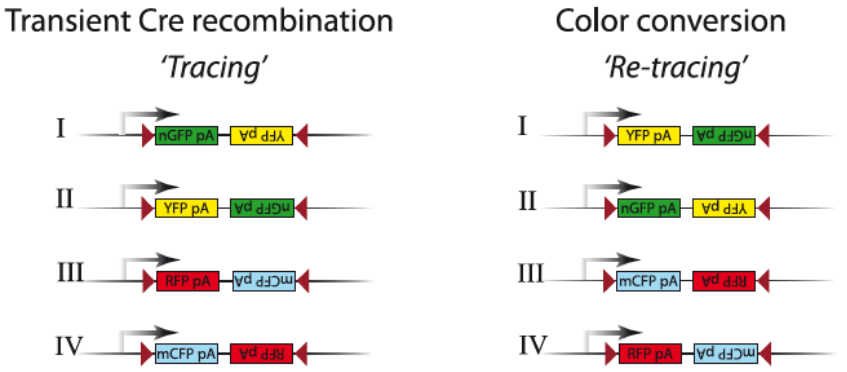
Driessens et al. Nature 2012

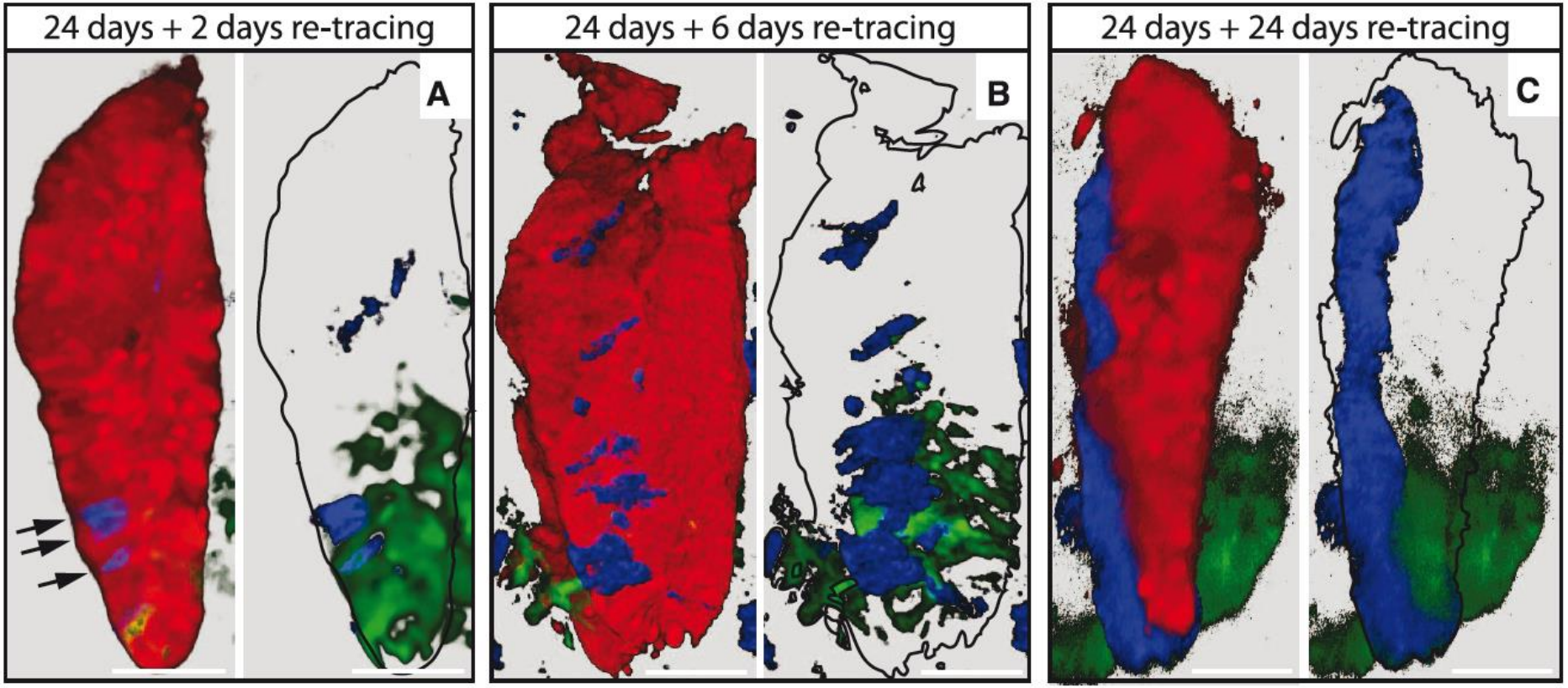
Mascré et al. Nature 2012

Lineage Tracing Reveals Lgr5^{+} Stem Cell Activity in Mouse Intestinal Adenomas

Arnout G. Schepers,* Hugo J. Snippert,*† Daniel E. Stange, Maaike van den Born
Johan H. van Es, Marc van de Wetering, Hans Clevers‡

10 AUGUST 2012 VOL 337 **SCIENCE**



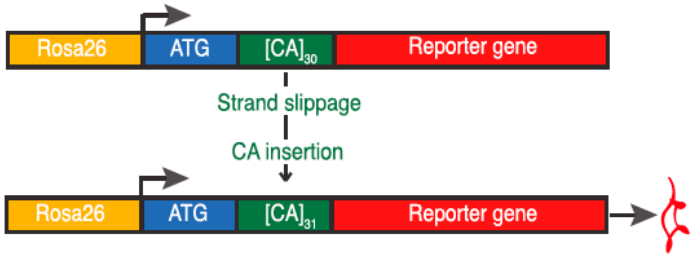


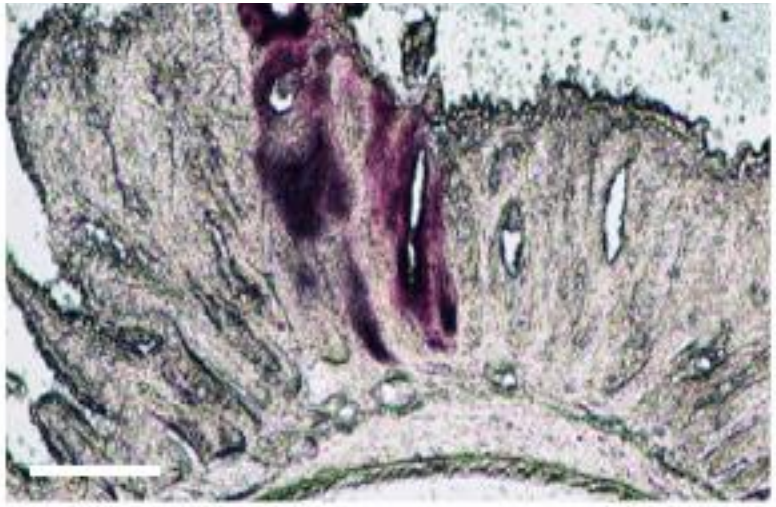
Continuous Clonal Labeling Reveals Small Numbers of Functional Stem Cells in Intestinal Crypts and Adenomas

Sarah Kozar,[1,3] Edward Morrissey,[1,3] Anna M. Nicholson,[1] Maartje van der Heijden,[1,2] Heather I. Zecchini,[1] Richard Kemp,[1] Simon Tavaré,[1] Louis Vermeulen,[1,2] and Douglas J. Winton[1,*]

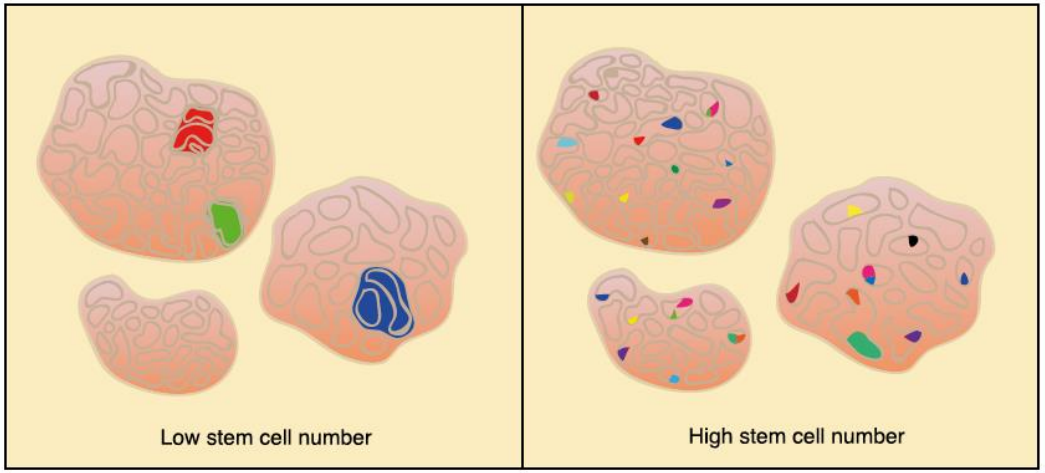
Cell Stem Cell *13*, 626–633, November 7, 2013

B





C

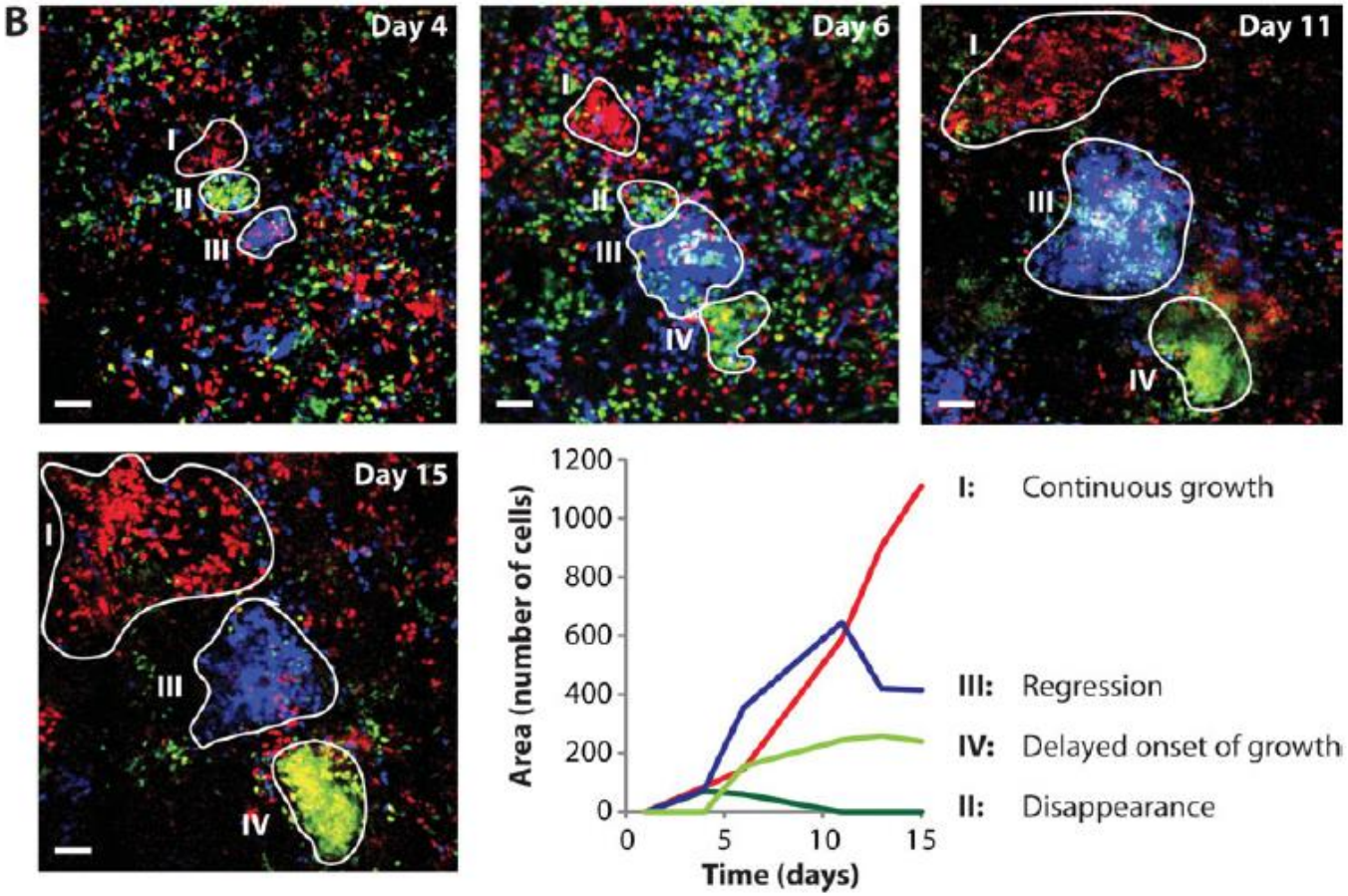


N_{gland} (Figure 3A). These data confirm the hypothesis that clones observed in adenomas are the result of a small number of stem cells per gland (Figure 3C).

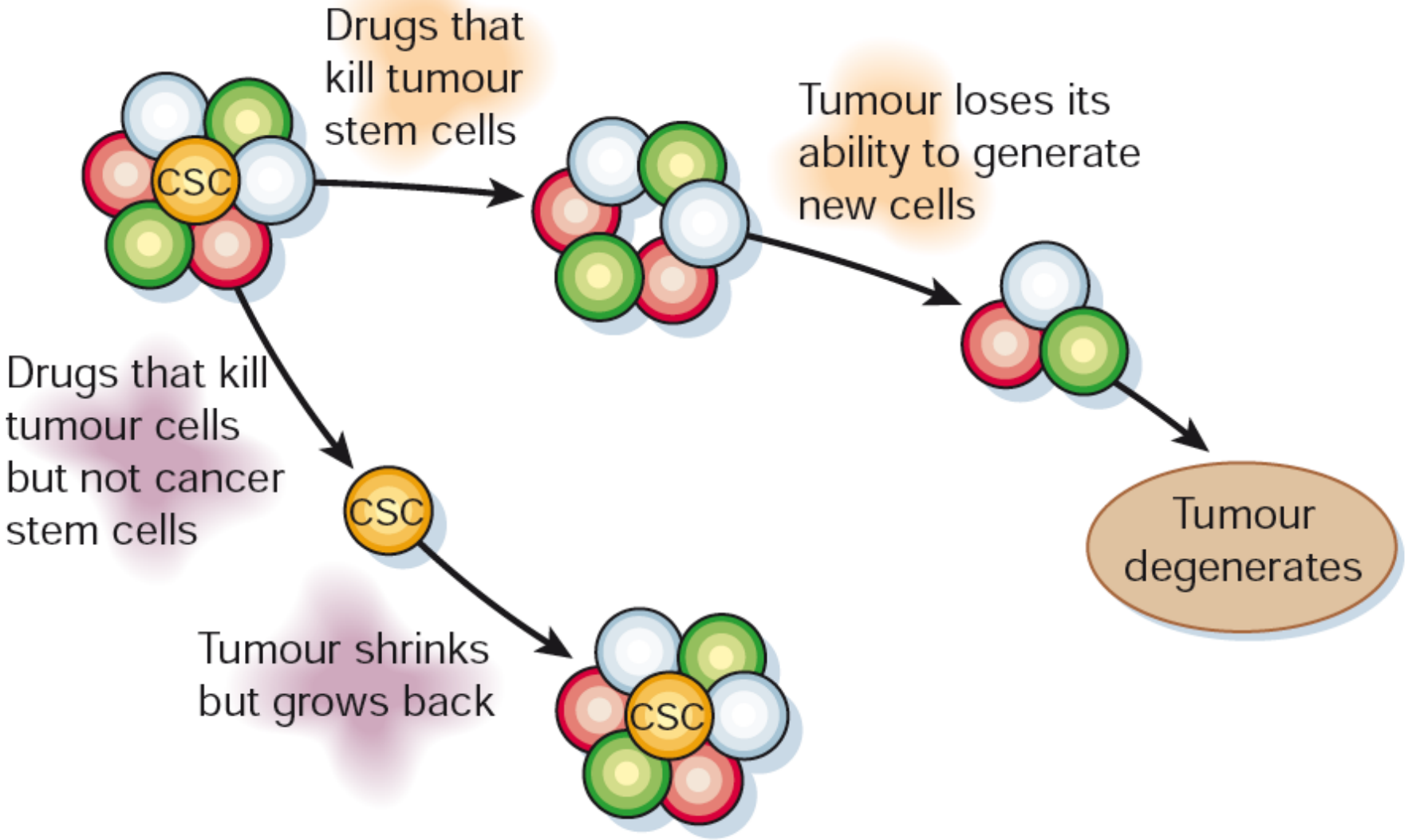
Brief Report: Intravital Imaging of Cancer Stem Cell Plasticity in Mammary Tumors

Anoek Zomer, Saskia Inge Johanna Ellenbroek, Laila Ritsma, Evelyne Beerling, Nienke Vrisekoop, Jacco Van Rheenen

Stem Cells 2013;31:602–606

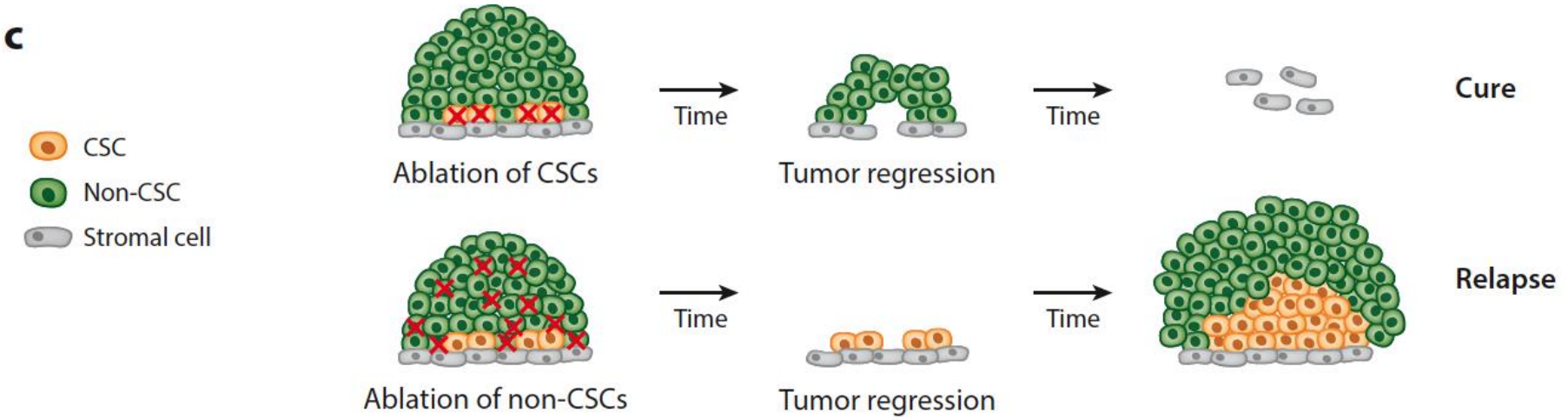


Cancer stem cells: implications for therapy



Reya et al. Nature 2001

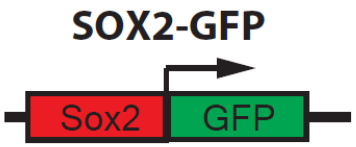
Unraveling the role of cancer stem cell by lineage ablation experiments

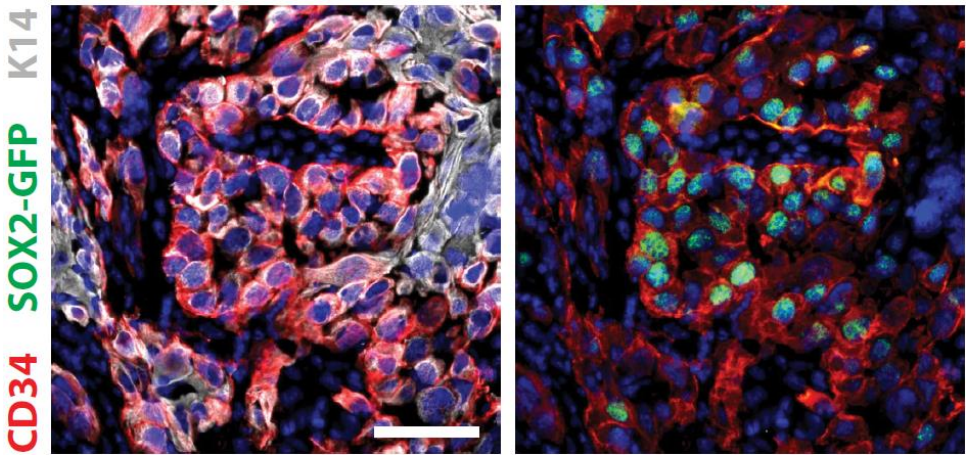


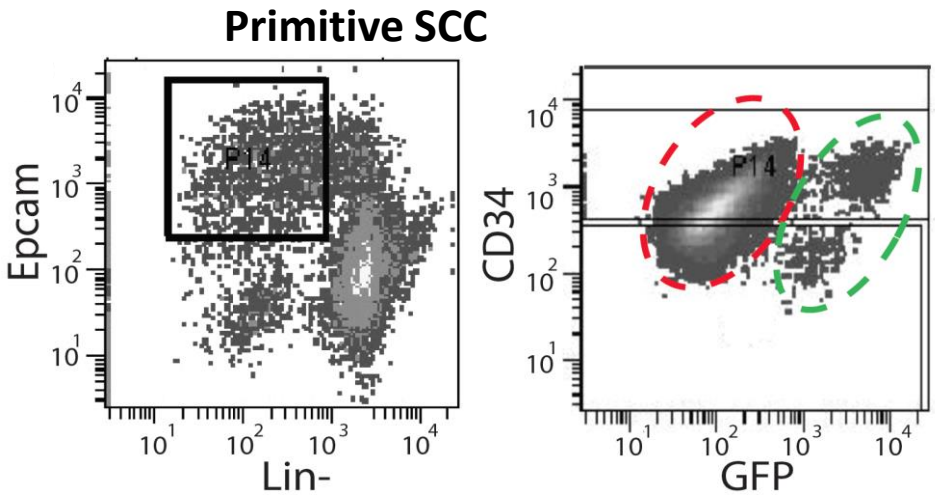
Nassar & Blanpain Annual Reviews of Pathology 2016

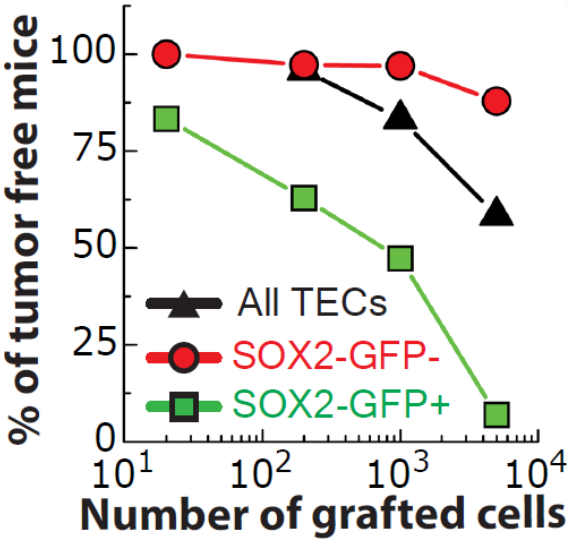
Sox2-GFP expressing cells are greatly enriched in tumor propagating cells in skin cancers

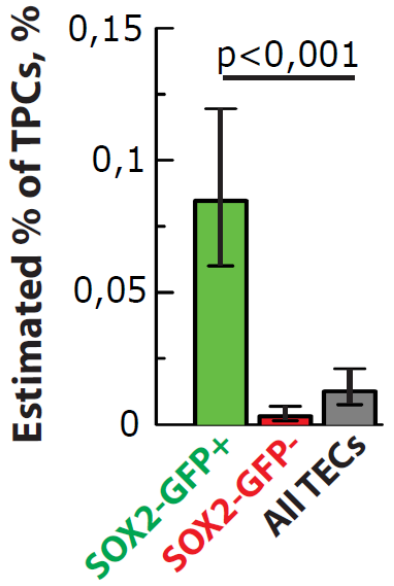
Soufiane Boumhadi



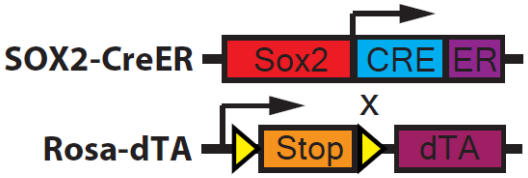


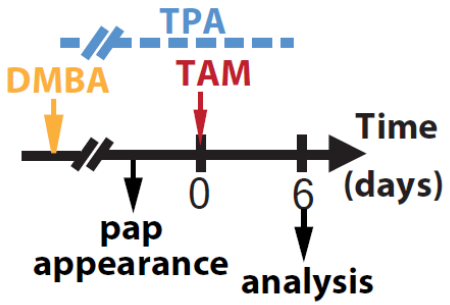




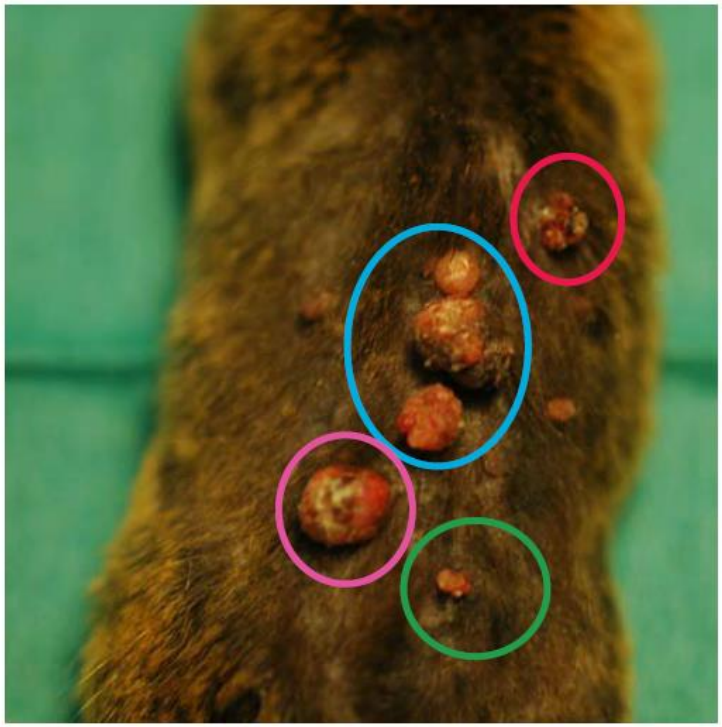


Lineage ablation of Sox2 expressing cells leads to tumor regression

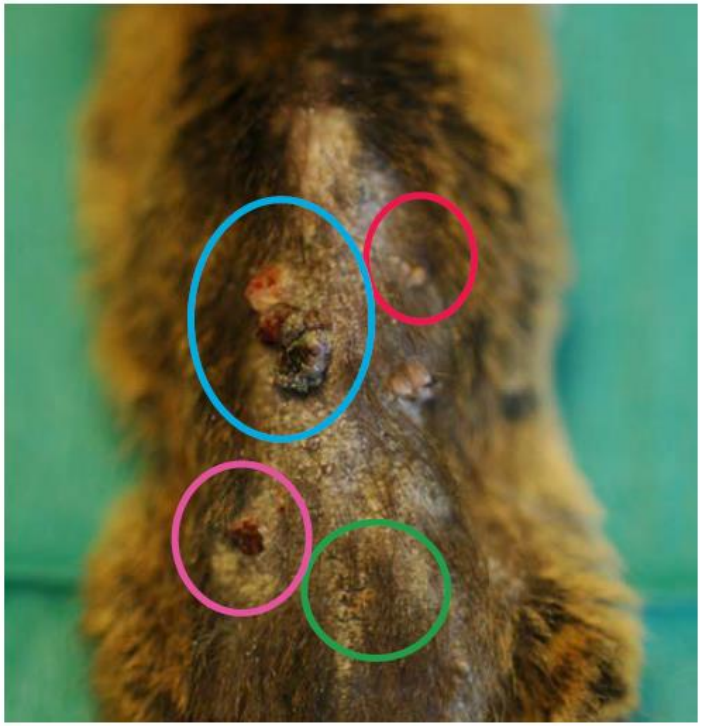




Before TAM

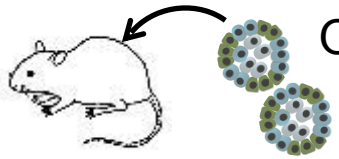


TAM 1 week

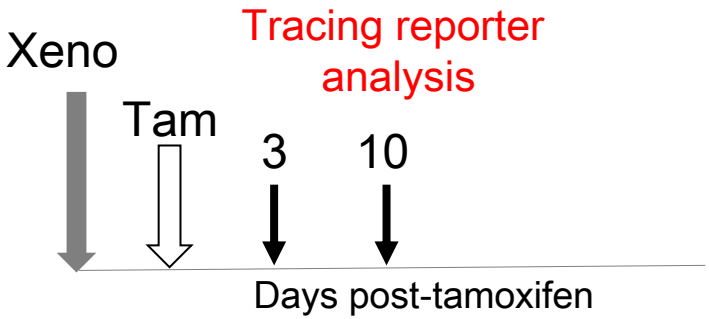


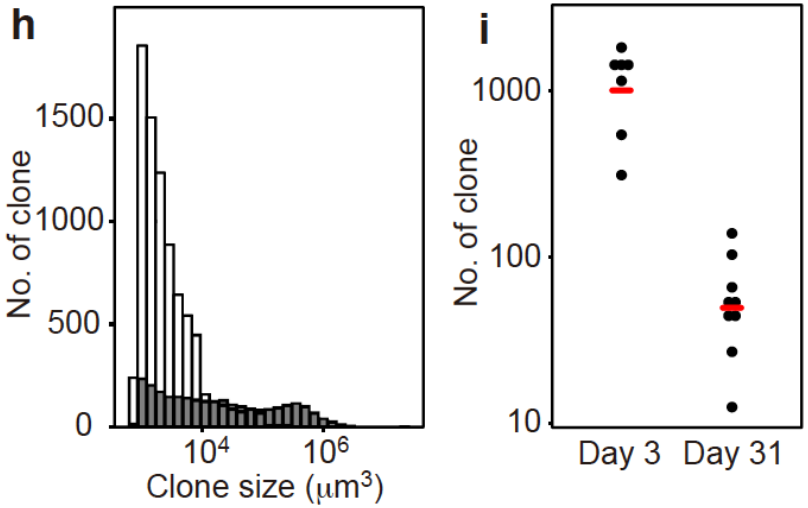
Boumhadi, et al. Nature 2014

LGR5+ marks CSCs in human CRCs

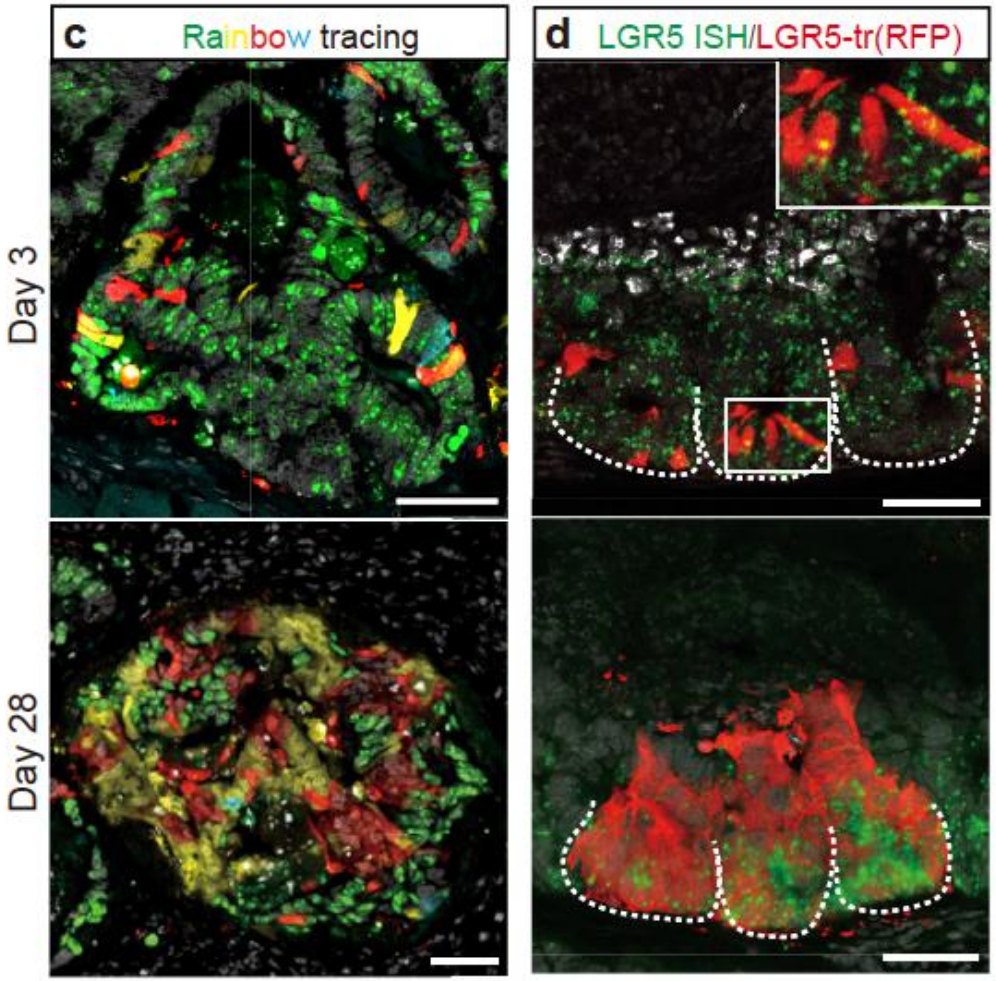


LGR5-CreER/Rainbow
Organoids



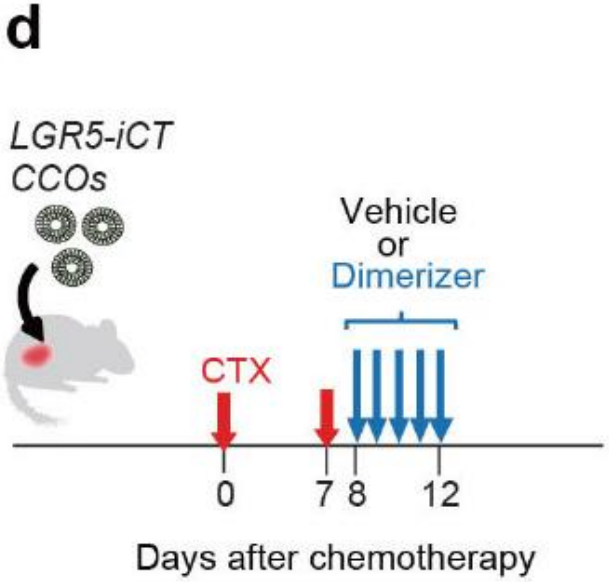


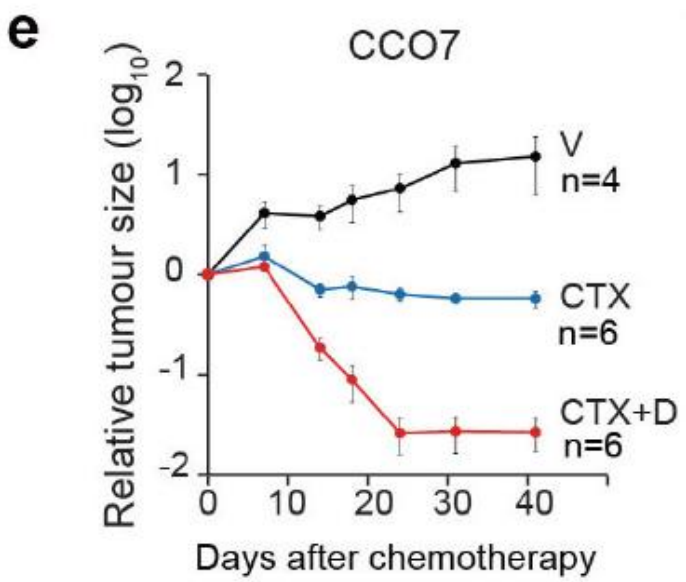
RFP: Tracing reporter

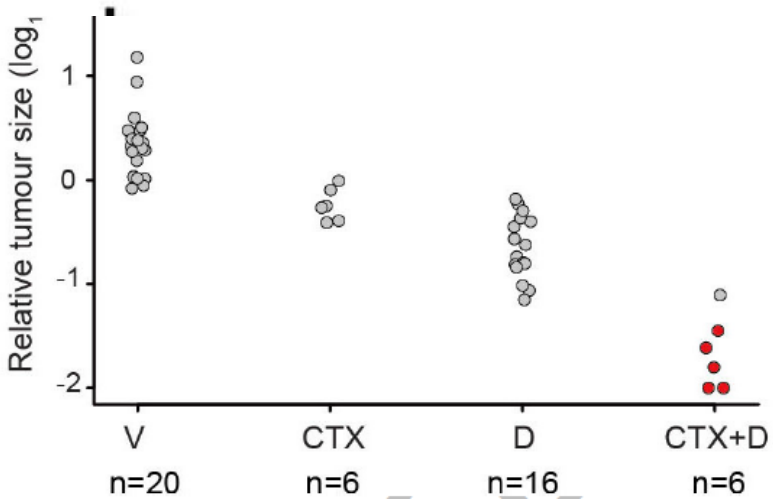


Shimokawa Nature 2017

Synergy between LGR5+ CSC Targeting and conventional chemotherapy

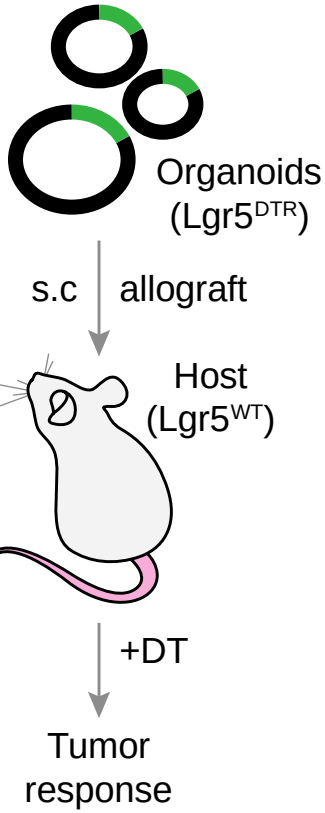


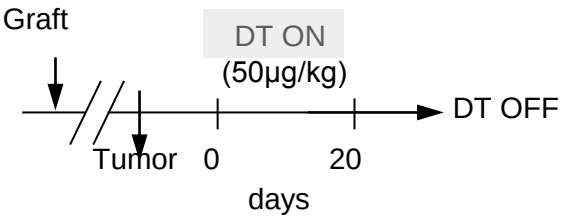


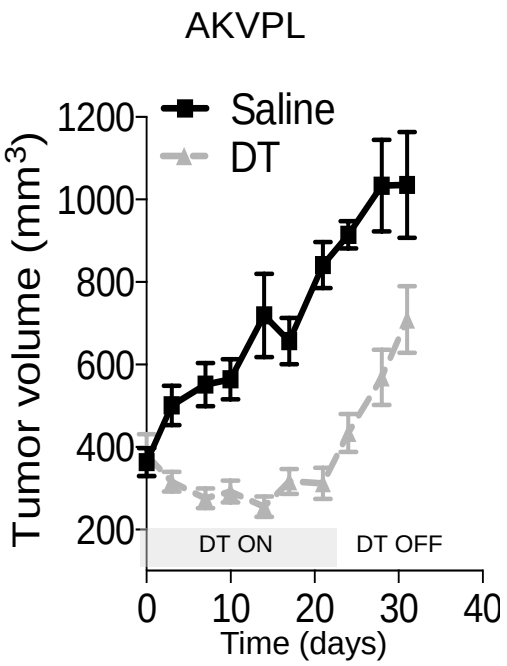


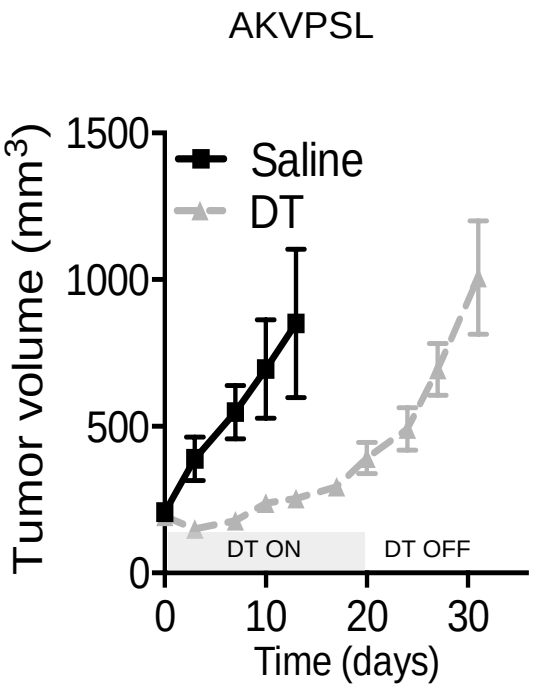
Shimokawa Nature 2017

LGR5+ cells depletion decreases tumor growth



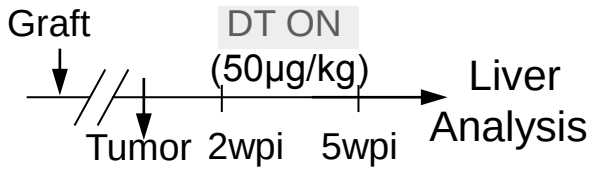




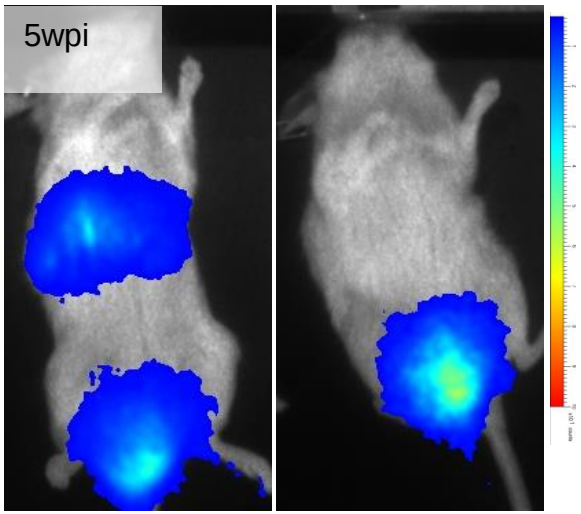


F. de Sousa e Melo et al. Nature 2017

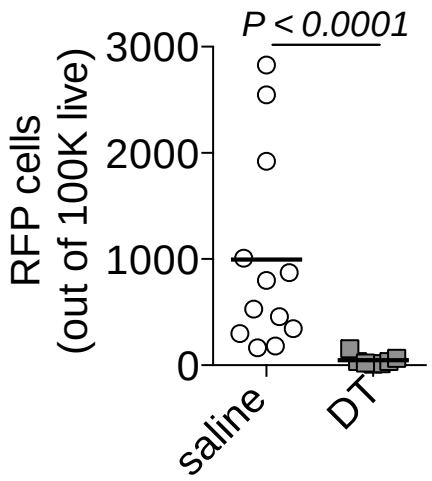
Lgr5+ cells are critical for metastasis formation



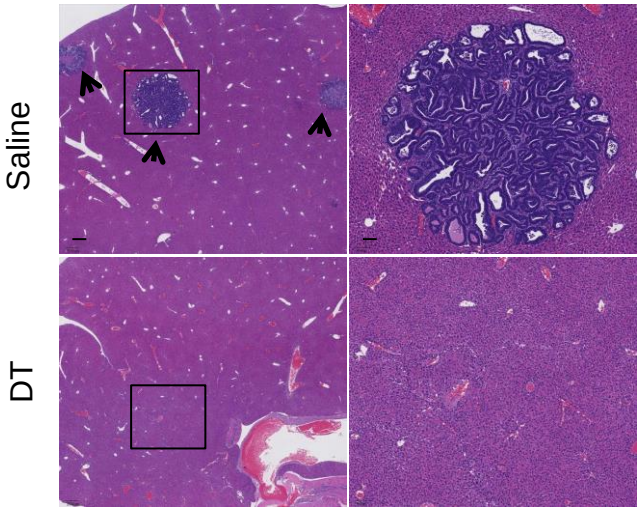
BLI



FACS

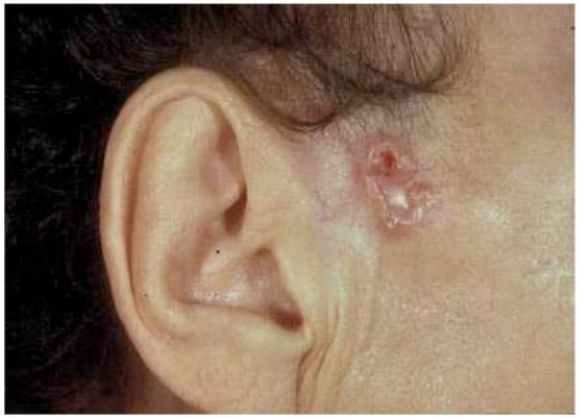


Histology



F. de Sousa e Melo et al. Nature 2017

BCC current treatments



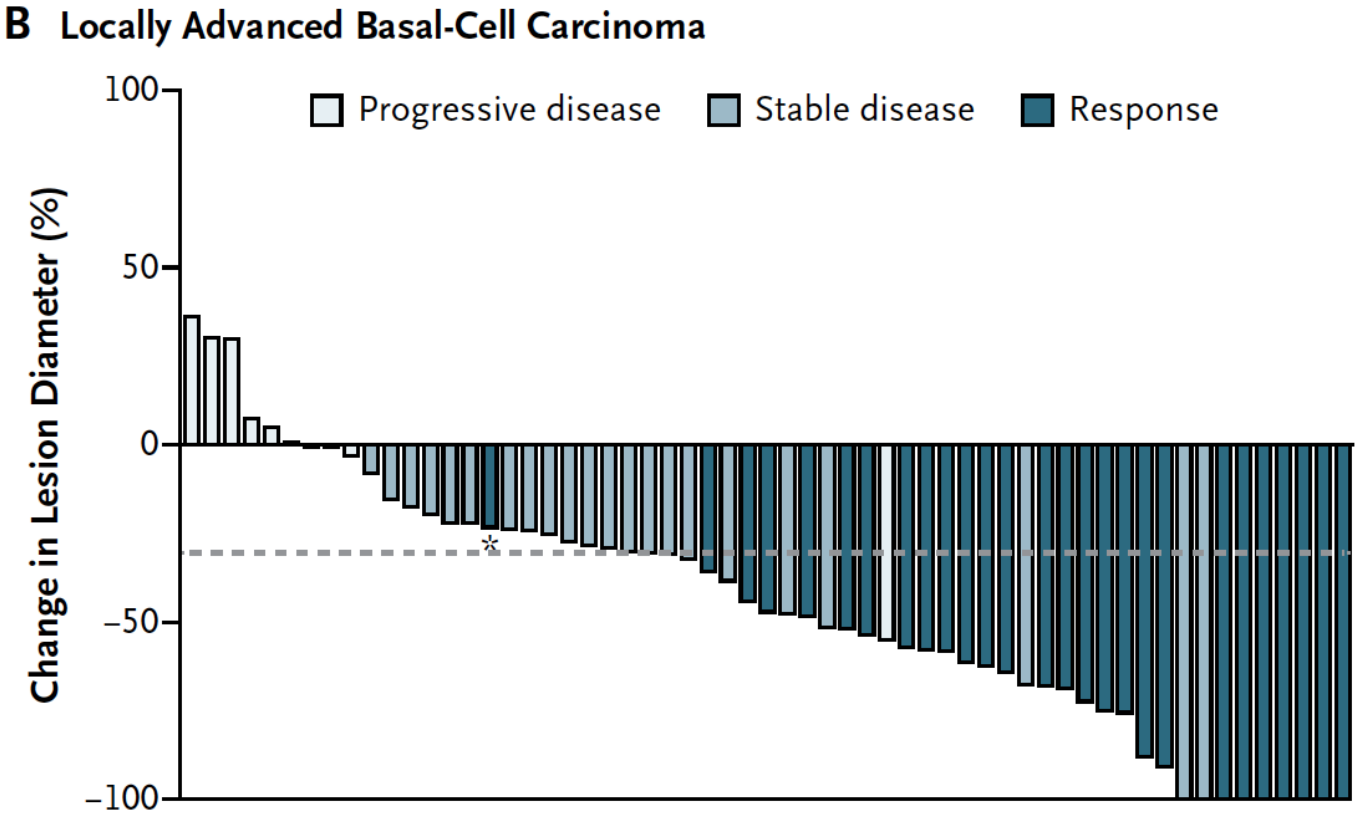
BCC is the most common diagnosed human cancer

1) Physical removal of the BCC
(surgical excision, Mohs micrographic sugery or cryosurgery)

2)Topical medications
-Imiquimod
-5'-Fluorouracil (chemotherapy)

3)Oral medication (HH inhibitors)
-Vismodegib Metastatic or
-Sonidegib locally advanced BCC

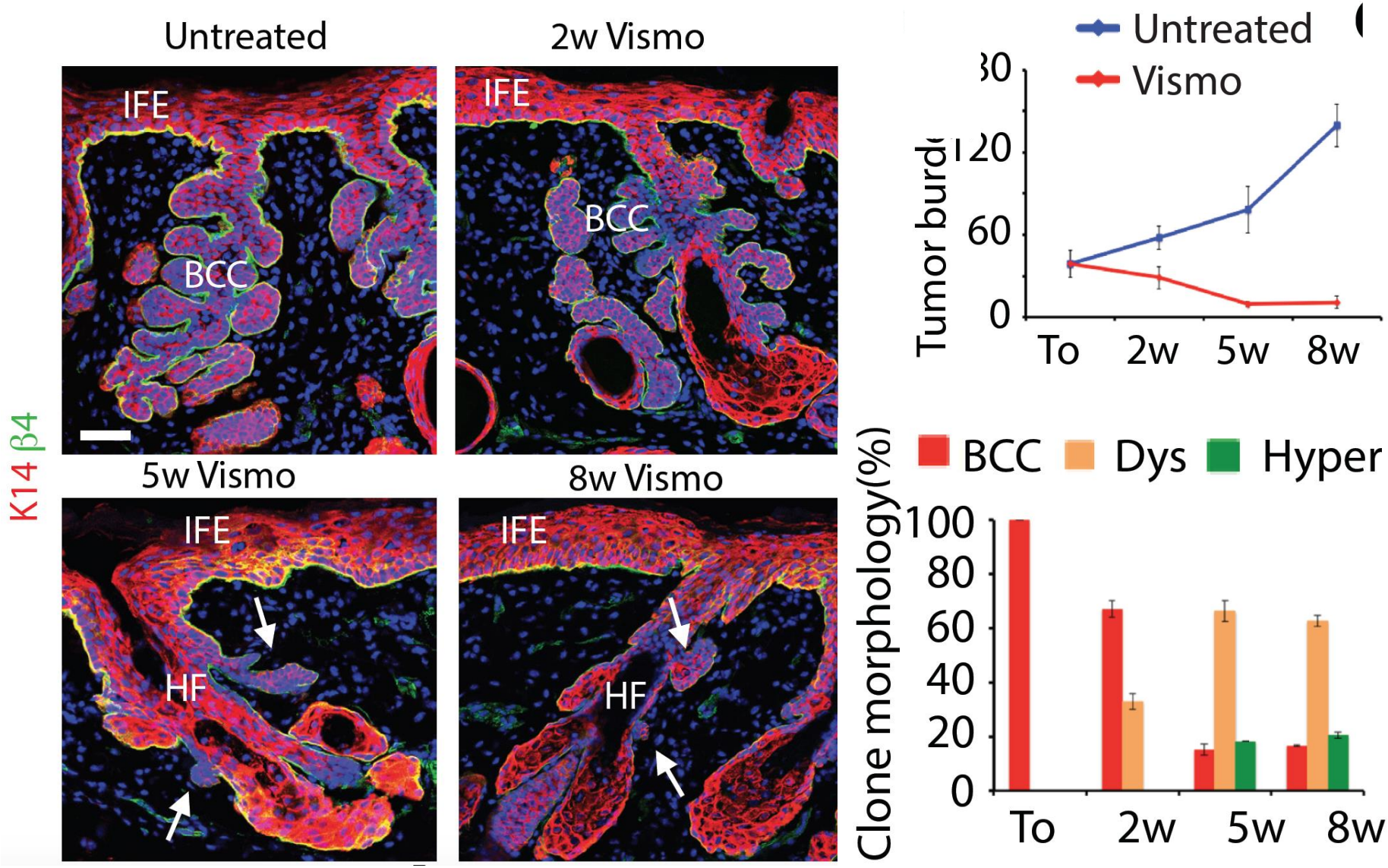
Resistance to vismodegib therapy in patients



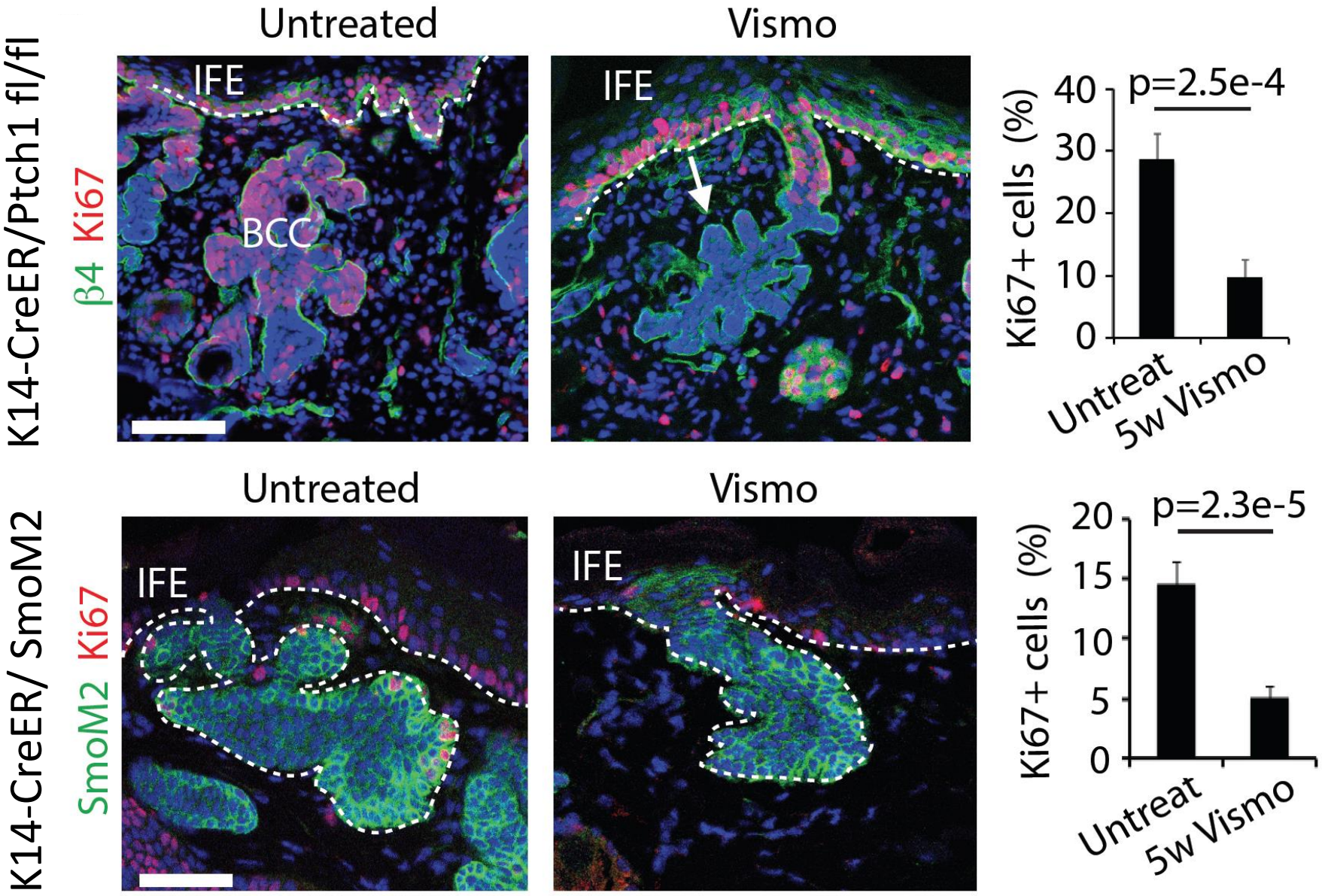
Sekulic A, et al., NEJM, 2012

Sekulic A, et al., BMC Cancer, 2017

Development of tumor resistant lesions during vismodegib treatment in the Ptch1KO model

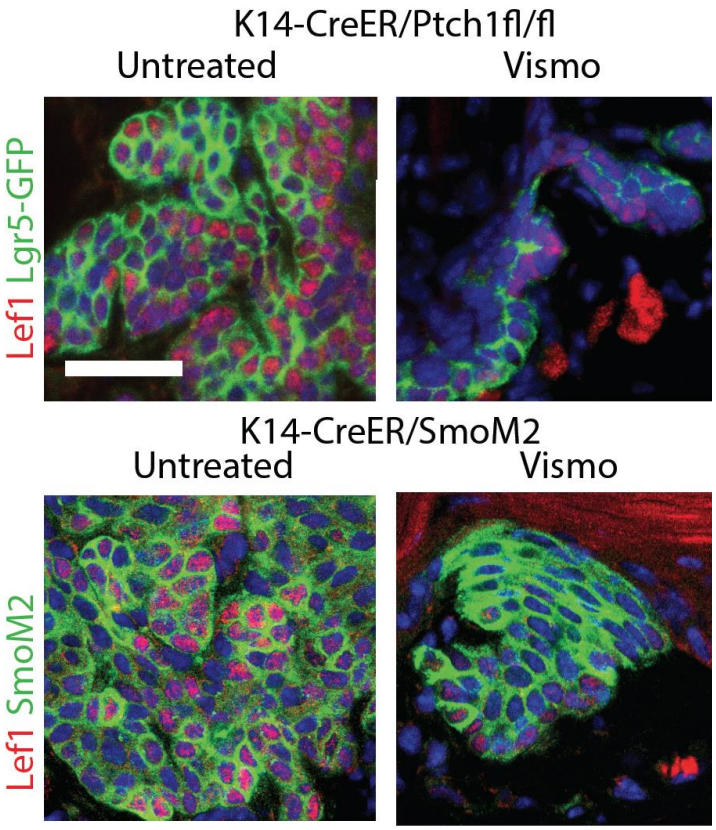


Vismodegib-resistant tumor cells are slow-cycling

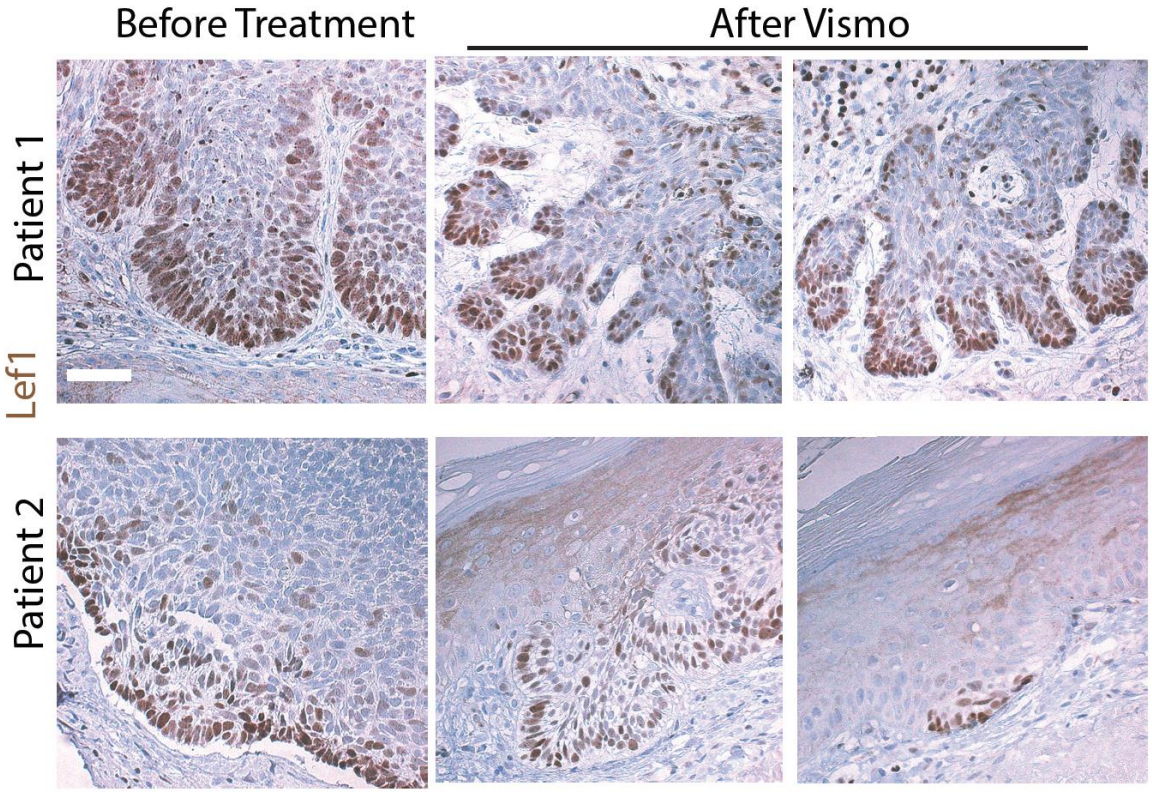


Wnt signaling pathway remains active in vismodegib-resistant lesions

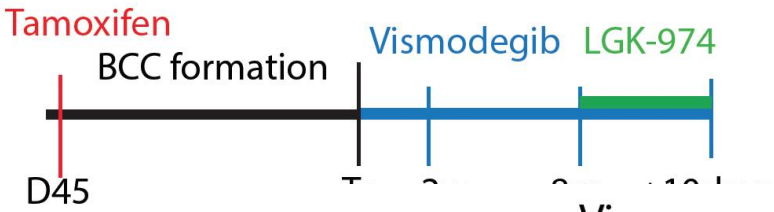
Mouse models

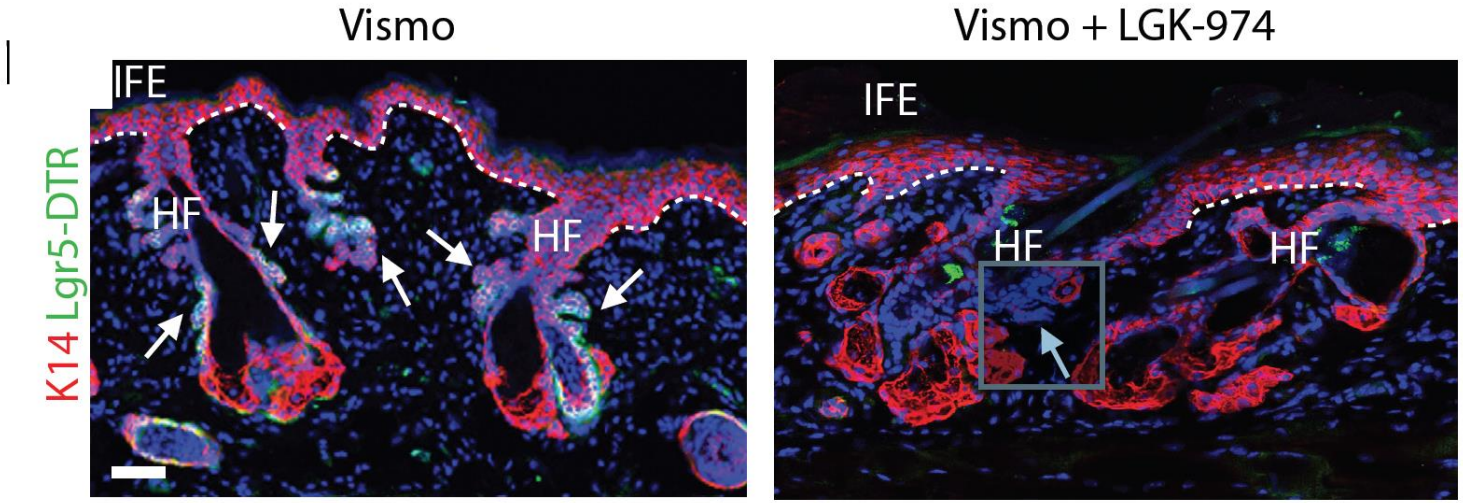


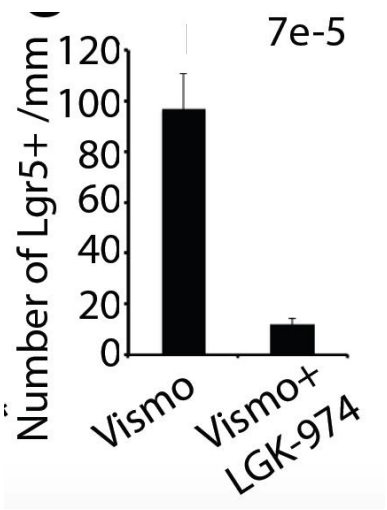
BCC patients

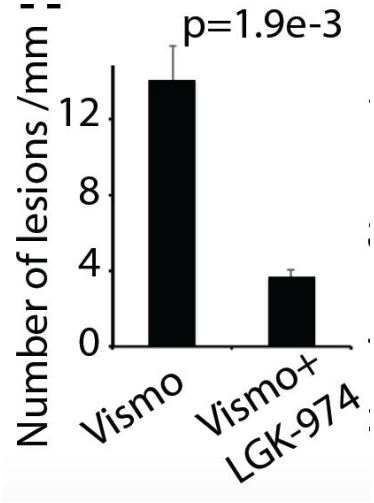


Synergy between Wnt and Smo inhibition

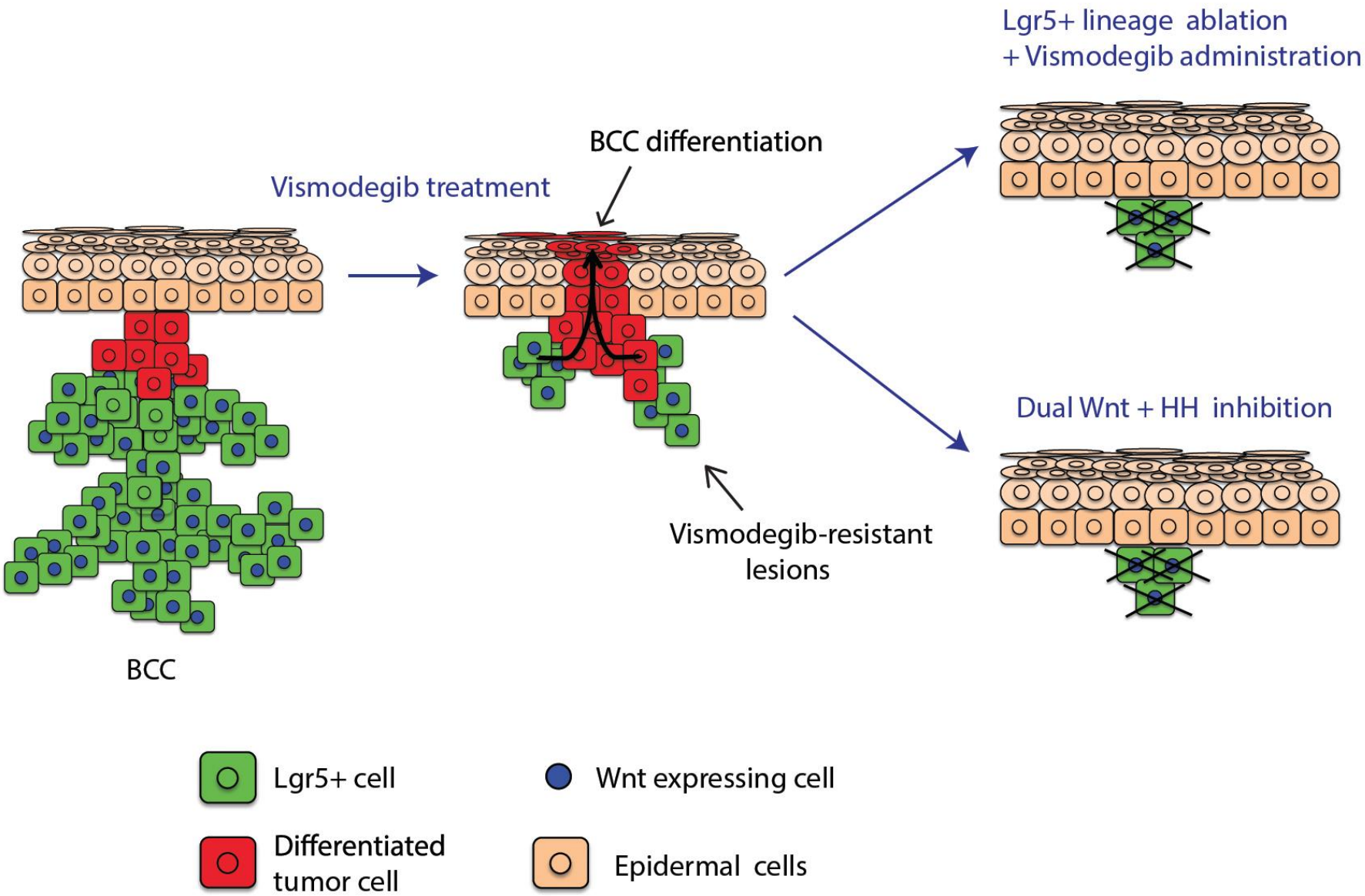








Overcoming the resistance to HH inhibitor in BCC



Sanchez-Danes et al. in revision 2018

ULB

welbio

EMBO

fnrs
LA LIBERTÉ DE CHERCHER

erc

HFSP

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Fondation contre le Cancer

FONDATION BETTENCOURT SCHUELLER