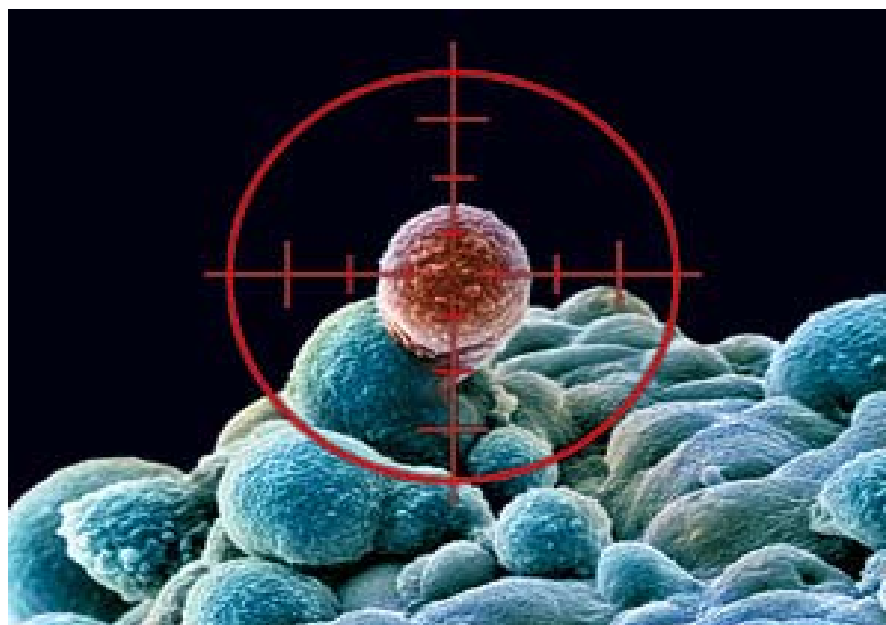


Latvian Biomedical
Research and Study Centre
research and education in biomedicine from genes to human



Uz vēža cilmes šūnām mērķētu pretvēža zāļu izstrāde

- 13:00** **Aija Linē (BMC):** Jaunākās tendences vēža cilmes šūnu izpētē
- 13:20** **Viktors Kozirovskis (PSKUS):** Jaunami ne-sīkšūnu plaušu vēža bioloģijā un to ieviešana klīniskajā praksē (ASCO 2013 kongresa ziņojumi)
- 13:35** **Pēteris Trapencieris (OSI):** Jauni multi mērķu Zn enzīmu inhibitori
- 14:00** **Lāsma Ivanova (BMC):** Ogļskābes anhidrāze IX kā zāļu mērķis: tās ietekme uz vēža cilmes šūnu fenotipu un imunoloģiskās tolerances veidošanos audzēja mikrovidē
- 14:25** **Edgars Endzeliņš (BMC):** Multicelulāro sfēru testi uz vēža cilmes šūnām mērķētu zāļu vielu skrīningam
- 14:45** **Valdis Pīrāgs:** Piezīmes par VPP izpildes gaitu.



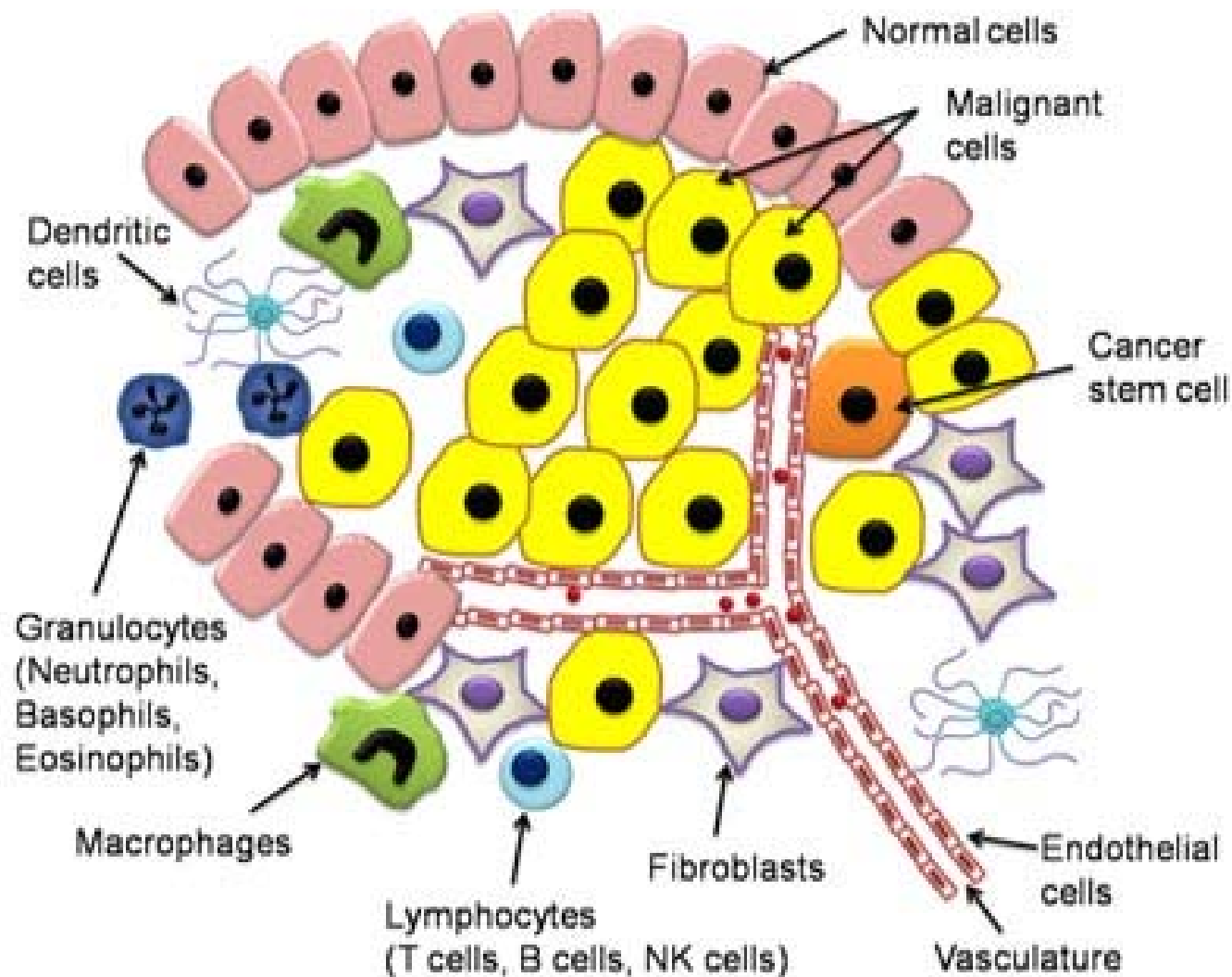
“Vēža cilmes šūnas”

Heterogenitāte, plasticitāte un zāļu mērķi

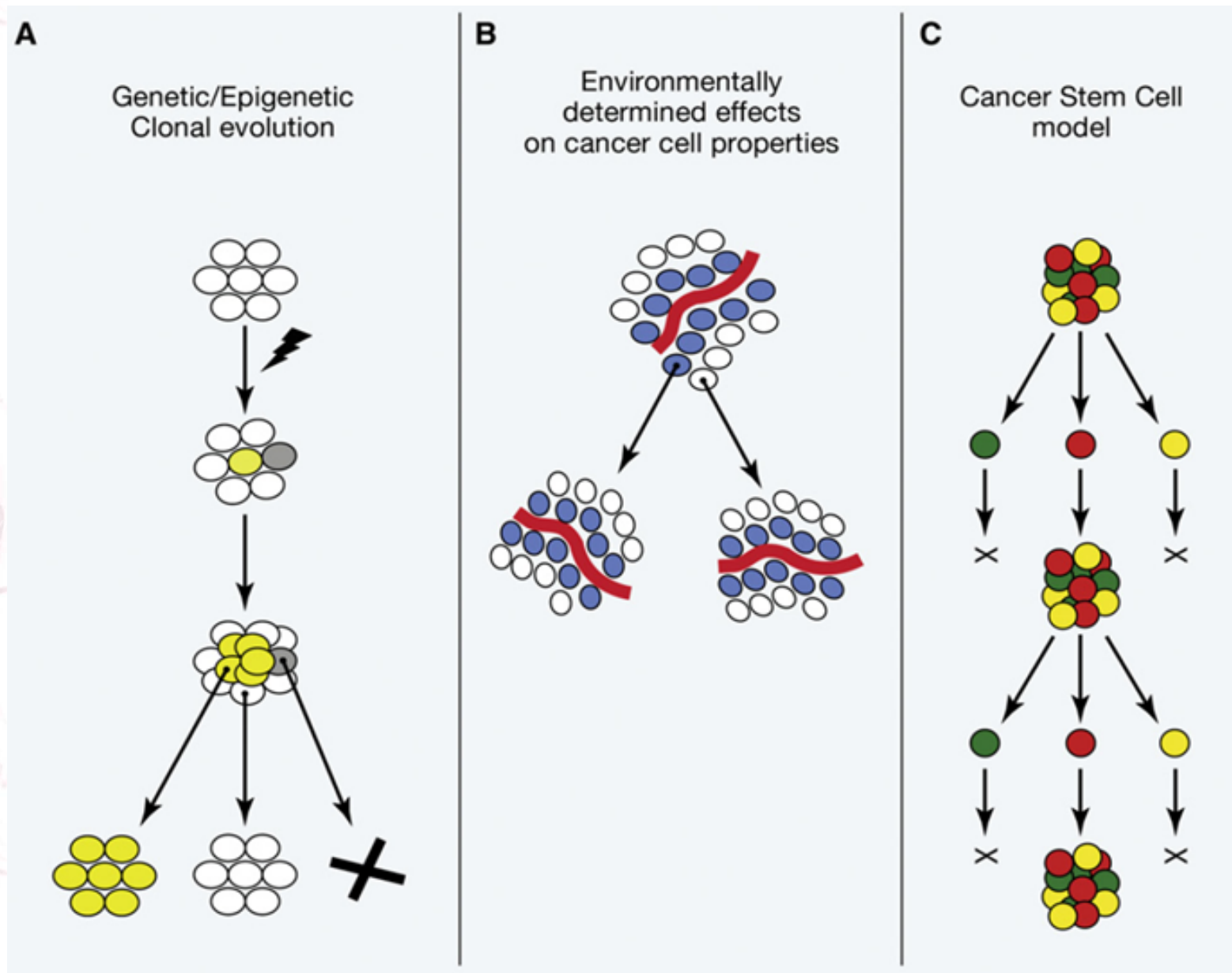
Aija Linē

**VPP 5. projekta ceturtais pārskata
seminārs, 27.06.2013**

Audzēju celulārā, ģenētiskā un funkcionālā heterogenitāte



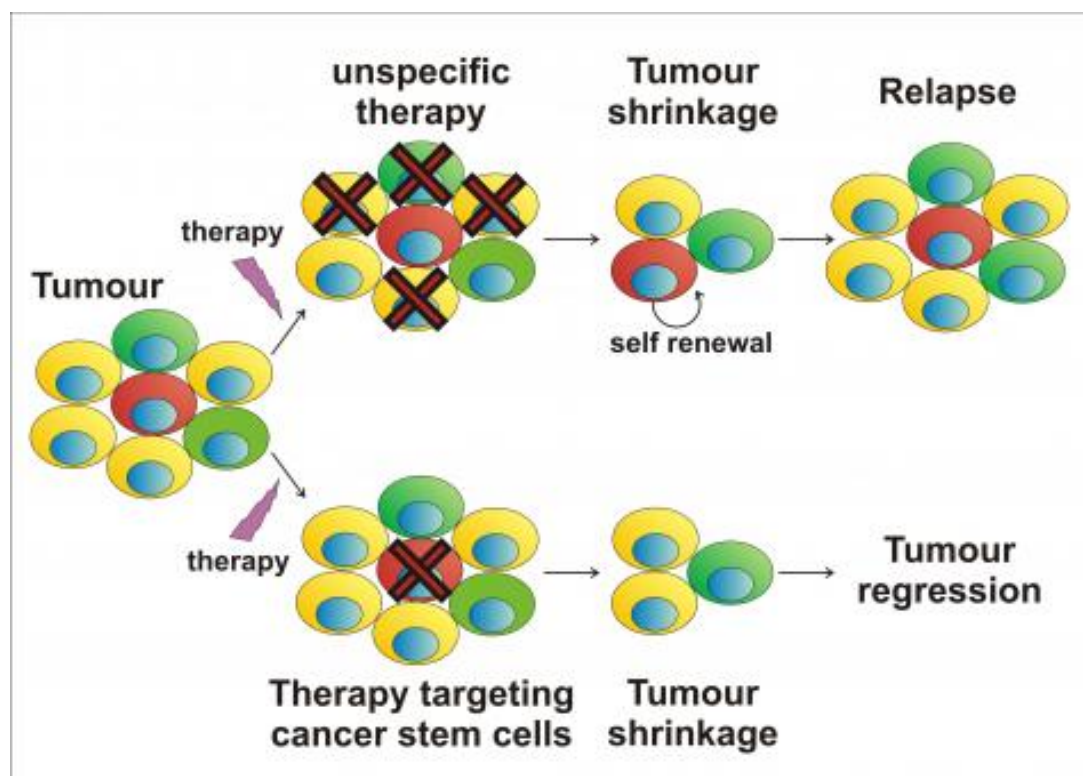
Heterogenitātes veidošanās modeļi



Vēža cilmes šūnas

(Cancer stem cells (CSC), Tumour initiating cells (TIC), Stem cell-like cells (SCLC))

Vēža šūnu populācija, kam piemīt cilmes šūnu īpašības (pašatjaunošanās un spēja radīt daļēji diferencētas meitšūnas), spēja iniciēt audzēja veidošanos eksperimenta dzīvniekos un rezistence pret staru un ķīmijterapiju



CSC izolēšana no cilvēka primārajiem audzējiem

letters to nature

Nature **367**, 645–648 (17 February 1994); doi:10.1038/367645a0

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

TSVEE LAPIDOT, CHRISTIAN SIRARD, JOSEF VORMOOR, BARBARA MURDOCH, TRANG HOANG*, JULIO CACERES-CORTES*, MARK MINDENT†, BRUCE PATERSON‡, MICHAEL A. CALIGIURI§ & JOHN E. DICK

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)

[CANCER RESEARCH 63, 5821–5828, September 15, 2003]

Identification of a Cancer Stem Cell in Human Brain Tumors

Sheila K. Singh, Ian D. Clarke, Mizuhiko Terasaki, Victoria E. Bonn, Cynthia Hawkins, Jeremy Squire, and Peter B. Dirks

The Arthur and Sonia Labatt Brain Tumour Research Centre, The Hospital for Sick Children, Toronto, Ontario M5G 1X8, Canada [S. K. S., I. D. C., M. T., V. E. B., P. B. D.], and Program in Developmental Biology [S. K. S., I. D. C., M. T., V. E. B., P. B. D.], Division of Neurosurgery [S. K. S., P. B. D.], Department of Pediatric Laboratory Medicine [C. H.], and Department of Laboratory Medicine and Pathobiology [J. S.], University of Toronto, Toronto, Ontario M6G 1M8, Canada

Cell Death and Differentiation (2008) 15, 504–514

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www.nature.com/cdd

Identification and expansion of human colon-cancer-initiating cells

Lucia Ricci-Vitiani¹, Dario G. Lombardi², Emanuela Pilozi³, Mauro Biffoni¹, Matilde Todaro⁴, Cesare Peschle¹ & Ruggero De Maria^{1,2}

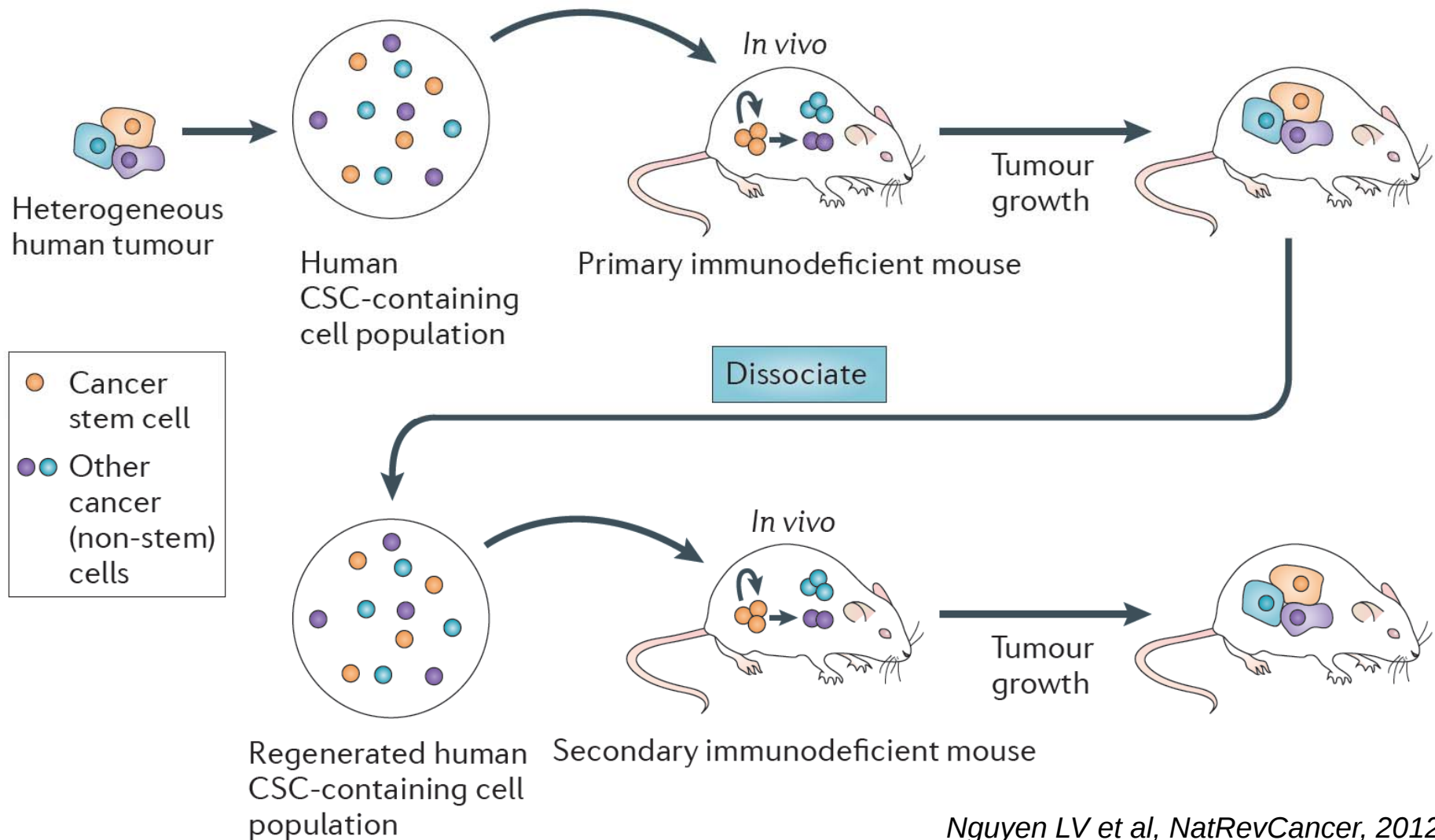
Identification and expansion of the tumorigenic lung cancer stem cell population

A Eramo¹, F Lotti², G Sette², E Pilozi³, M Biffoni¹, A Di Virgilio⁴, C Conticello², L Ruco³, C Peschle¹ and R De Maria^{1,2}

Vēža cilmes šūnu īpašības

- ✓ Ir specifiski šūnas virsmas marķieri, piemēram CD133, CD44, CD90, ABCB5 utt
- ✓ Bezseruma barotnē veido multielulāras sfēras
- ✓ Ekspresē cilmes šūnām raksturīgus transkripcijas faktorus un gēnu ekspresijas regulatorus – Oct4, Lin28, Nanog, Sox2
- ✓ Rezistentas pret staru un ķīmijterapiju
- ✓ Iespējams, ka tās ir šūnas, no kā veidojas metastāzes
- ✓ CSC biežums dažādos audzējos var būt dažāds – 0.1-30% no visas šūnu masas

Vienīgais īstais pierādījums tam, ka izolētajām šūnām piemīt CSC īpašības, ir to spēja veidot histoloģiski identisku audzēju imunodeficitās pelēs



Bet...

- ✓ Iespējams, ka ksenografti selekcionē šūnas, kas ir spējīgas augt svešā (peles) mikrovidē; fakts, ka vairums CSC marķieru ir iesaistīti šūnu adhēzijā vai kontaktu veidošanā to netieši apstiprina

Vol 456 | 4 December 2008 | doi:10.1038/nature07567

nature

ARTICLES

Efficient tumour formation by single human melanoma cells

Elsa Quintana^{1*}, Mark Shackleton^{1*}, Michael S. Sabel², Douglas R. Fullen³, Timothy M. Johnson⁴ & Sean J. Morrison¹

- ✓ Melanomas iniciējošo šūnu proporcija atšķiras peļu modeļos ar dažādu imunosupresijas pakāpi (NOD/SCID vs NSG) – selekcionē šūnas, kas izdzīvo imunoloģiskā spiediena apstākļos

Biežāk lietotie CSC marķieri (CD133, CD90, CD44):

- ✓ Nav strikti specifiski cilmes šūnām;
- ✓ Arī marķiera negatīvās (piem. CD34-, CD133-) šūnas var veidot audzēju;
- ✓ Marķieru ekspresija var mainīties dažādu faktoru, piemēram, hipoksijas ietekmē;
- ✓ Visticamāk tie ir surogātmarķieri, kam nav funkcionāla loma CSC fenotipa uzturēšanā

Int J Oncol. 2012 Jan;40(1):71-9. doi: 10.3892/ijo.2011.1207. Epub 2011 Sep 22.

Hypoxia induces CD133 expression in human lung cancer cells by up-regulation of OCT3/4 and SOX2.

Iida H, Suzuki M, Goitsuka R, Ueno H.

Department of Biochemistry, University of Occupational and Environmental Health, Fukuoka, Japan.

CD133 expression is not restricted to stem cells, and both CD133⁺ and CD133⁻ metastatic colon cancer cells initiate tumors

Sergey V. Shmelkov,¹ Jason M. Butler,¹ Andrea T. Hooper,¹ Adilia Hormigo,¹ Jared Kushner,¹ Till Milde,¹ Ryan St. Clair,¹ Muhamed Baljevic,¹ Ian White,¹ David K. Jin,¹ Amy Chadburn,¹ Andrew J. Murphy,² David M. Valenzuela,² Nicholas W. Gale,² Gavin Thurston,² George D. Yancopoulos,² Michael D'Angelica,³ Nancy Kemeny,³ David Lyden,¹ and Shahin Rafii¹

¹Howard Hughes Medical Institute, Ansary Center for Stem Cell Therapeutics, and Department of Genetic Medicine, Weill Medical College of Cornell University, New York, New York, USA.

Normal and neoplastic nonstem cells can spontaneously convert to a stem-like state

Christine L. Chaffer^{a,b}, Ines Brueckmann^a, Christina Scheel^{a,b}, Alicia J. Kaestli^a, Paul A. Wiggins^a, Leonardo O. Rodrigues^{a,b}, Mary Brooks^{a,b}, Ferenc Reinhardt^{a,b}, Ying Su^c, Kornelia Polyak^c, Lisa M. Arendt^{d,e}, Charlotte Kuperwasser^{d,e}, Brian Bierie^{a,b}, and Robert A. Weinberg^{a,b,f,1}

Int J Cancer. 2008 Feb 15;122(4):761-8.

CD133 negative glioma cells form tumors in nude rats and give rise to CD133 positive cells.

Wang J, Sakariassen PØ, Tsinkalovsky O, Immervoll H, Bøe SO, Svendsen A, Prestegarden L, Røsland G, Thorsen F, Stuhr L, Molven A, Bjerkvig R, Enger PØ.

Department of Biomedicine, University of Bergen, Bergen, Norway.

Funkcionāli CSC marķieri

- ✓ **ALDH1 – iesaistīta detoksifikācijā un retīnskābes signālceļā, iespējams, piedalās diferenciācijas regulācijā. Korelē ar tumorsfēru un ksenograftu veidošanas potenciālu**

Cancer Res. 2009 Apr 15;69(8):3382-9. doi: 10.1158/0008-5472.CAN-08-4418. Epub 2009 Mar 31.

Aldehyde dehydrogenase 1 is a marker for normal and malignant human colonic stem cells (SC) and tracks SC overpopulation during colon tumorigenesis.

Huang EH, Hynes MJ, Zhang T, Ginestier C, Dontu G, Appelman H, Fields JZ, Wicha MS, Boman BM.

Department of Surgery, University of Florida, Gainesville, Florida, USA.

- ✓ **MDR zāļu transportieri (ABCB5) – izvada Hoeschst krāsvielu (side population)**

Dis Sci. 2013 Jan;58(1):132-9. doi: 10.1007/s10620-012-2330-1. Epub 2012 Aug 10.

Not all side population cells contain cancer stem-like cells in human gastric cancer cell lines.

Zhang H, Xi H, Cai A, Xia Q, Wang XX, Lu C, Zhang Y, Song Z, Wang H, Li Q, Chen L, Guo Z.

Department of General Surgery, General Hospital of Chinese People's Liberation Army (PLA), Beijing, 100853, People's Republic of China.

- ✓ **Wnt, Hedgehog u.c. «cilmīguma» signālceļu aktivitātes marķieri (promoteru reportieri)**

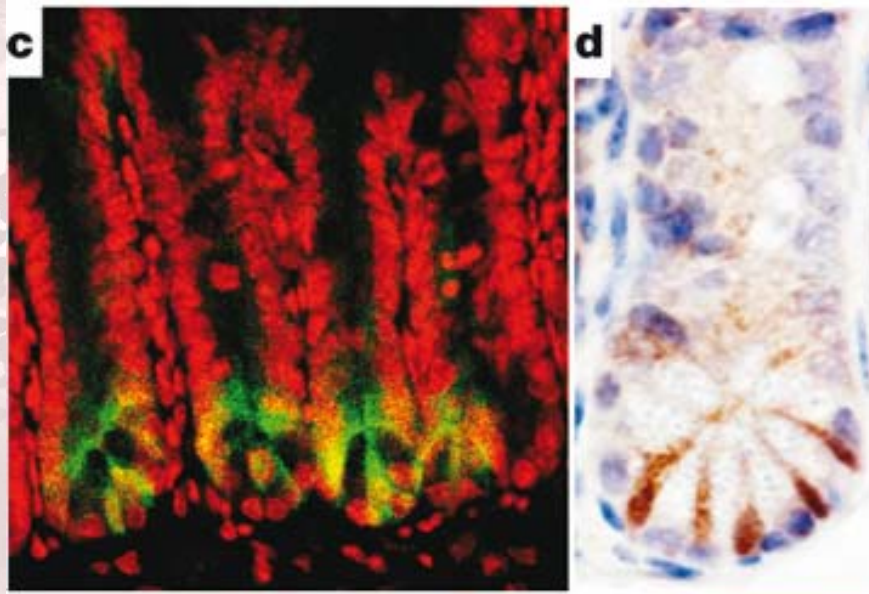
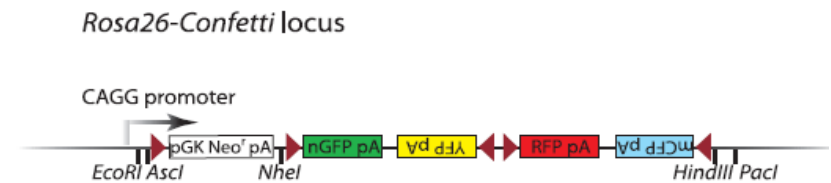
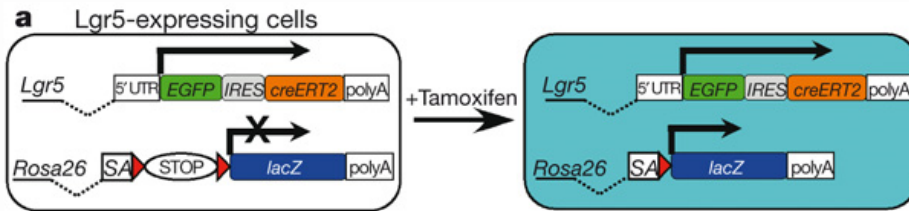
Biochem Biophys Res Commun. 2013 Jun 21. pii: S0006-291X(13)01025-5. doi: 10.1016/j.bbrc.2013.06.038. [Epub ahead of print]

Isolation and characterization of human breast cancer cells with SOX2 promoter activity.

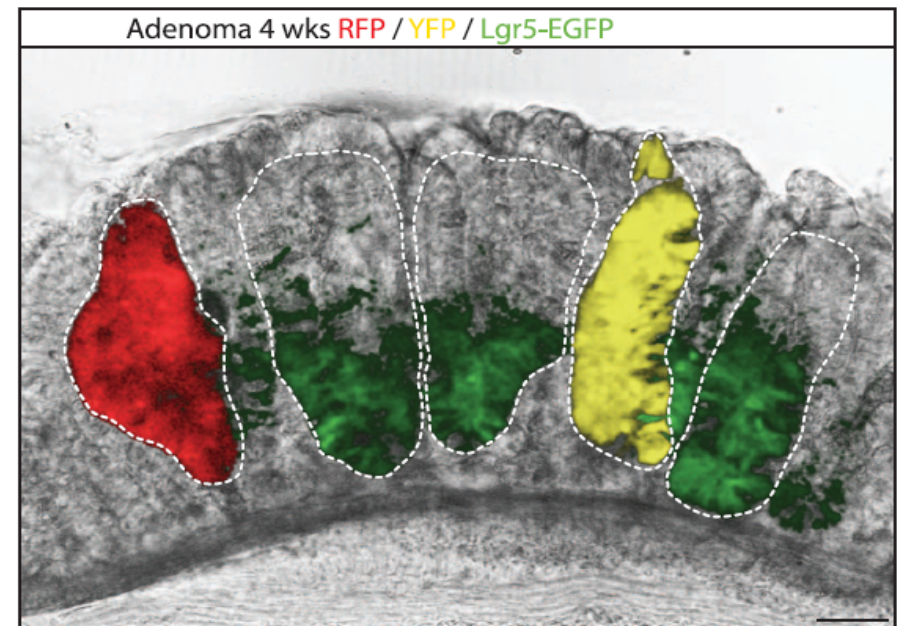
Liang S, Furuhashi M, Nakane R, Nakazawa S, Hamada JI, Iizasa H.

Division of Stem Cell Biology, Institute for Genetic Medicine, Hokkaido University, Kita 15, Nishi 7, Sapporo 060-0815, Japan.

«*Lineage tracing*» eksperimenti apstiprina klonālu zarnu adenomas izcelsmi no cilmes šūnām



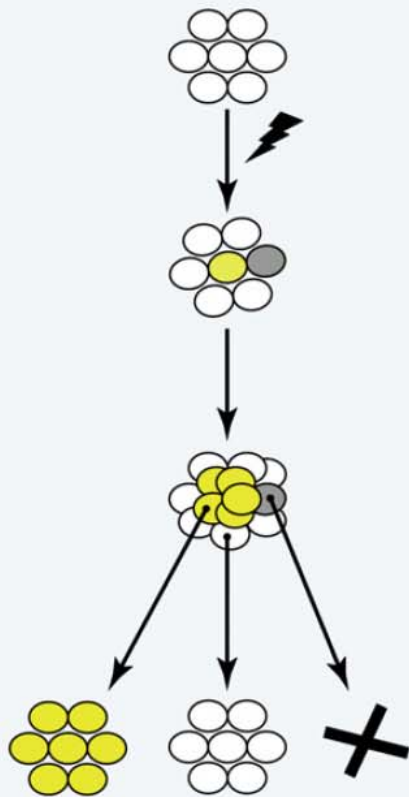
Barker N et al, Nature, 2007,



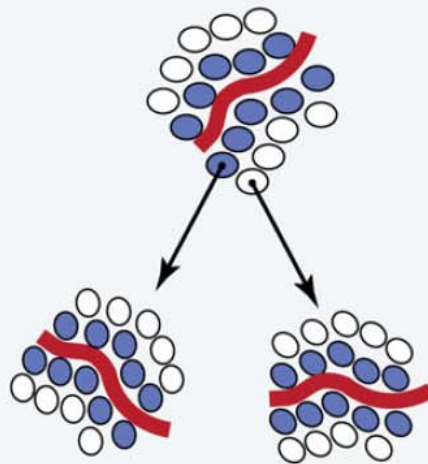
Schepers AG et al, Science, 2012

A

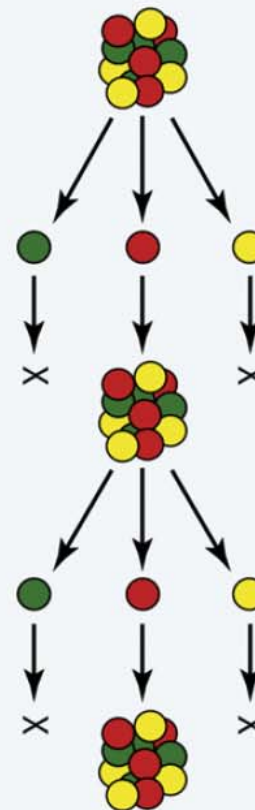
Genetic/Epigenetic
Clonal evolution

**B**

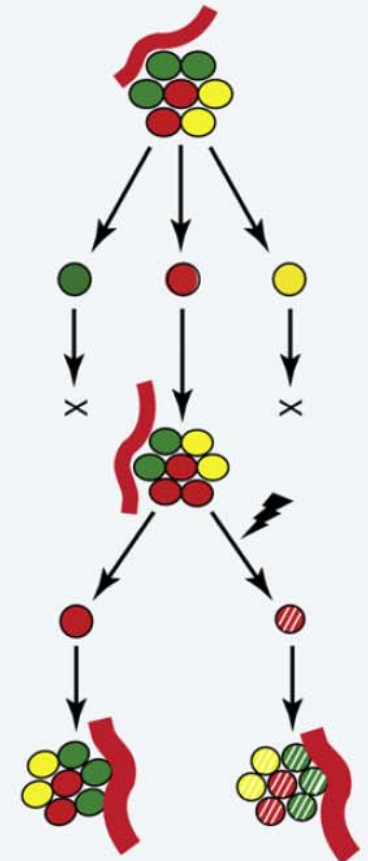
Environmentally
determined effects
on cancer cell properties

**C**

Cancer Stem Cell
model

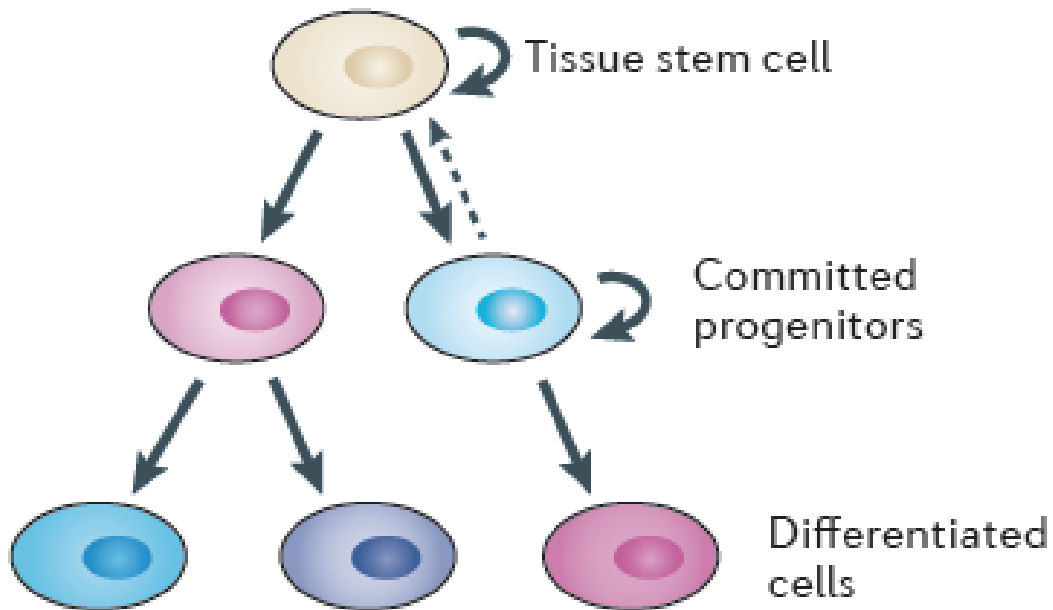
**D**

Cancers in which heterogeneity
is determined by cancer stem
cell differentiation, clonal
evolution and environmental
effects

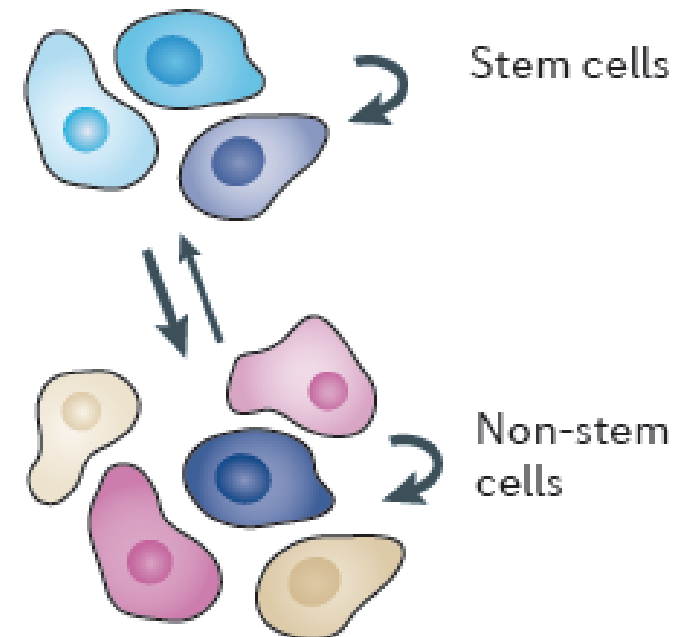


Vēža (cilmes) šūnu plasticitāte

a Normal



b Cancer



Faktori, kas varētu nodrošināt paaugstinātu plasticitāti/adaptācijas spēju:

Epigēnētiska mainība uz ģenētiskās heterogenitātes fona, transkripcijas troksnis, dažādi mikrovides signāli

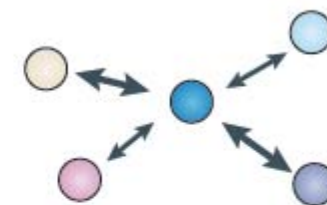
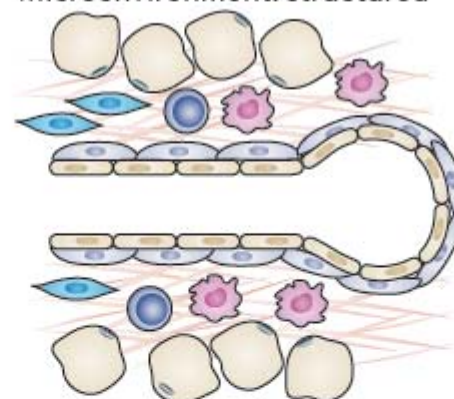
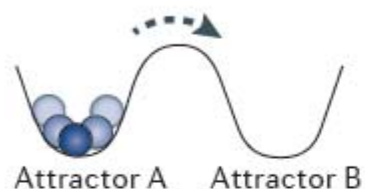
Normal tissue: low phenotypic heterogeneity

Noise: low

Genotypes: homogeneous

Microenvironment: structured

Network architecture: robust



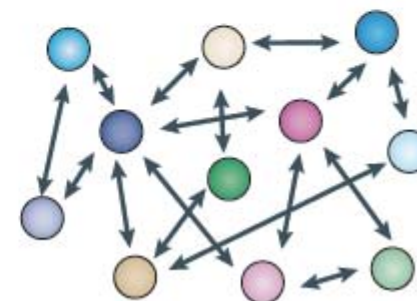
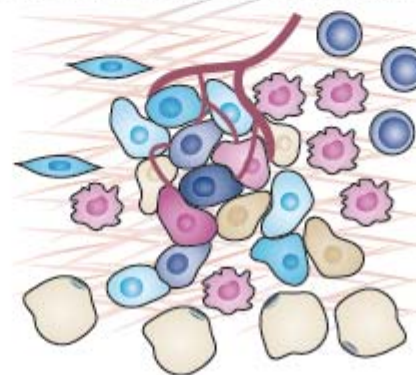
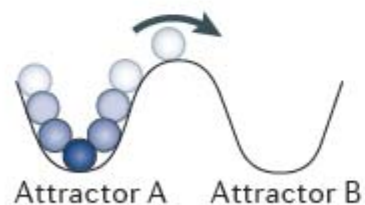
Tumour: high phenotypic heterogeneity

Noise: high

Genotypes: heterogeneous

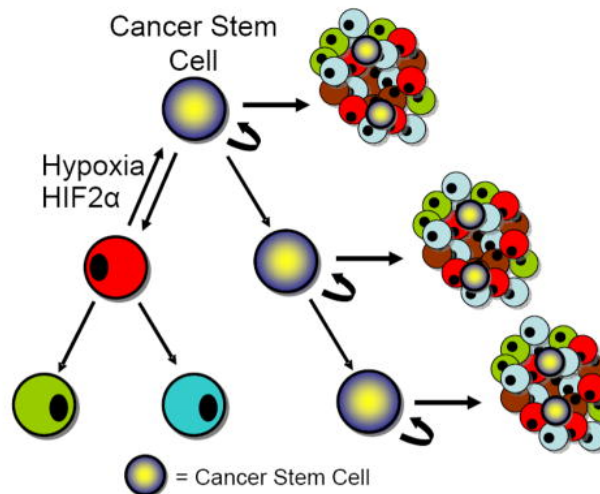
Microenvironment: disorganized

Network architecture: noisy



Audzēja mikrovides/nišas signāli, kas ietekmē CSC fenotipu

✓ Hipoksija un acidoze



Cell Cycle. Author manuscript; available in PMC 2010 October 15.

Published in final edited form as:

[Cell Cycle. 2009 October 15; 8\(20\): 3274–3284.](#)

Published online 2009 October 3.

PMCID: PMC2825672

NIHMSID: NIHMS165167

The Hypoxic Microenvironment Maintains Glioblastoma Stem Cells and Promotes Reprogramming towards a Cancer Stem Cell Phenotype

[John M. Heddleston](#),* [Zhizhong Li](#),* [Anita B. J.](#)

Cell Death Differ. 2011 May; 18(5): 829–840.

Published online 2010 December 3. doi: [10.1038/cdd.2010.150](#)

PMCID: PMC3095828

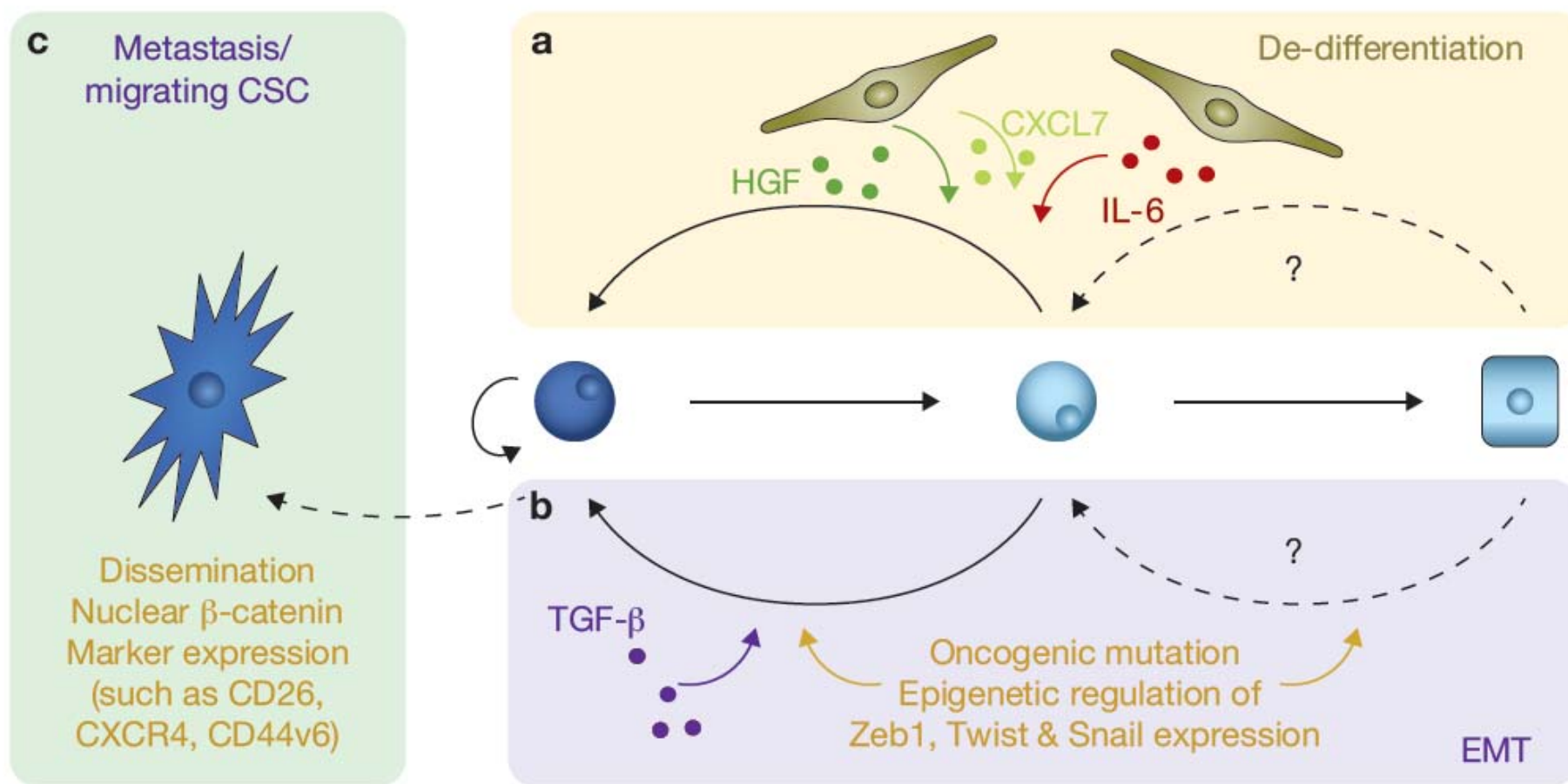
NIHMSID: [NIHMS289257](#)

Acidic stress promotes a glioma stem cell phenotype

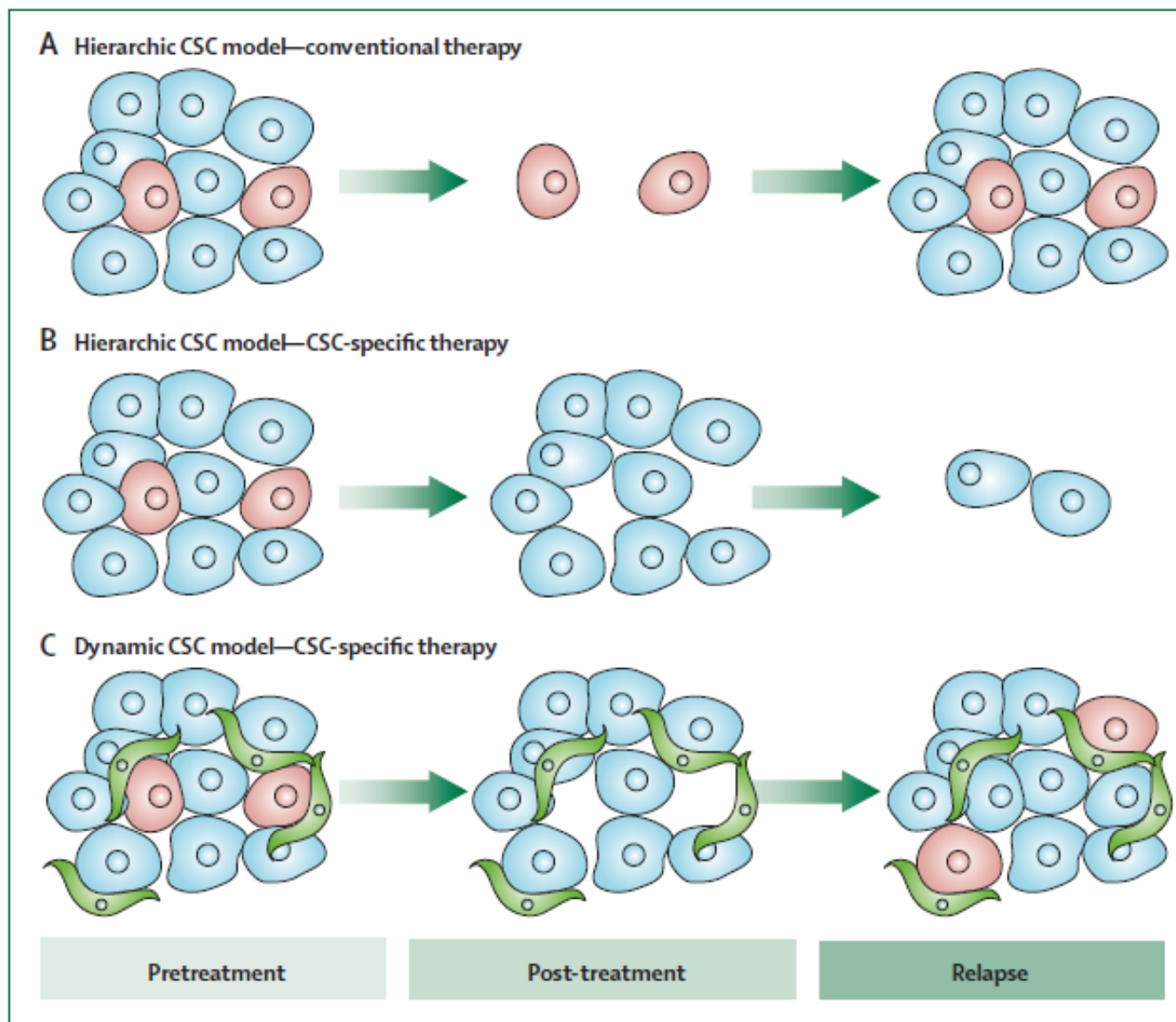
[A B Hjelmeland](#),^{1,*} [Q Wu](#),¹ [J M Heddleston](#),¹ [G S Choudhary](#),² [J MacSwords](#),¹ [J D Lathia](#),¹ [R McLendon](#),³ [D Lindner](#),⁴ [A Sloan](#),⁵ and [J N Rich](#)^{1,*}

Audzēja mikrovides/nišas signāli, kas ietekmē CSC fenotipu

✓ Stromas sekretēti faktori un EMT



Kāda ir šo modeļu ietekme uz terapijas iznākumu?



Jauni molekulārie mērķi uz vēža cilmes šūnām mērķētai terapijai

- ✓ **Signālceļi, kas ir atbildīgi par cilmes šūnu pašatjaunošanos (Hedgehog, Wnt, Notch u.c.)**
- ✓ **Epiģenētiskie regulatori (metiltransferāzes, HDAC, HAT u.c.), kas nodrošina CSC fenotipa plasticitāti**
- ✓ **Audzēja mikrovides signāli, kas inducē CSC fenotipu (hipoksija, EMT, acidoze, u.c.)**