

What is stemness and how does that matter?

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Outline

Intro: what are stem cells?

What kind of property is stemness?

Does stemness nature matter?

Categorical

Dispositional

Is stemness nature stable?

Systemic

Relational

“Stem cell” unity?

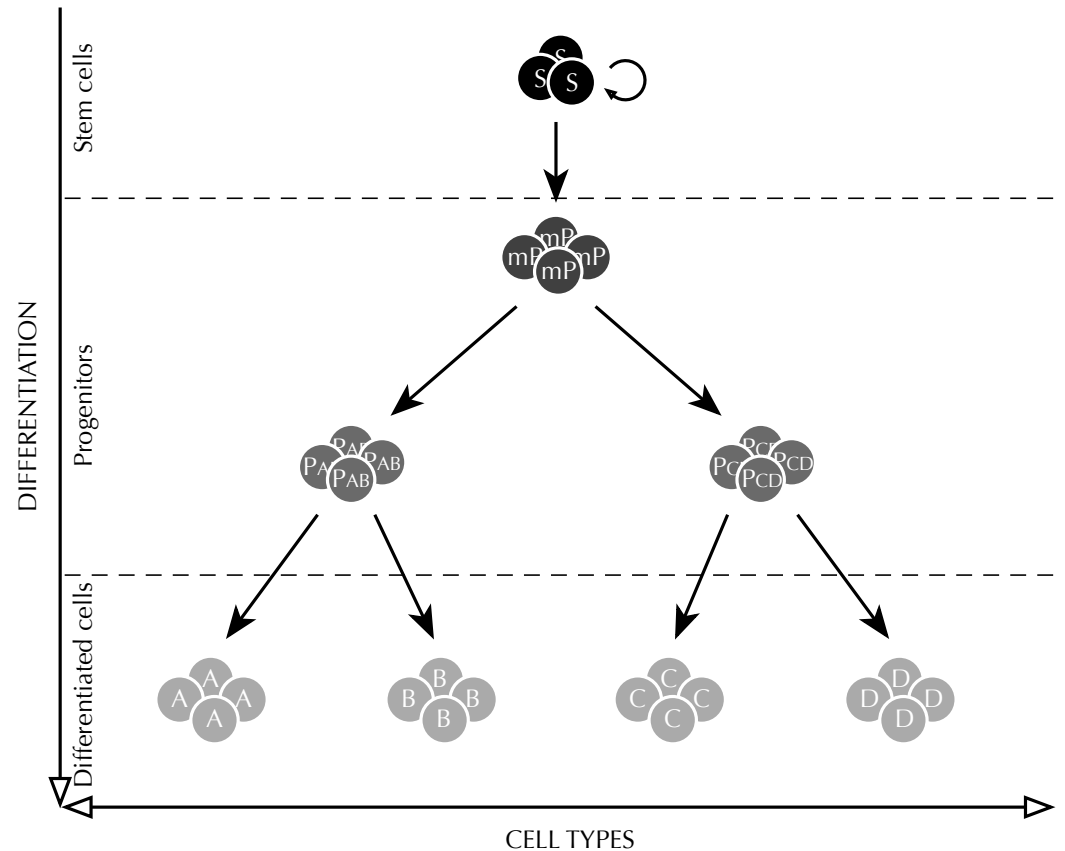
Stem cells: the classical view

- **Stem cell definition**

- Self-renewal
- Differentiation

- **Differentiation hierarchy**

- Irreversible



Differentiation hierarchy

- Cloning

- iPSC

John Gurdon



Shinya Yamanaka

Nobel Prize for Physiology or medicine 2012 “for the discovery that mature cells can be reprogrammed to be pluripotent”

A microscopic image showing a large, clear, spherical cell (likely an egg) being manipulated by a thin glass needle. The cell is surrounded by a thin layer of fluid and contains numerous small, dark granules. The background is a light blue color.

“In vitro phenomenon”?

De-differentiation and cellular plasticity in vivo

Plants



Grafi. Dev Biol 2004.
Lohmann, Springer 2008.

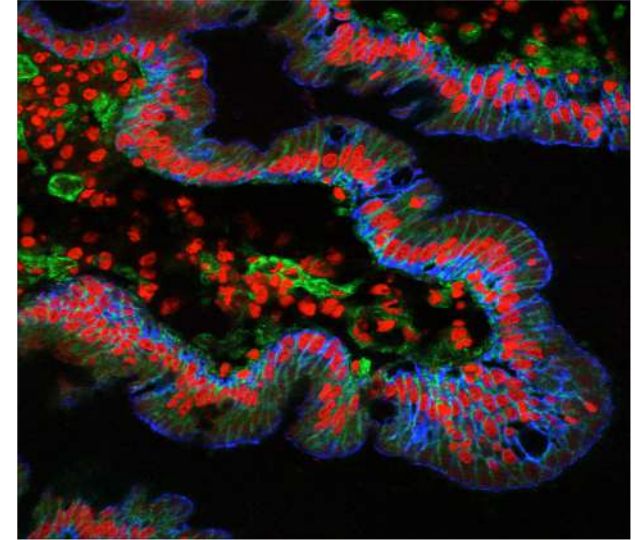
Regeneration



Bernardos et al. J Neurosci 2007
Ramachandran, Fausett & Goldman. Nat Cell Biol 2010
Wan, Ramachandran & Goldman. Dev Cell 2012

Echeverri, Clarke, & Tanaka. Developmental Biology 2001
Nye, et al. Dev Dyn 2003
Satoh, Bryant & Gardiner. Dev Growth Differ 2008
Satoh, et al. Dev Biol 2008

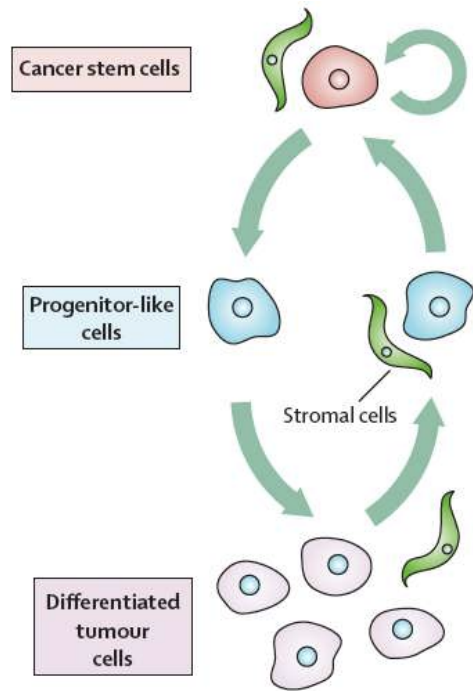
Mammal/Human



Blanpain & Fuchs. Science 2014
Tetteh, Farin & Clevers. Trends Cell Biol 2015
Donati & Watt. Cell Stem Cell 2015
Visvader and Clevers. Nature Cell Biol 2016

Redifferentiation and cellular plasticity in vivo

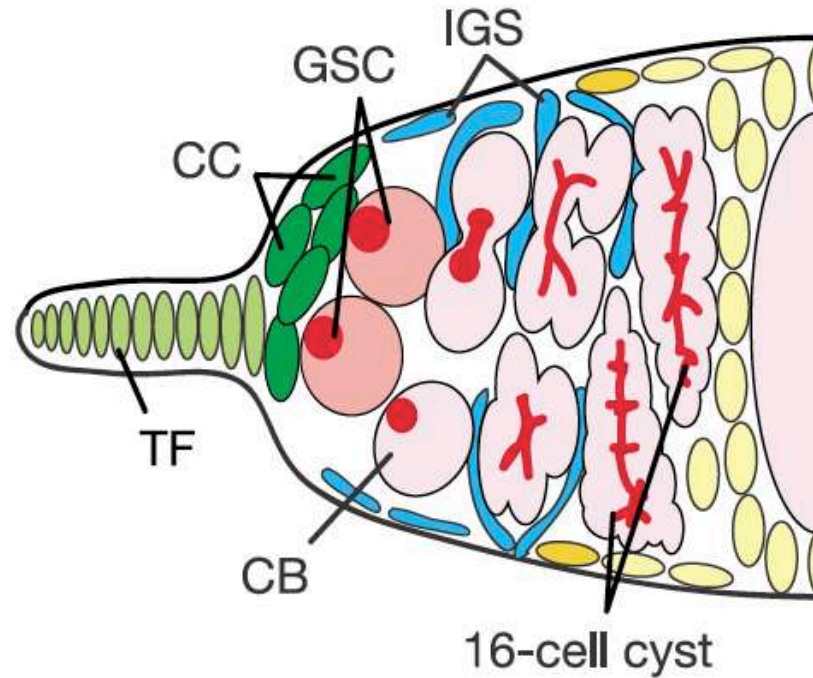
Cancer



- Ge et al. *Cell* 2017.
- Shimokawa et al. *Nature* 2017.
- De Sousa e Melo et al. *Nature* 2017.
- Davis et al. *Nature medicine* 2015.
- Krieger and Simons. *Development* 2015.
- Pereira et al. *Frontiers in Oncology* 2015.
- Plaks, Kong, and Werb. *Cell Stem Cell* 2015.
- Safa, et al. *Genes & Diseases* 2015.
- Singh, et al. *EMBO* 2015.
- Van Keymeulen, et al. *Nature* 2015.
- Ye, et al. *Nature* 2015.
- Auffinger et al. *Cell Death and Differentiation* 2014.
- Easwaran et al. *Molecular Cell* 2014.
- Pattabiraman and Weinberg *Nature Reviews. Drug Discovery* 2014.
- Chaffer et al. *Cell* 2013.
- Marjanovic, Weinberg, and Chaffer. *Clin Chem* 2013.
- Zhang, et al. *Stem Cells* 2013.
- Zhou, et al. *Quantitative Biology* 2013.
- Zhu, et al. *Cancer Cell International* 2013.
- Landsberg et al. *Nature* 2012.
- Quail, Taylor, and Postovit. *Current Stem Cell Research & Therapy* 2012.
- Vermeulen, et al. *Lancet Oncol* 2012.
- Yang, et al. *British Journal of Cancer* 2012.
- Chaffer et al. *PNAS* 2011.
- Gupta et al. *Cell* 2011.
- Lee et al. *International Journal of Hematology* 2011.
- Thirant, et al. *PLoS One* 2011.
- Hoek and Goding. *Pigment Cell & Melanoma Research* 2010.
- Oliveras-Ferraro, et al. *Rejuvenation Research* 2010.
- Vermeulen, et al. *Nat Cell Biol* 2010.
- Dufour et al. *Stem Cells* 2009.
- Morel et al. *PLoS One* 2008.
- Rapp, Ceteci, and Schreck. *Cell Cycle* 2008.

Dedifferentiation and cellular plasticity in vivo

Drosophila germ line



Brawley & Matunis. Science 2004

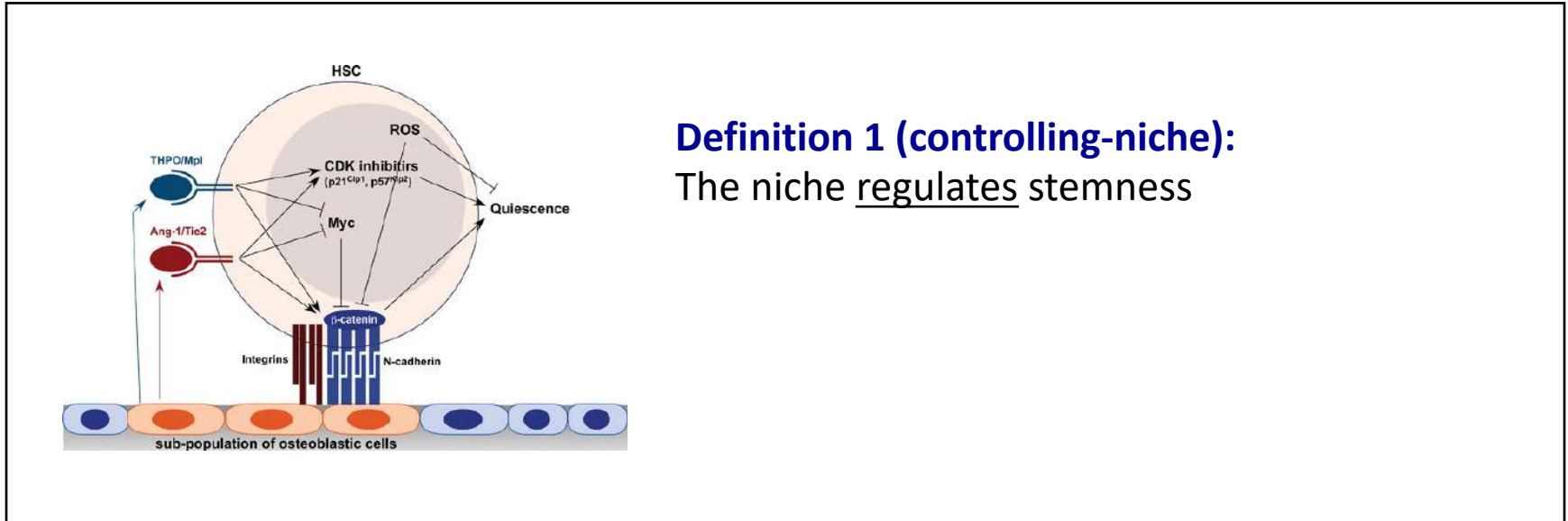
Cheng J, et al. Nature 2008

Kai & Spradling. Nature 2004

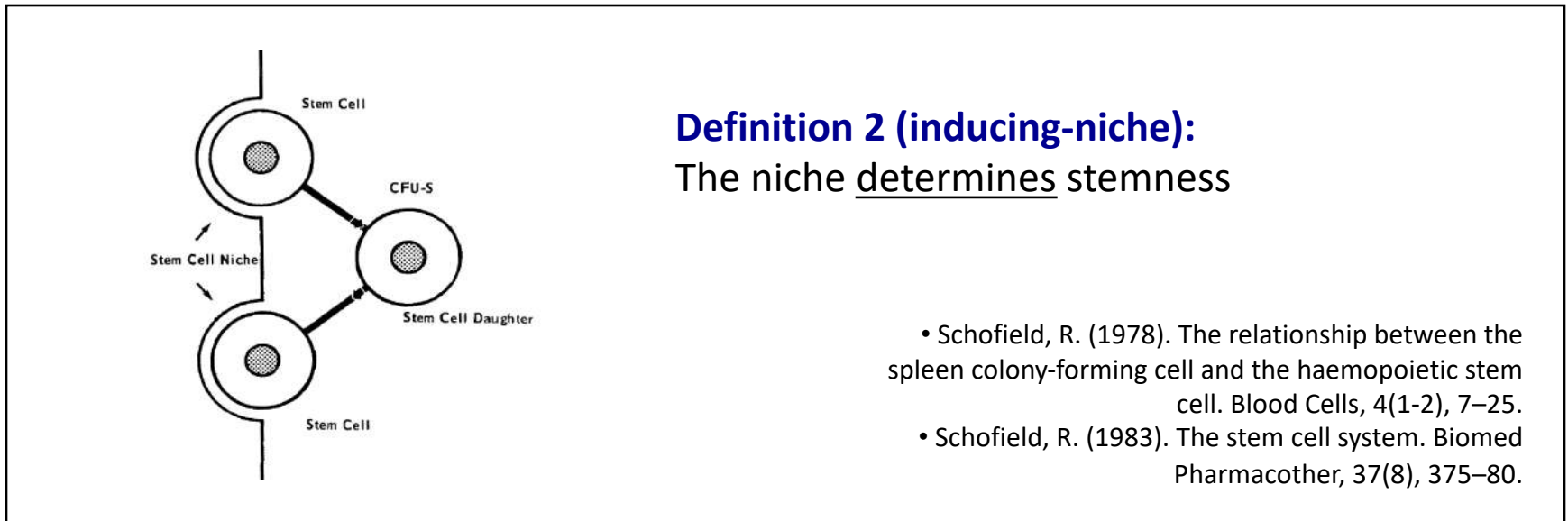
Sheng, Brawley & Matunis. Cell Stem Cell 2009

Barroca et al. Nat Cell Biol 2009

The stem cell niche: two views



Definition 1 (controlling-niche):
The niche regulates stemness

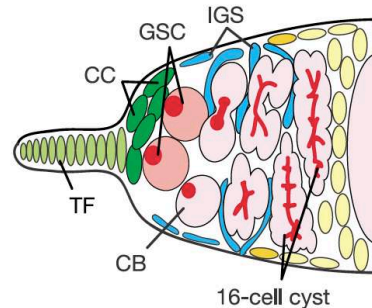


Definition 2 (inducing-niche):
The niche determines stemness

- Schofield, R. (1978). The relationship between the spleen colony-forming cell and the haemopoietic stem cell. *Blood Cells*, 4(1-2), 7–25.
- Schofield, R. (1983). The stem cell system. *Biomed Pharmacother*, 37(8), 375–80.

Dedifferentiation and cellular plasticity in vivo

Drosophila germ line



- Brawley & Matunis. *Science* 2004
- Cheng J, et al. *Nature* 2008
- Kai & Spradling. *Nature* 2004
- Sheng, Brawley & Matunis. *Cell Stem Cell* 2009
- Barroca et al. *Nat Cell Biol* 2009

→ Inducing-niche (def 2) ←

Dedifferentiation and cellular plasticity in vivo

Plants



Grafi. *Dev Biol* 2004.
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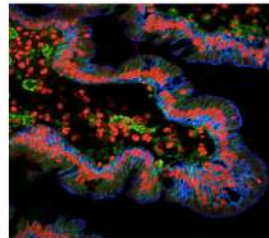
Animals



Bernardos et al. *J Neurosci* 2007
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Sato, Bryant & Gardiner. *Dev Growth Differ* 2008
Sato, et al. *Dev Biol* 2008

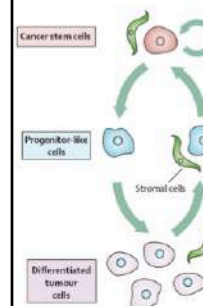
Human



Blanpain & Fuchs. *Science* 2014
Tetteh, Farin & Clevers. *Trends Cell Biol* 2015
Donati & Watt. *Cell Stem Cell* 2015
Visvader and Clevers. *Nature Cell Biol* 2016

Dedifferentiation and cellular plasticity in vivo

Cancer

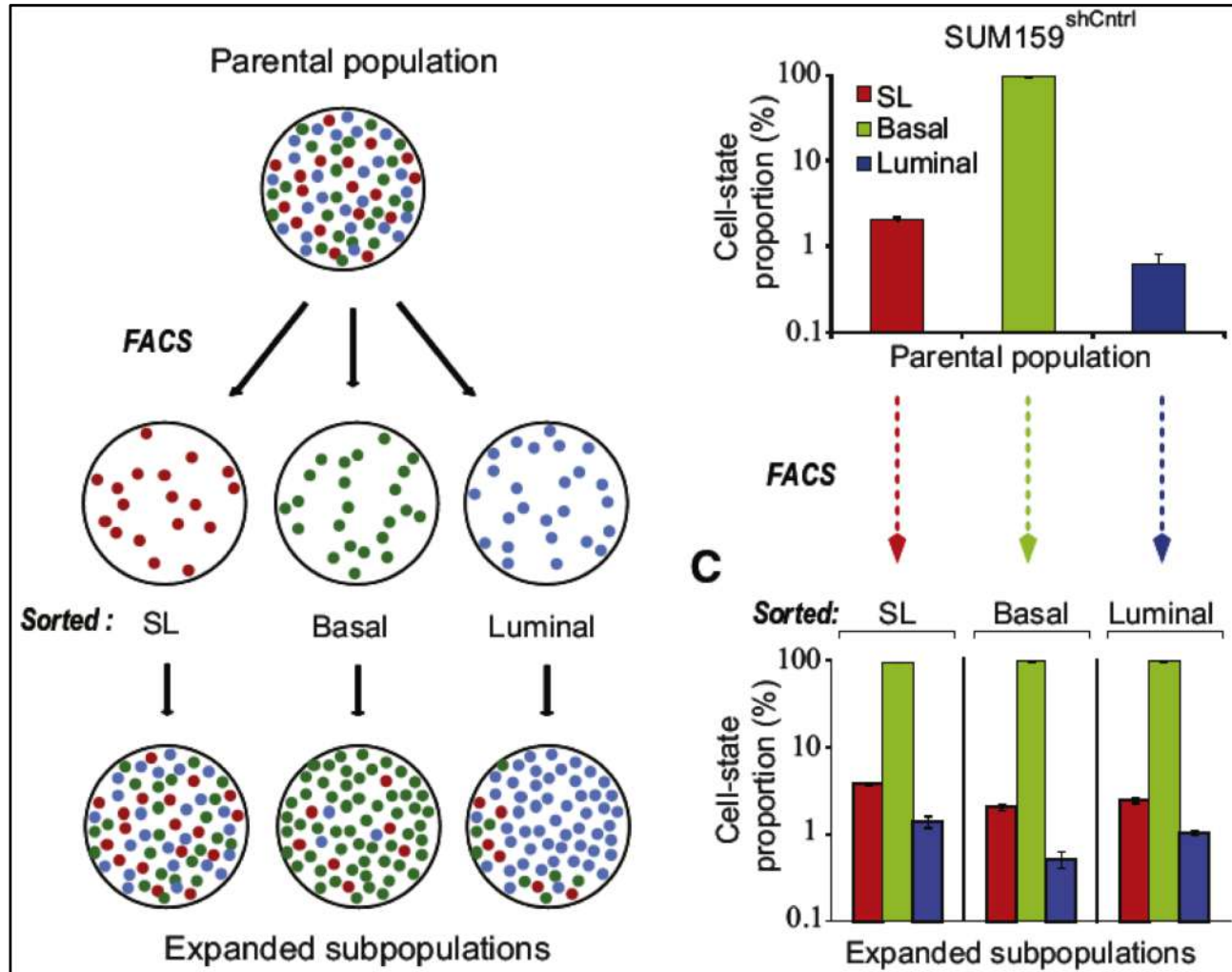


- Krieger and Simons. *Development* 2015.
- Pereira et al. *Frontiers in Oncology* 2015.
- Plaks, Kong, and Werb. *Cell Stem Cell* 2015.
- Safa, et al. *Genes & Diseases* 2015.
- Singh, et al. *EMBO* 2015.
- Van Keymeulen, et al. *Nature* 2015.
- Ye, et al. *Nature* 2015.
- Auffinger et al. *Cell Death and Differentiation* 2014.
- Easwaran et al. *Molecular Cell* 2014.
- Pattabiraman and Weinberg *Nature Reviews Drug Discovery* 2014.
- Chaffer et al. *Cell* 2013.
- Marianovic, Weinberg, and Chaffer. *Clin Chem* 2013.
- Zhang, et al. *Stem Cells* 2013.
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- Zhu, et al. *Cancer Cell International* 2013.
- Landberg et al. *Nature* 2012.
- Quail, Taylor, and Postovit. *Current Stem Cell Research & Therapy* 2012.
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- Morel et al. *PLoS One* 2008.
- Rapp, Cetecci, and Schreck. *Cell Cycle* 2008.

→ How do cells acquire stemness?

→ Is the niche necessary?

De-differentiation and cellular plasticity in vivo

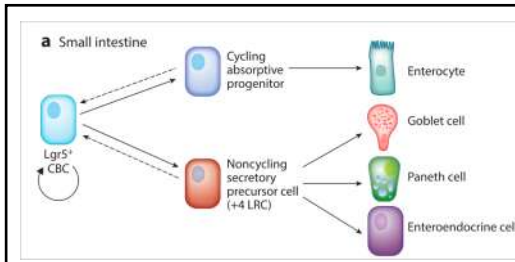


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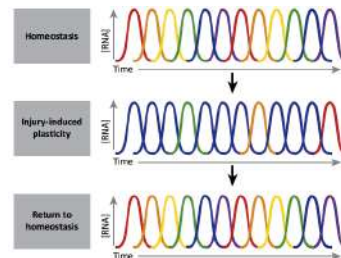
What kind of property is stemness?

Conflicting views of stem cells



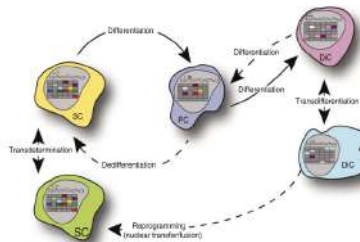
« **Phenotype or Function?** »

Clevers and Watt, *Annual Rev Biochem* 2018



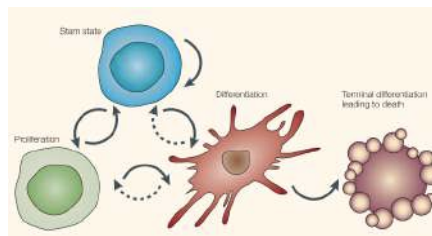
« **Types or states?** »

Alder & Sanchez Alvarado, *Trends in Cell Biol* 2015



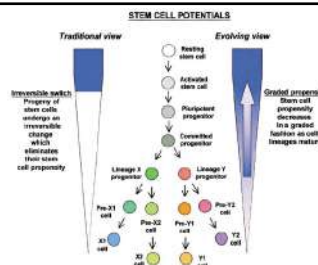
« **Nature or nurture?** »

Mikkers & Frisen, *EMBO* 2005



« **Entity or state?** »

Zipori, *Nature Rev Genet* 2004

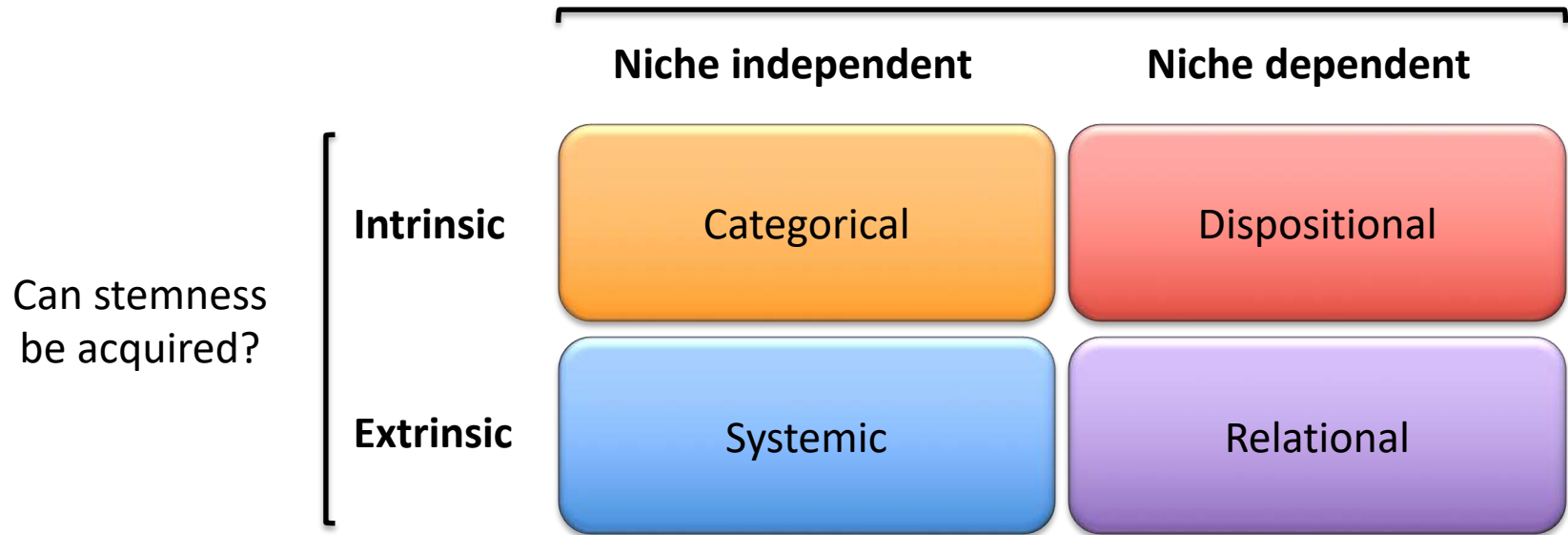


« **Entity or function?** »

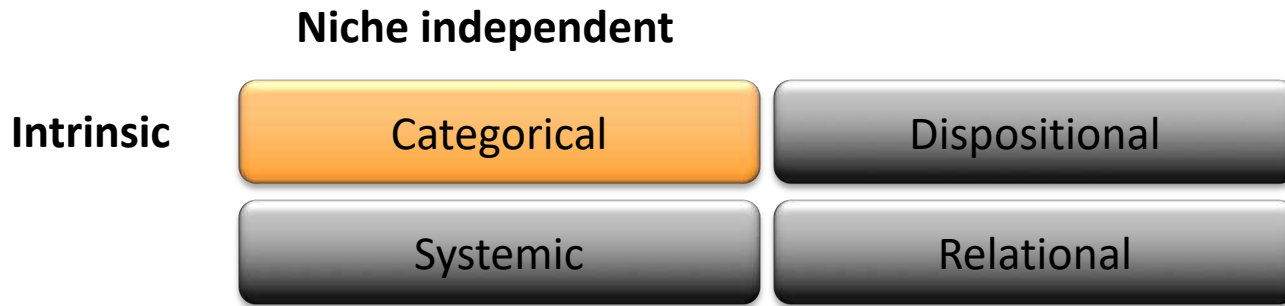
Blau, Brazelton, Weimann, *Cell* 2001

What is stemness?

Does the microenvironment play a determinant role in stemness?

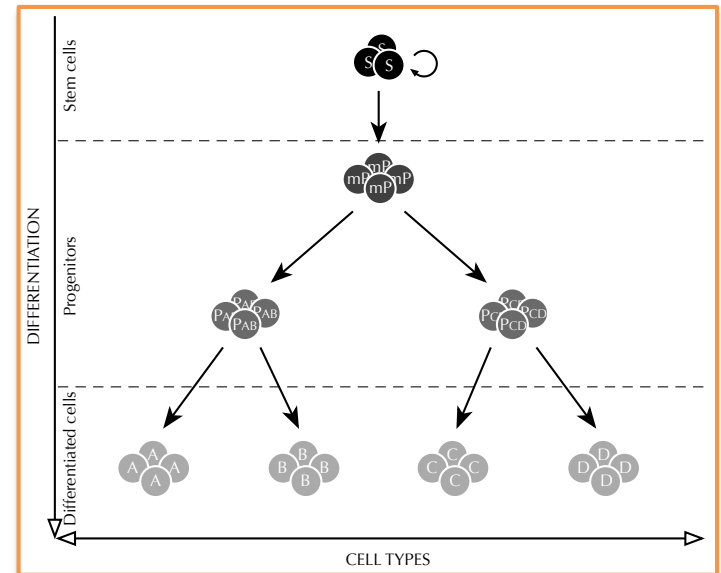


What is stemness? The classical view

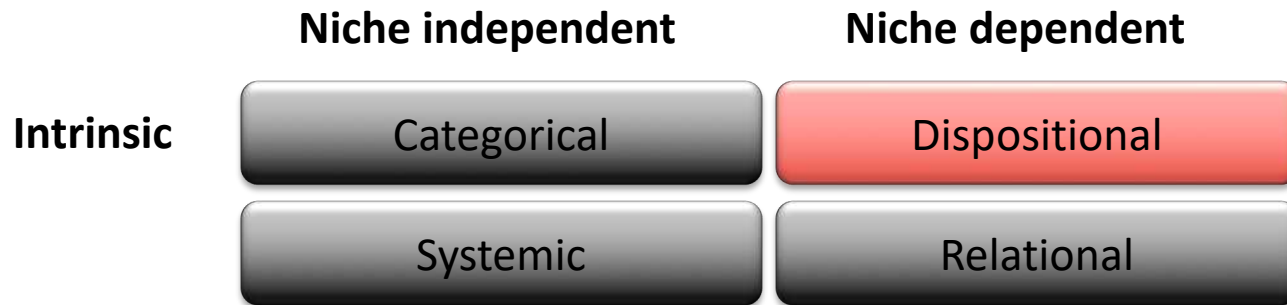


Example: Atomic structure of elements

Group	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
1	1 H																	2 He
2	3 Li	4 Be											5 B	6 C	7 N	8 O	9 F	10 Ne
3	11 Na	12 Mg											13 Al	14 Si	15 P	16 S	17 Cl	18 Ar
4	19 K	20 Ca	21 Sc	22 Ti	23 V	24 Cr	25 Mn	26 Fe	27 Co	28 Ni	29 Cu	30 Zn	31 Ga	32 Ge	33 As	34 Se	35 Br	36 Kr
5	37 Rb	38 Sr	39 Y	40 Zr	41 Nb	42 Mo	43 Tc	44 Ru	45 Rh	46 Pd	47 Ag	48 Cd	49 In	50 Sn	51 Sb	52 Te	53 I	54 Xe
6	55 Cs	56 Ba	57 La	72 Hf	73 Ta	74 W	75 Re	76 Os	77 Ir	78 Pt	79 Au	80 Hg	81 Tl	82 Pb	83 Bi	84 Po	85 At	86 Rn
7	87 Fr	88 Ra	89 Ac	104 Rf	105 Db	106 Sg	107 Bh	108 Hs	109 Mt	110 Ds	111 Rg	112 Cn	113 Nh	114 Fl	115 Mc	116 Lv	117 Ts	118 Og
				58 Ce	59 Pr	60 Nd	61 Pm	62 Sm	63 Eu	64 Gd	65 Tb	66 Dy	67 Ho	68 Er	69 Tm	70 Yb	71 Lu	
				90 Th	91 Pa	92 U	93 Np	94 Pu	95 Am	96 Cm	97 Bk	98 Cf	99 Es	100 Fm	101 Md	102 No	103 Lr	



Stemness as a relational property

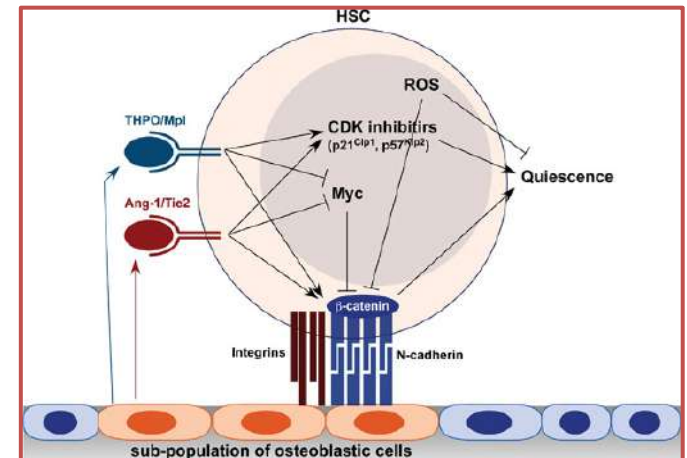


Definition: intrinsic property whose expression depends on extrinsic factors

Example: Fragility



Hematopoietic stem cells

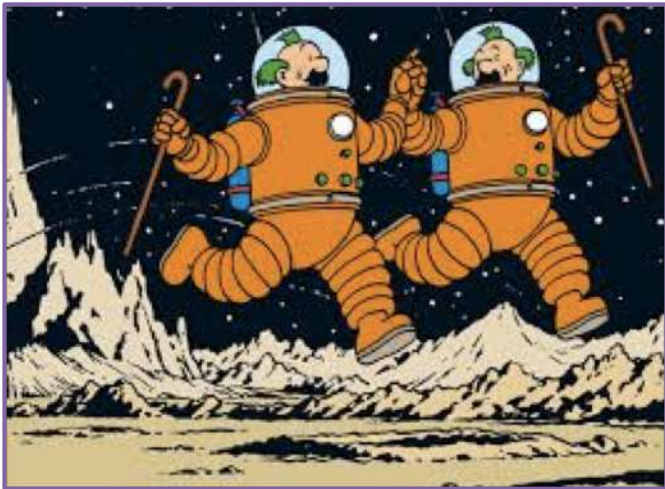


Stemness as a relational property

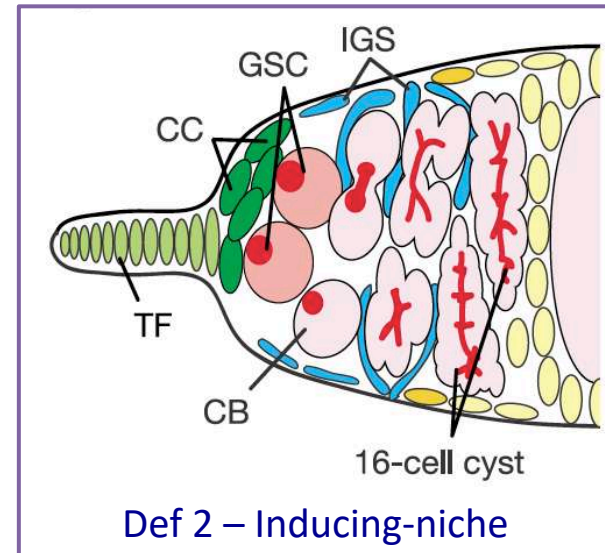
	Niche independent	Niche dependent
Intrinsic	Categorical	Dispositional
Extrinsic	Systemic	Relational

Definition: a relational property is a property that emerges from a particular relationship between two entities.

Example: Body weight



Example: Germ line

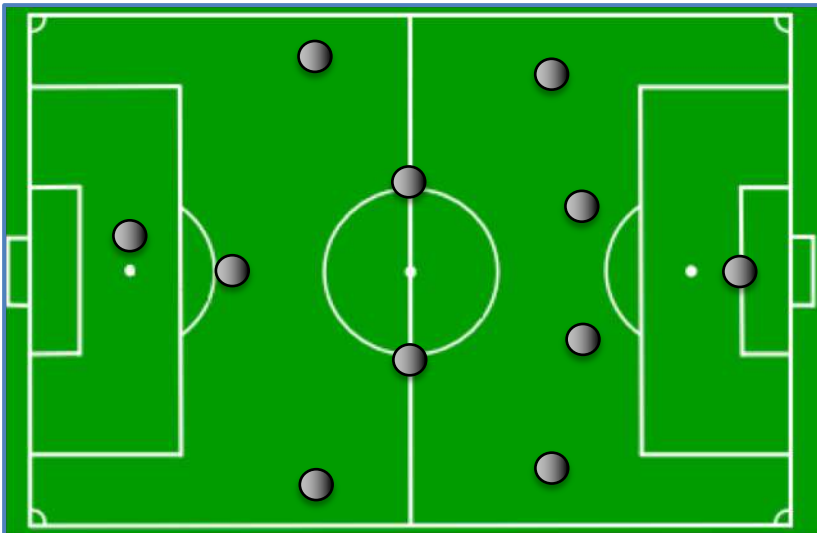


Stemness as a systemic property

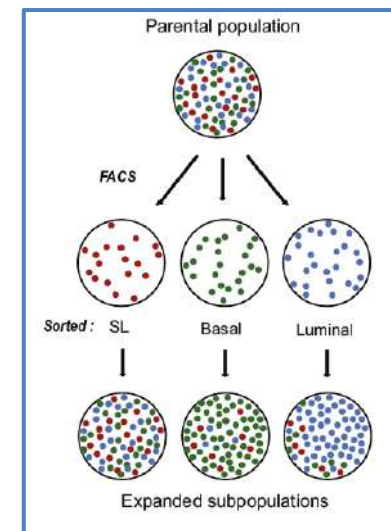
	Niche independent	Niche dependent
Intrinsic	Categorical	Dispositional
Extrinsic	Systemic	Relational

Definition: a property (generally a function) maintained by a system

Example: Soccer position



Example: Breast cancer cell lines



Gupta et al. Cell 2011

Outline

Intro: what are stem cells?

What kind of property is stemness?

Stemness can be 4 kinds of
properties

Depends on niche and
dedifferentiation

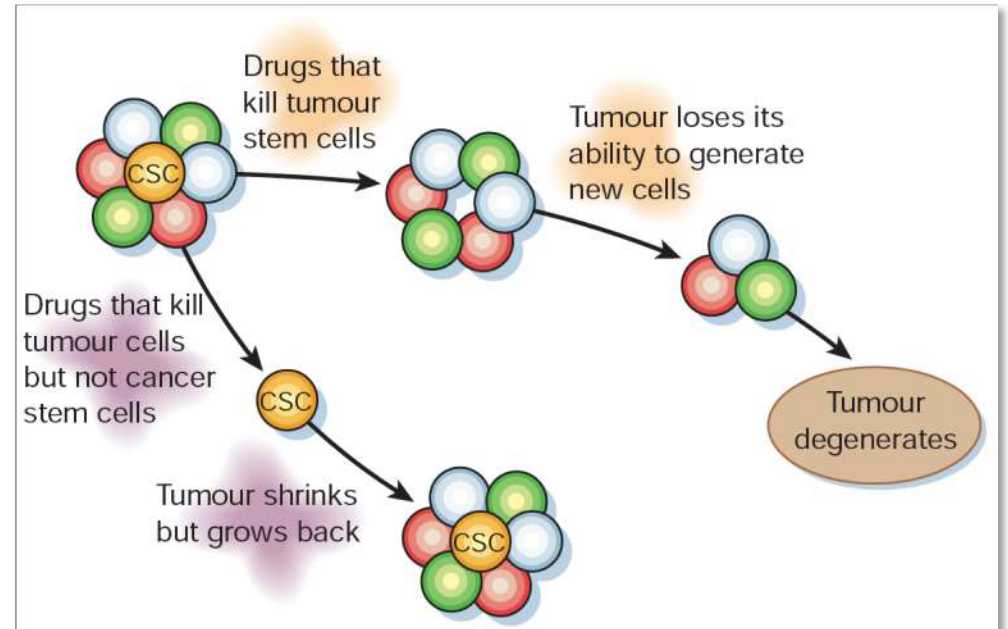
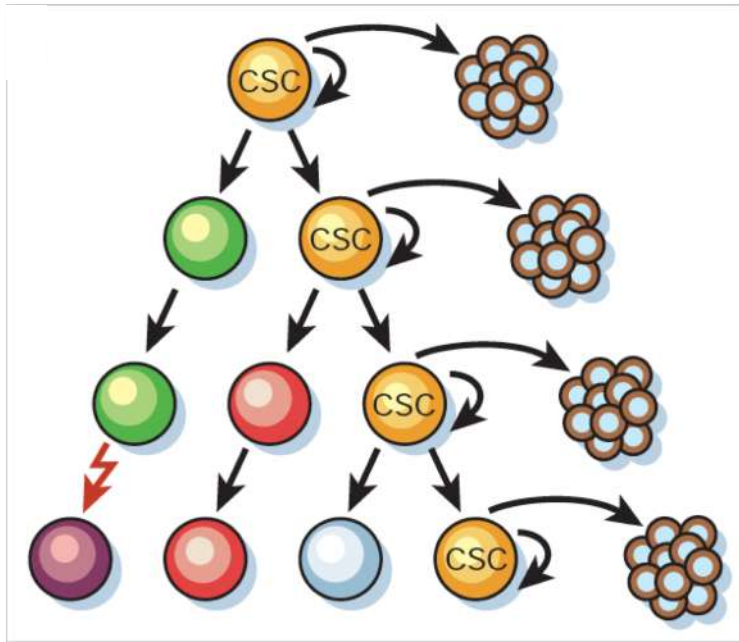
Outline

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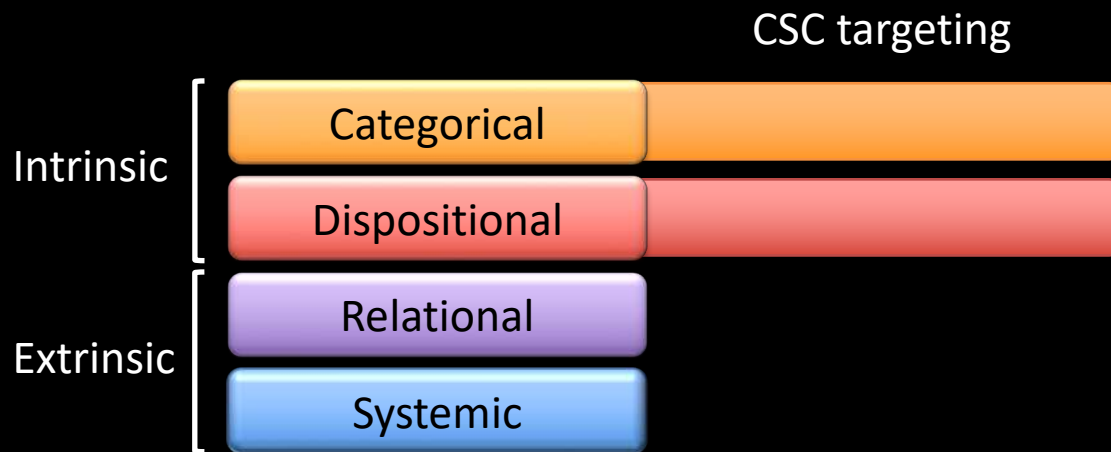
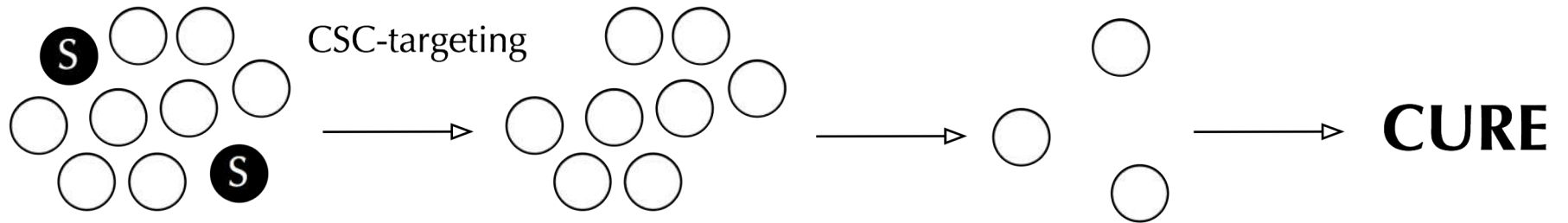
What kind of property is stemness?

Does stemness nature matter?

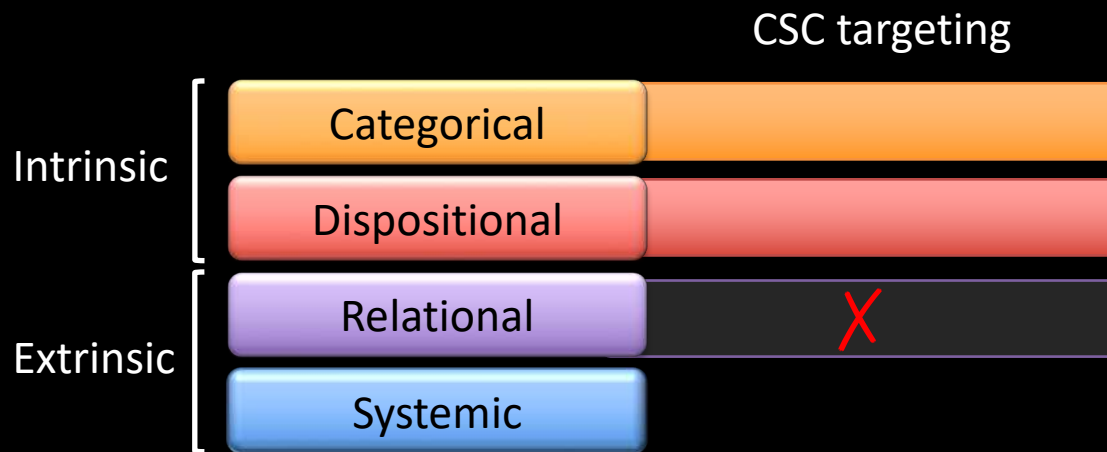
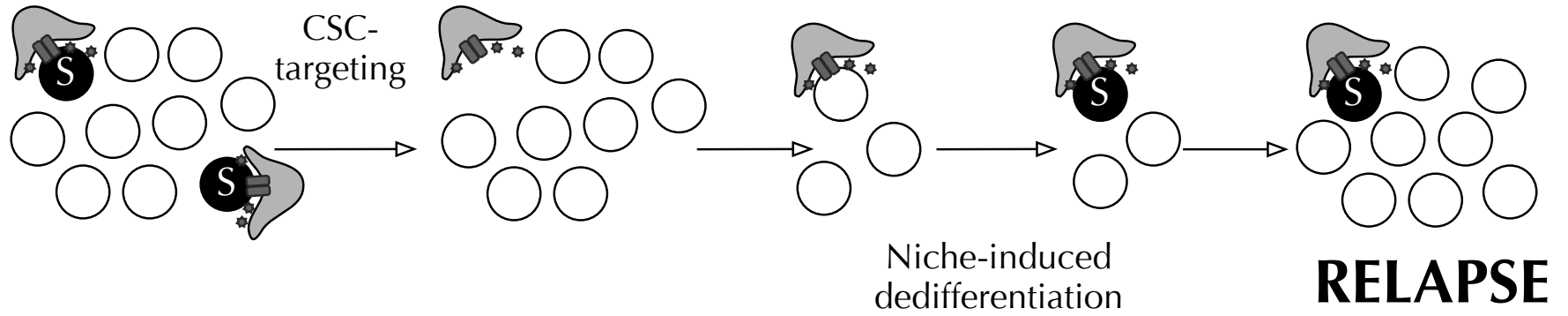
The CSC model

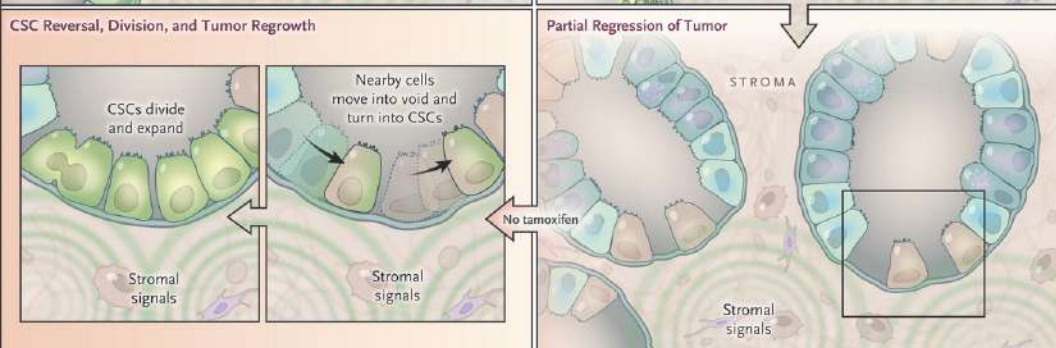
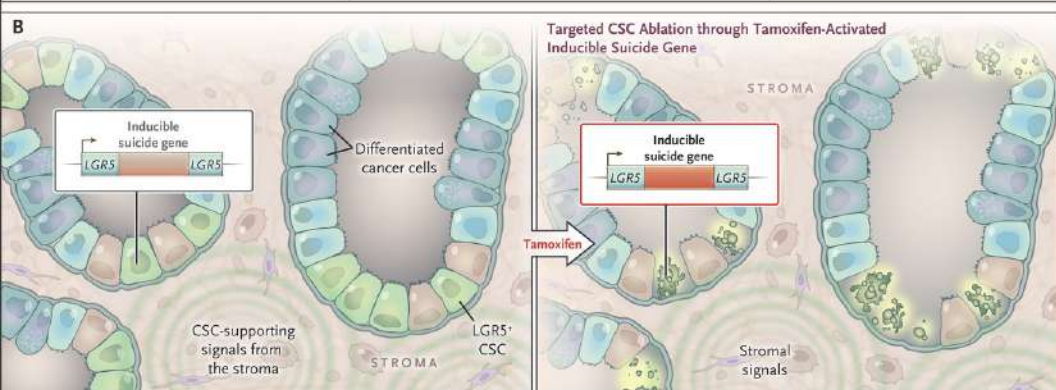
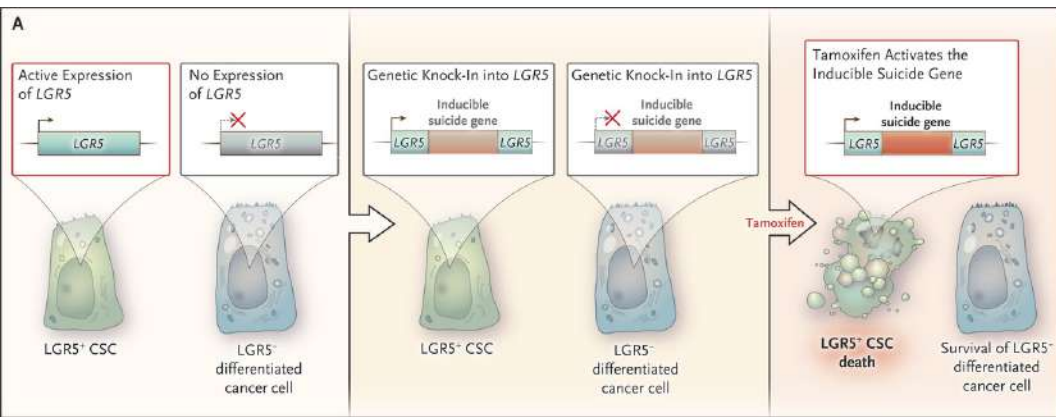


CSCs-targeting therapeutic strategy

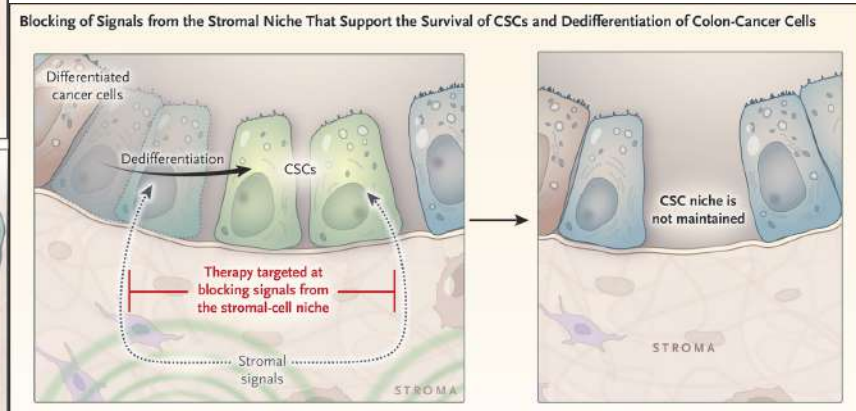


CSCs-targeting therapeutic strategy



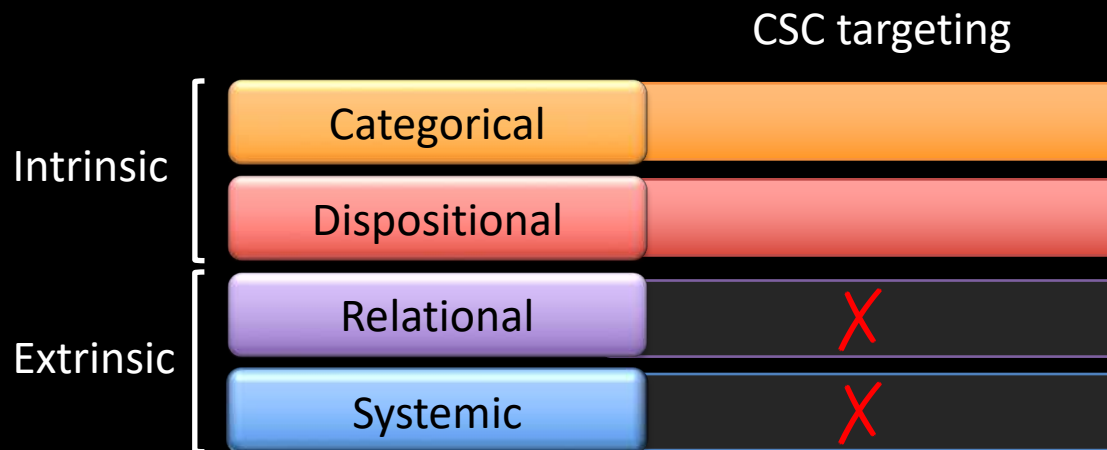
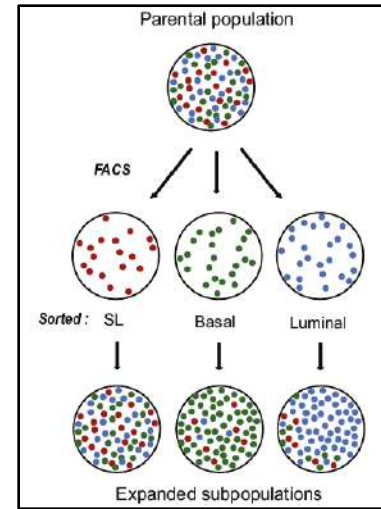
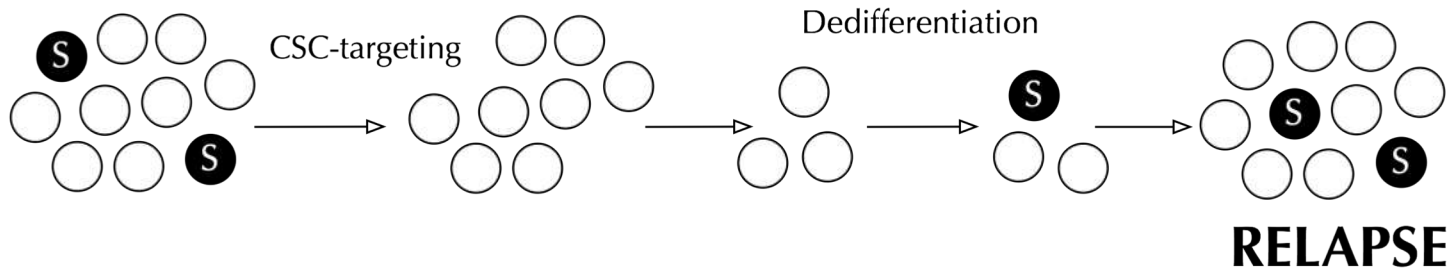


Medema JP. N Engl J Med 2017;377:888-890.

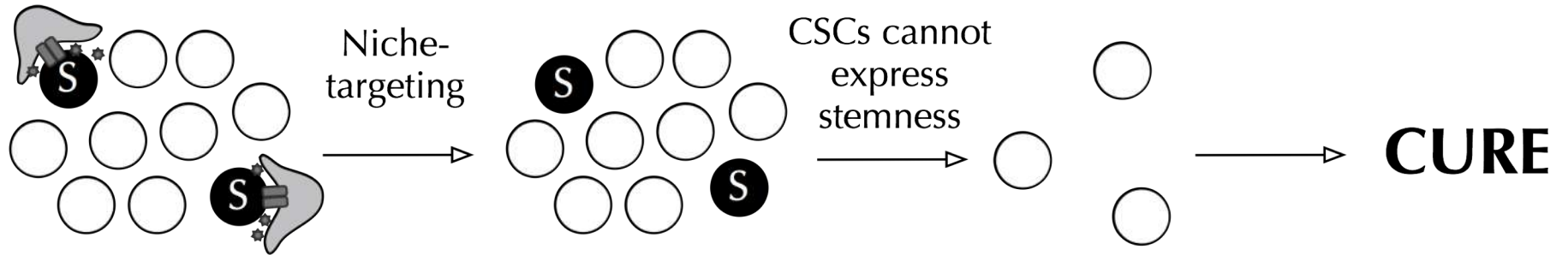


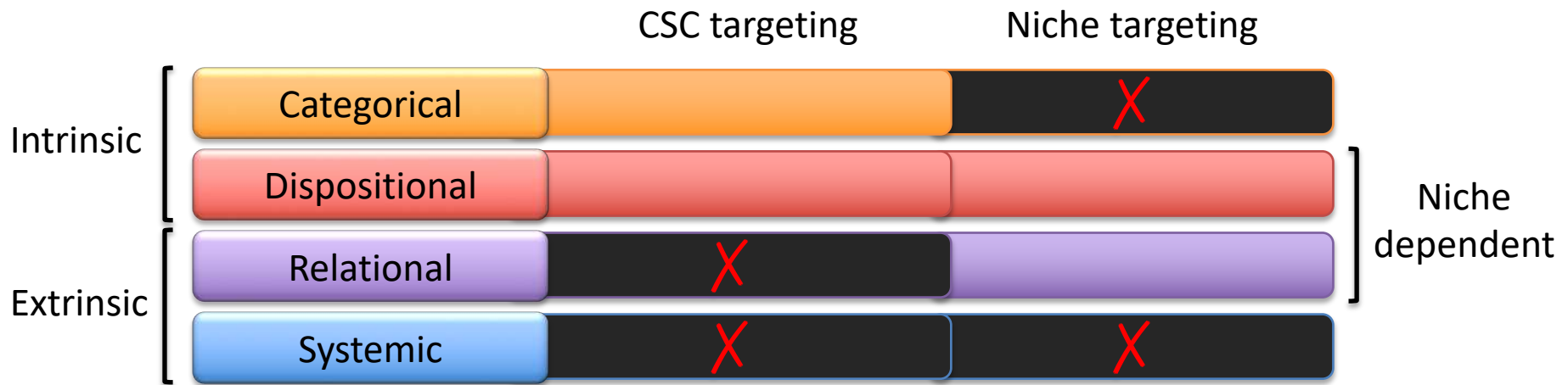
- Shimokawa et al. *Nature* 2017.
- De Sousa e Melo et al. *Nature* 2017.

CSCs-targeting therapeutic strategy



Targeting the niche-cell relationship?





Biol Philos (2018) 33:18
<https://doi.org/10.1007/s10539-018-9629-z>



Cancer stem cells modulate patterns and processes of evolution in cancers

Lucie Laplane^{1,2}

Outline

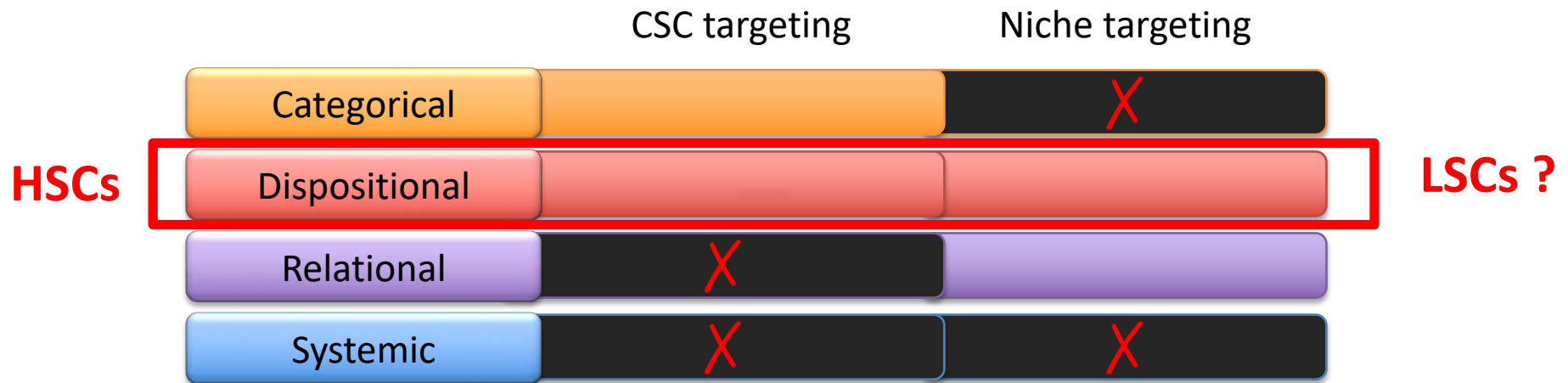
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Does stemness nature matter?

Is stemness nature stable?

Is stemness the same type of property in cancer?



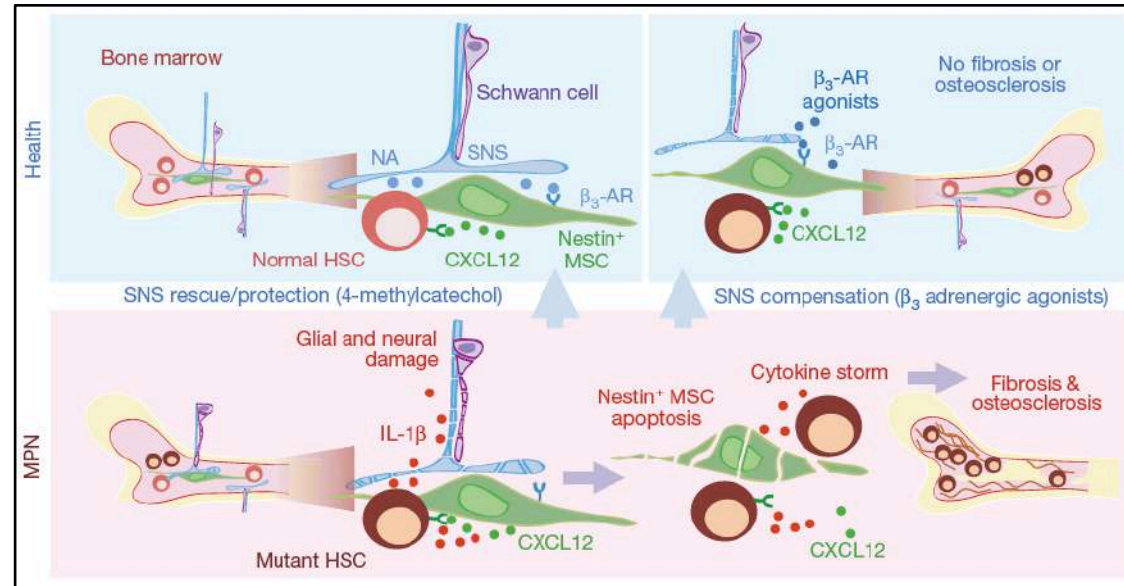
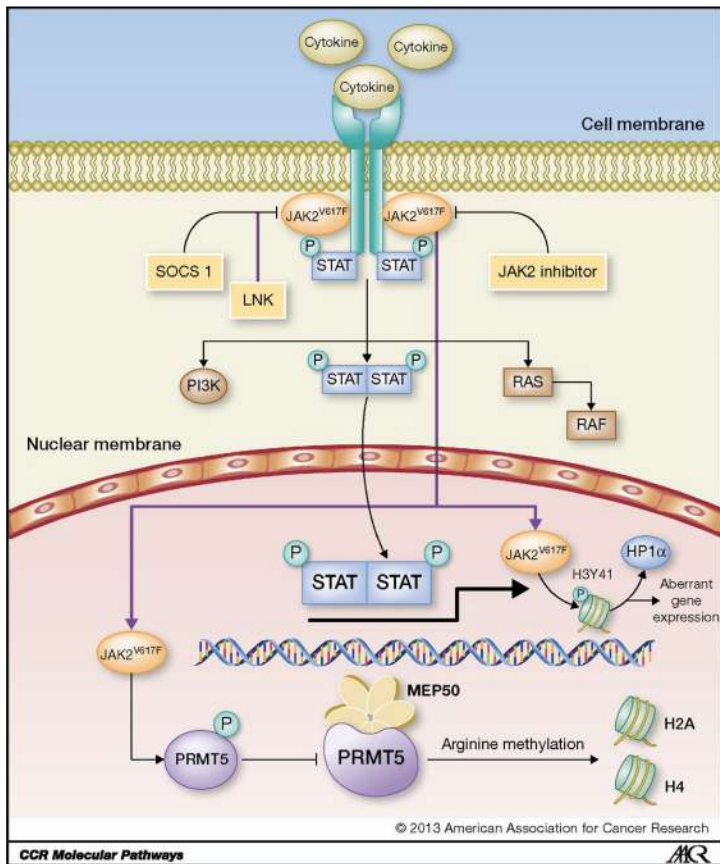
Eric Solary



William Vainchenker

Is stemness the same type of property in cancer?

- Constitutive activation of signaling pathways and niche degradation in myeloproliferative neoplasms

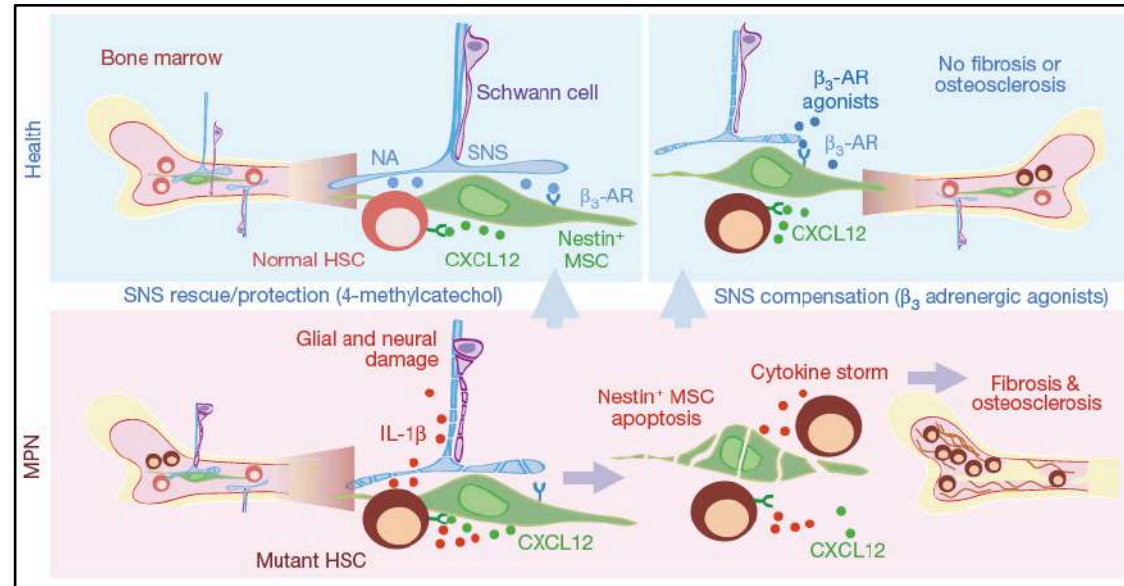
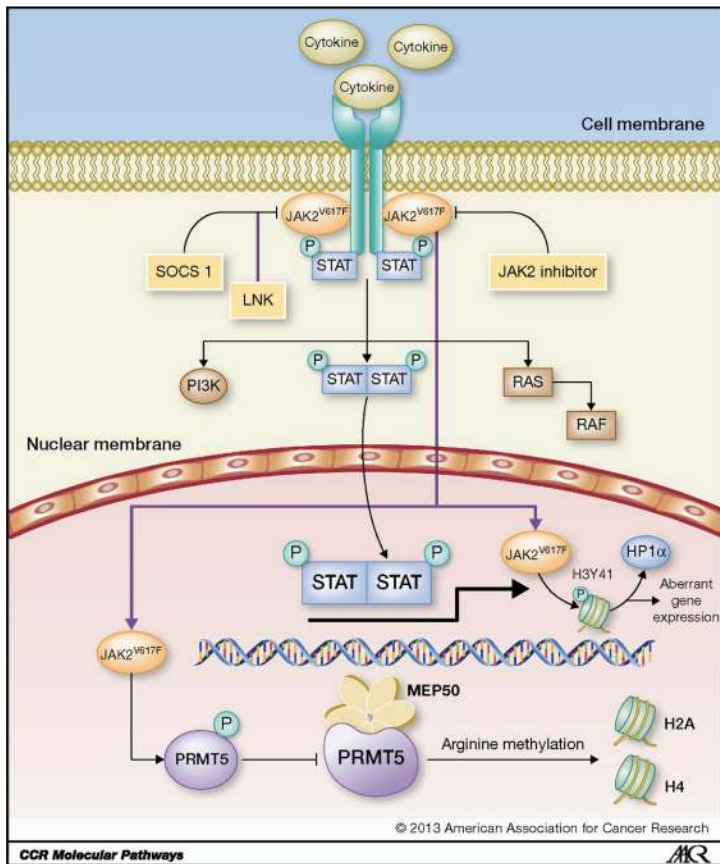


Arranz et al. Nature 2014

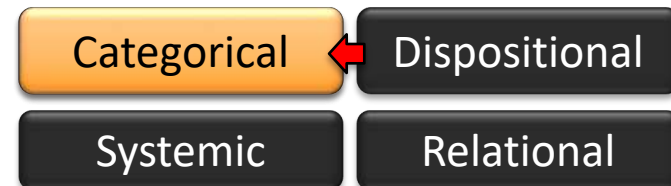


Is stemness the same type of property in cancer?

- Constitutive activation of signaling pathways and niche degradation in myeloproliferative neoplasms

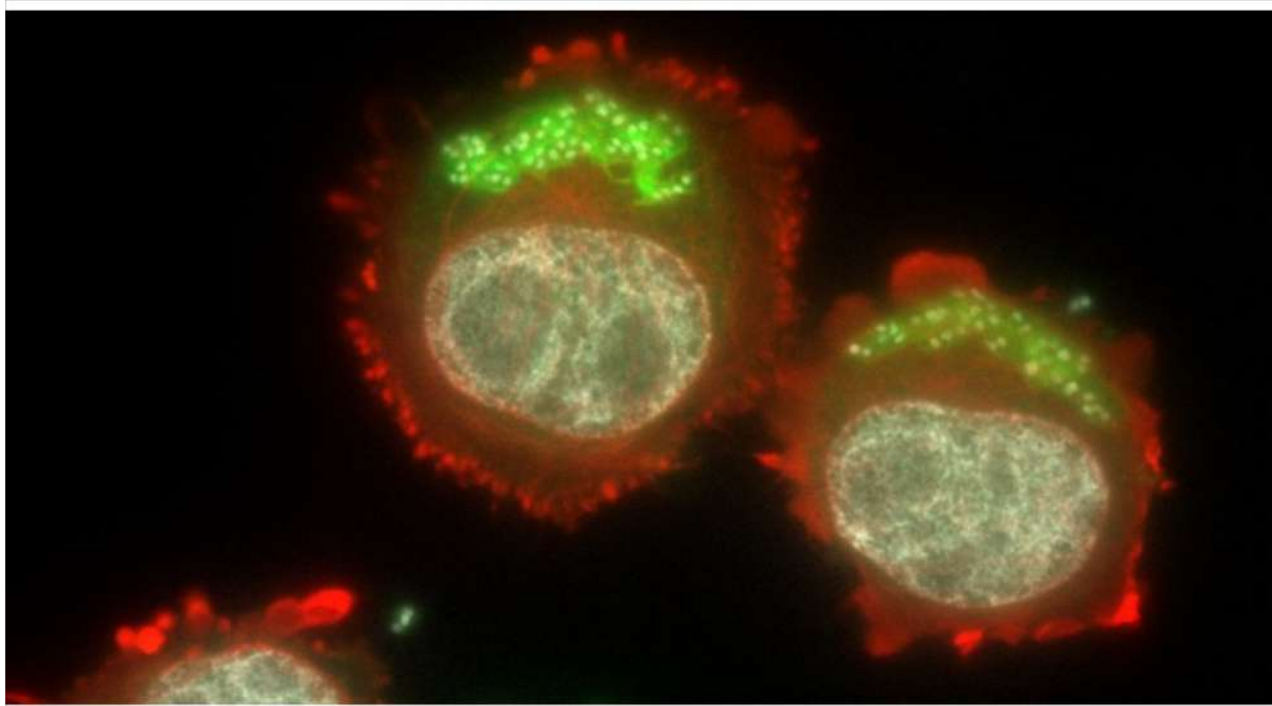


Arranz et al. Nature 2014



Is stemness the same type of property in cancer?

Monocytes/macrophages transformation by intracellular parasites



Jonathan Weitzman's courtesy

Categorical

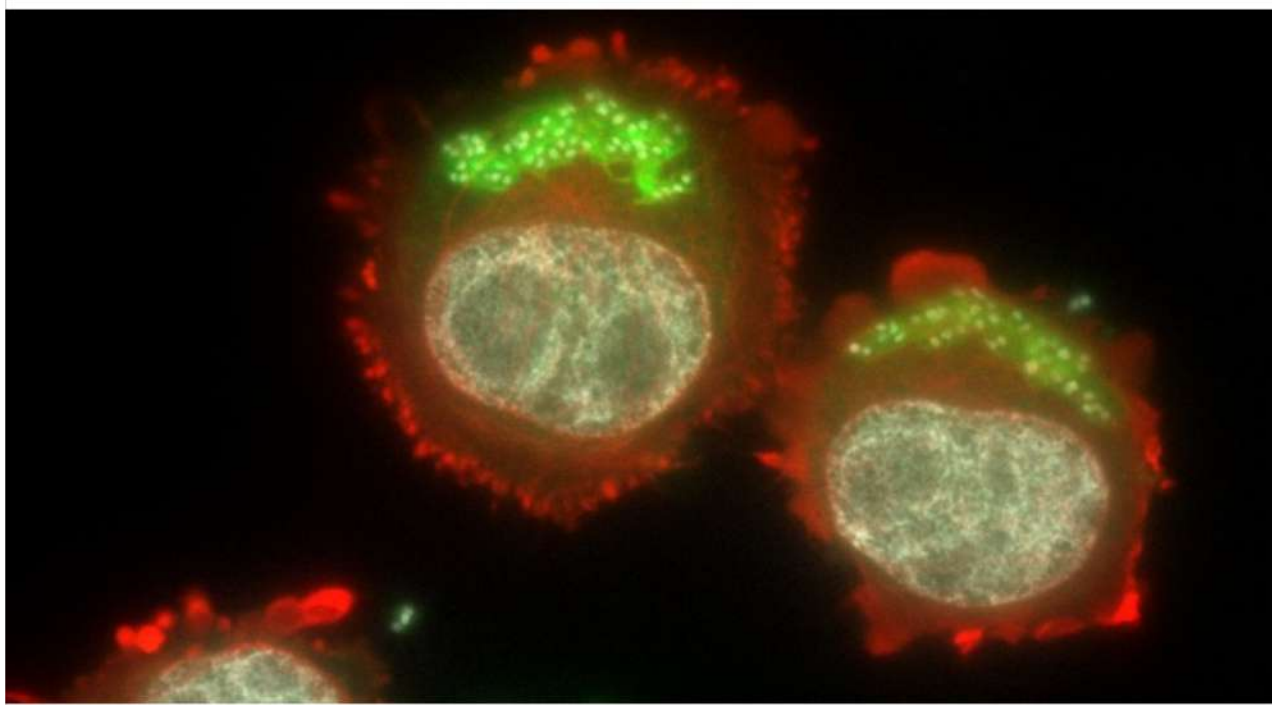
Dispositional

Systemic

Relational

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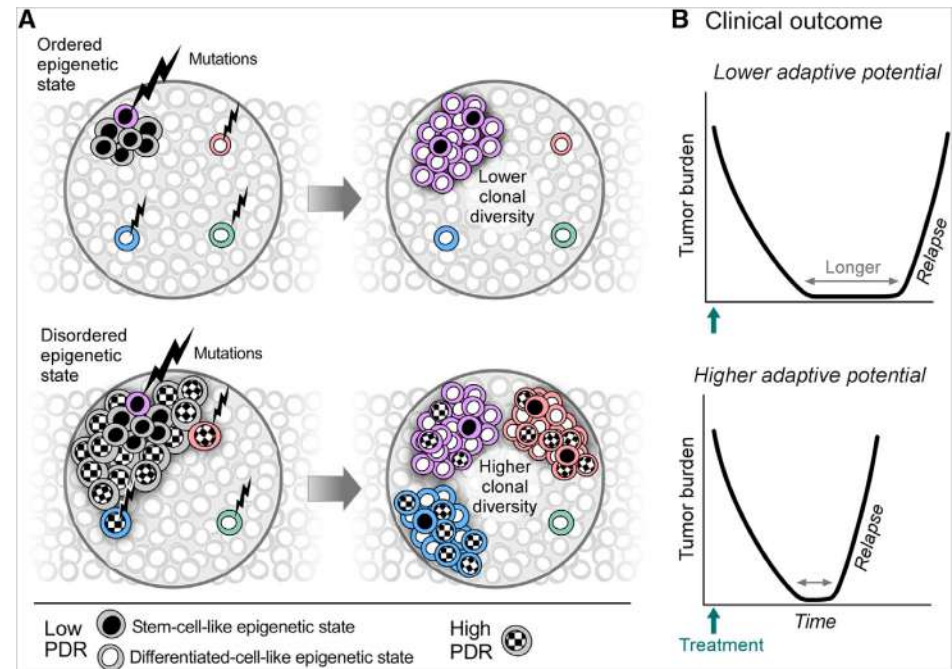
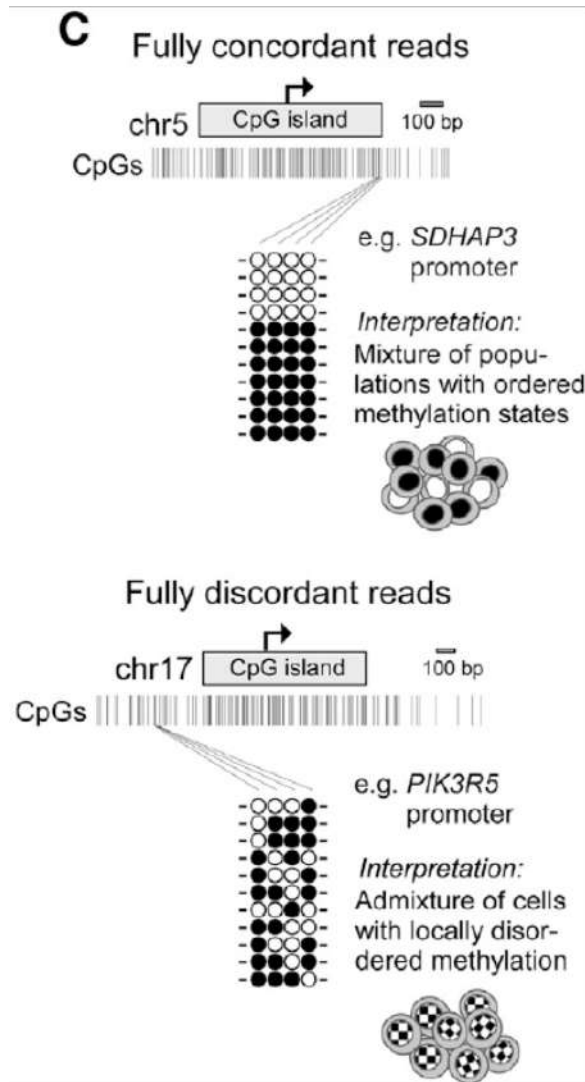


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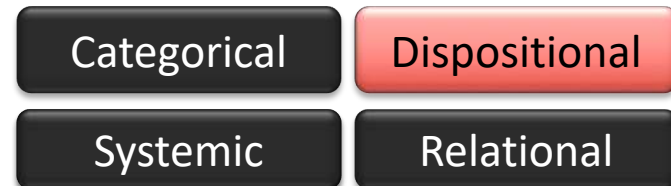


Is stemness the same type of property in cancer?

- Epigenetic alterations and cell plasticity

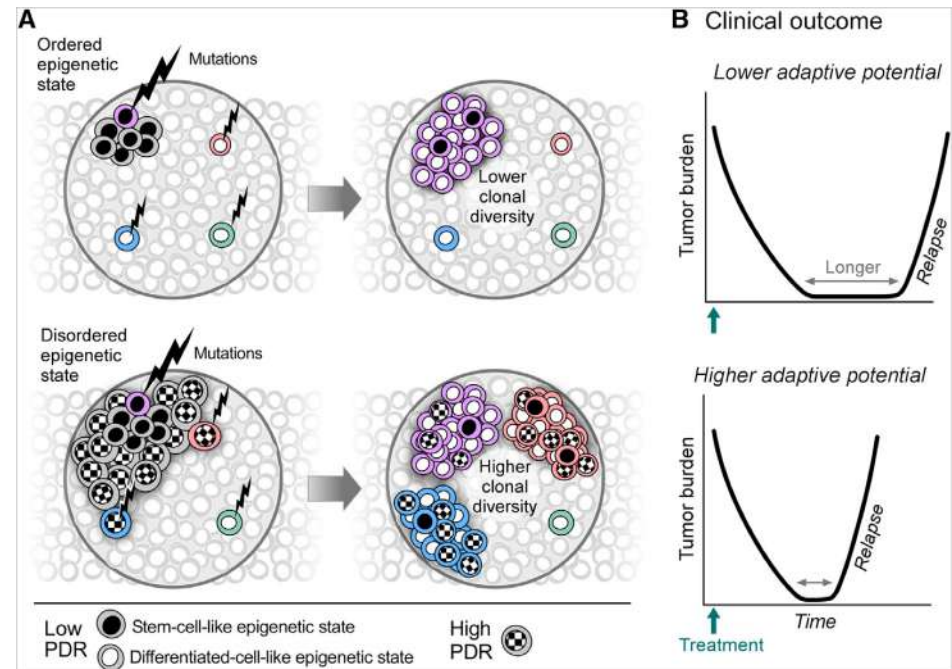
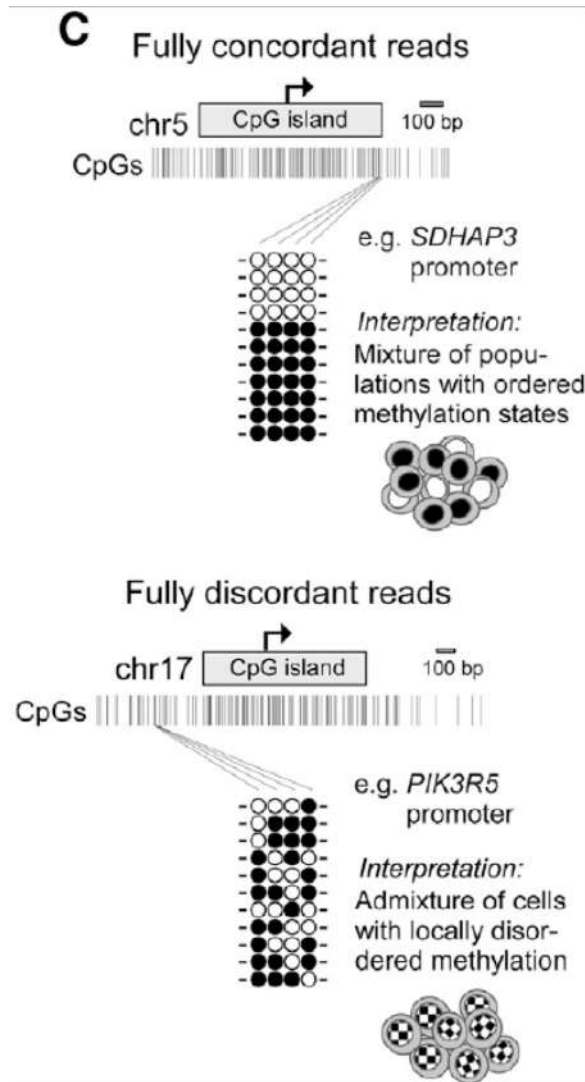


Landau et al. Cancer cell 2014

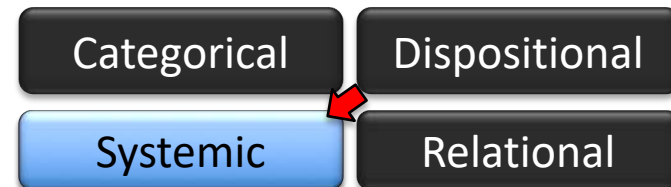


Is stemness the same type of property in cancer?

- Epigenetic alterations and cell plasticity



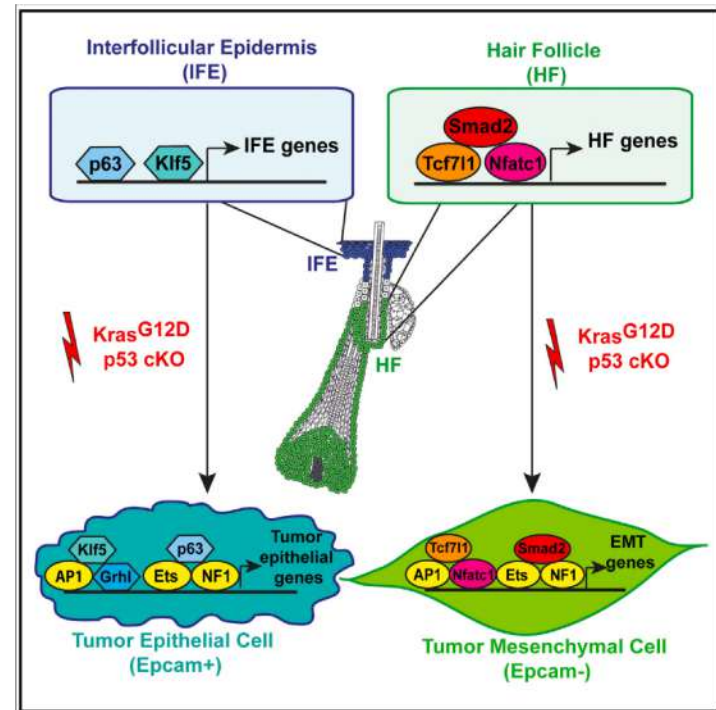
Landau et al. Cancer cell 2014



Is stemness the same type of property in cancer?

1. Stemness can be a different type of property in CSCs as compared to their normal counterparts
2. Can change throughout disease progression
3. Depends on the alterations
4. Depends on the cell of origin

Squamous cell carcinoma:



Latil et al. *Cell Stem Cell* 2017

Is stemness the same type of property in cancer?

1. Stemness can be a different type of property in CSCs as compared to their normal counterparts
 2. Can change throughout disease progression
 3. Depends on the alterations
 4. Depends on the cell of origin
-
- **Needs experimental validations**
 - **Might require therapeutic adaptations**
 - **Stemness transitions: cause or consequence of disease occurrence/progression**

Outline

Intro: what are stem cells?

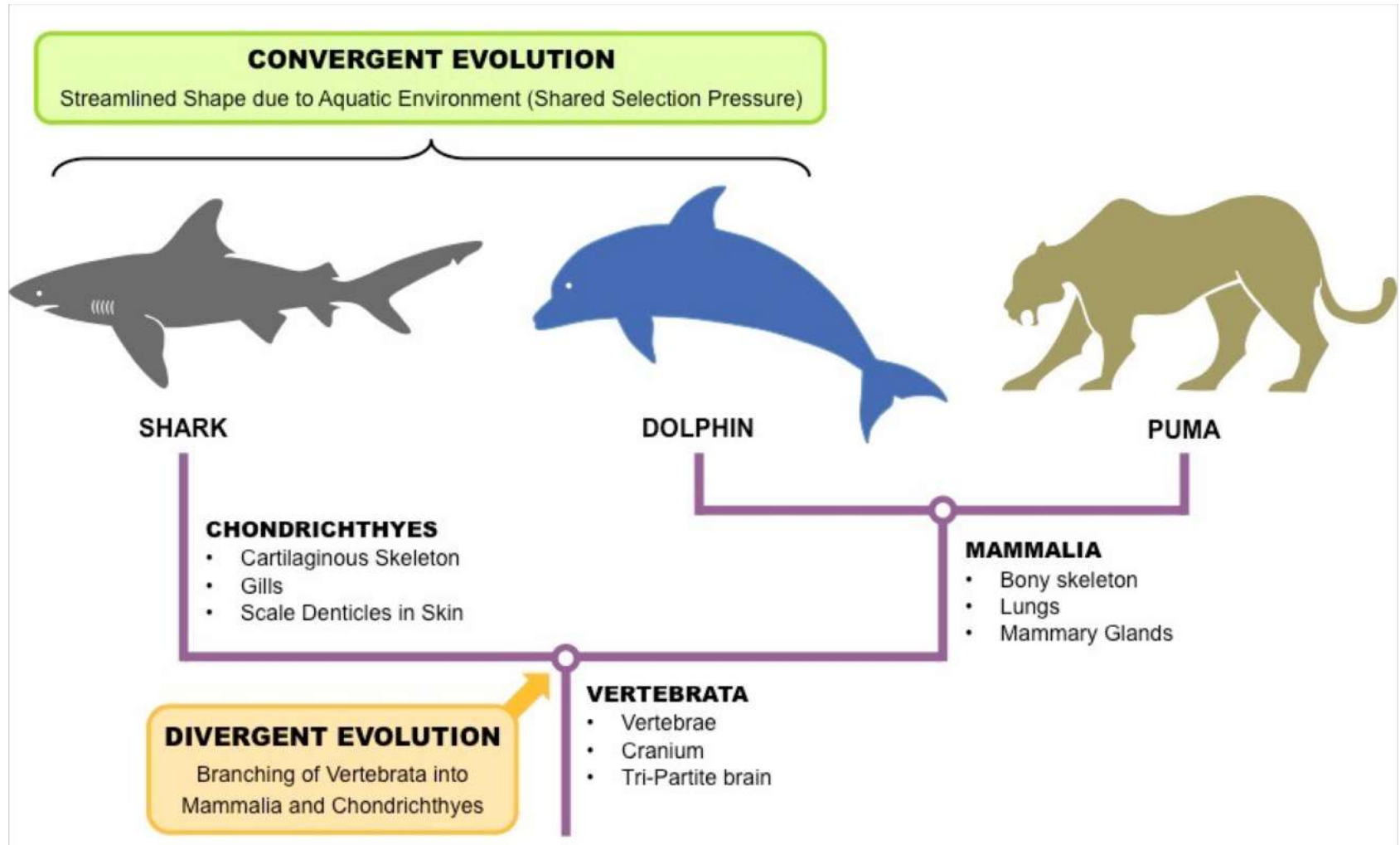
What kind of property is stemness?

Does stemness nature matter?

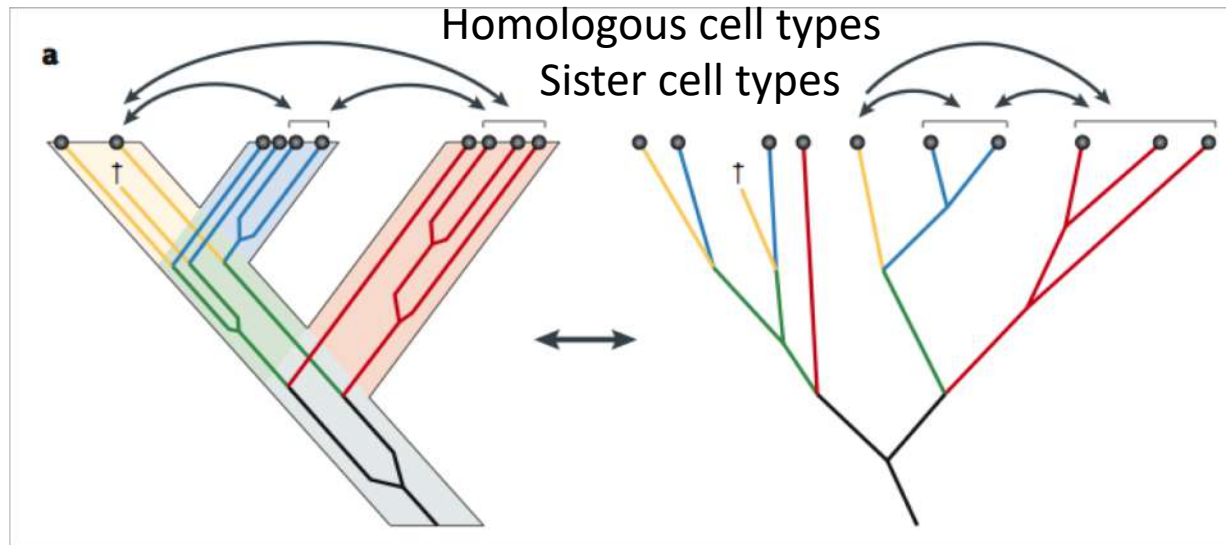
Is stemness nature stable?

“Stem cell” unity ?

“No such thing as a fish”



“No such thing as a stem cell?”



Arendt 2008



M. Vervoort



E. Gazave

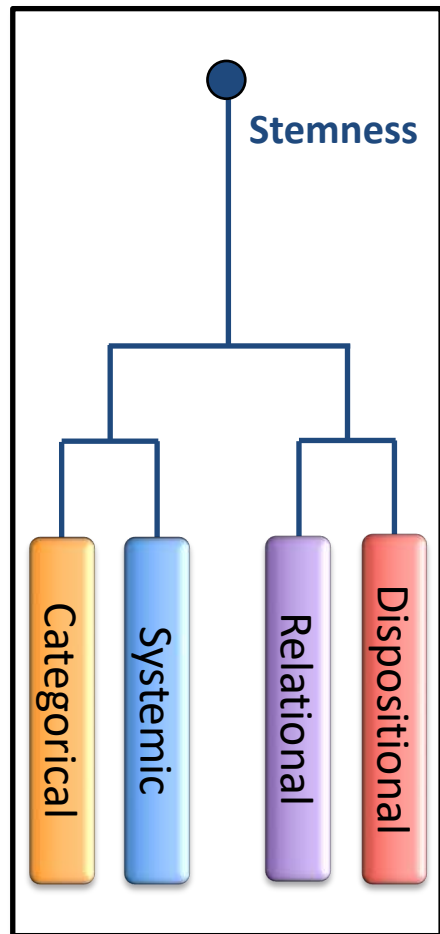


P. Kerner

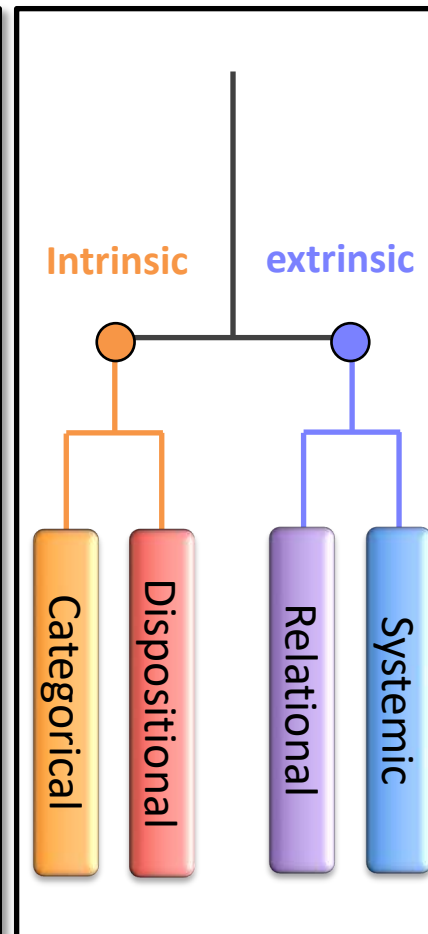
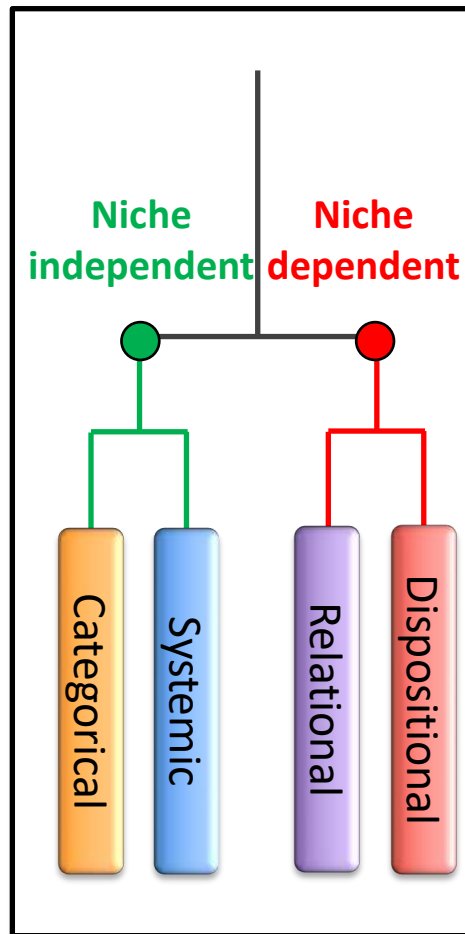
Institut Jacques Monod

“No such thing as a stem cell?”

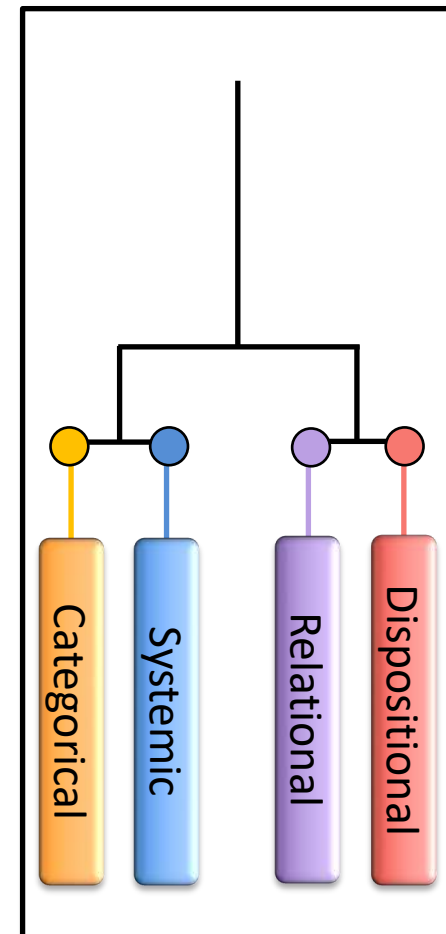
One common origin



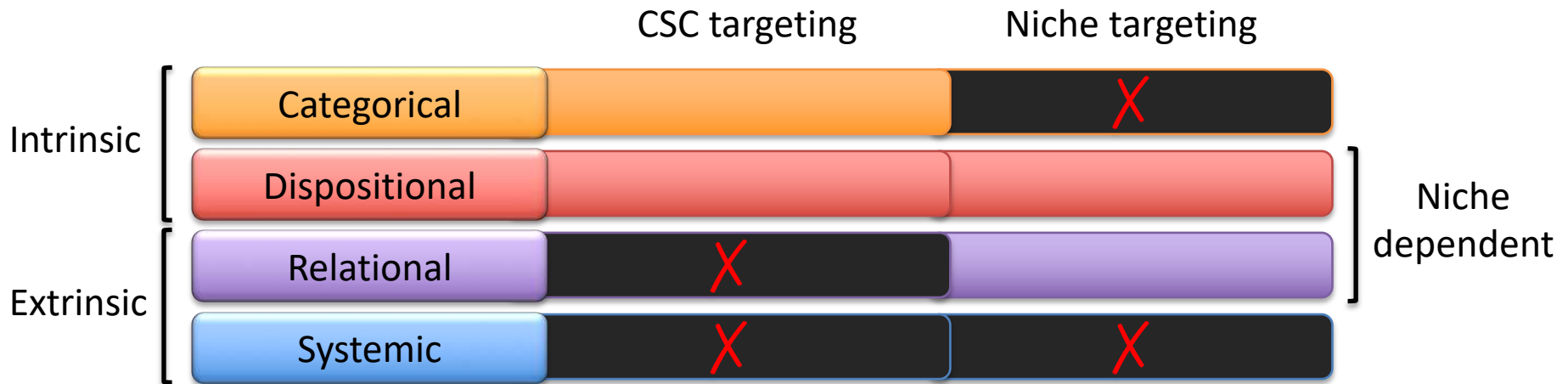
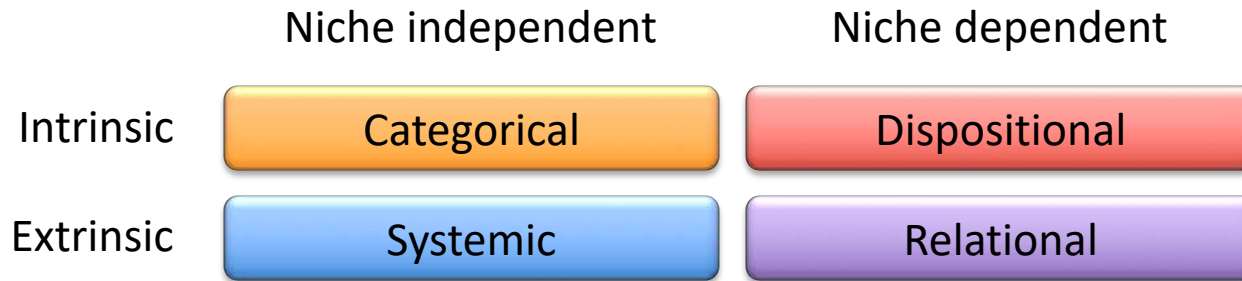
Several independent origins



Independent origins



Conclusion



- Stemness identity should be address in all stem cell types
- And in cancers depending on oncogenic alterations/cell of origin
- Experimental biology + phylogeny + philosophy required

Thank you

For the invitation

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- Institut Jacques Monod (Michel Vervoort team)

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Some ref:

- Laplane L (2016) *Cancer Stem Cells: Philosophy and Therapies*. Harvard University Press.
- Laplane L et Solary E (2017). "Identité des cellules souches normales et cancéreuses". *Médecine/Sciences* 33(10) : 899-904.
- Laplane L (2018) "Cancer stem cells modulate patterns and processes of evolution in cancers". *Biology and Philosophy* 33(3-4): 18