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de BORDEAUX

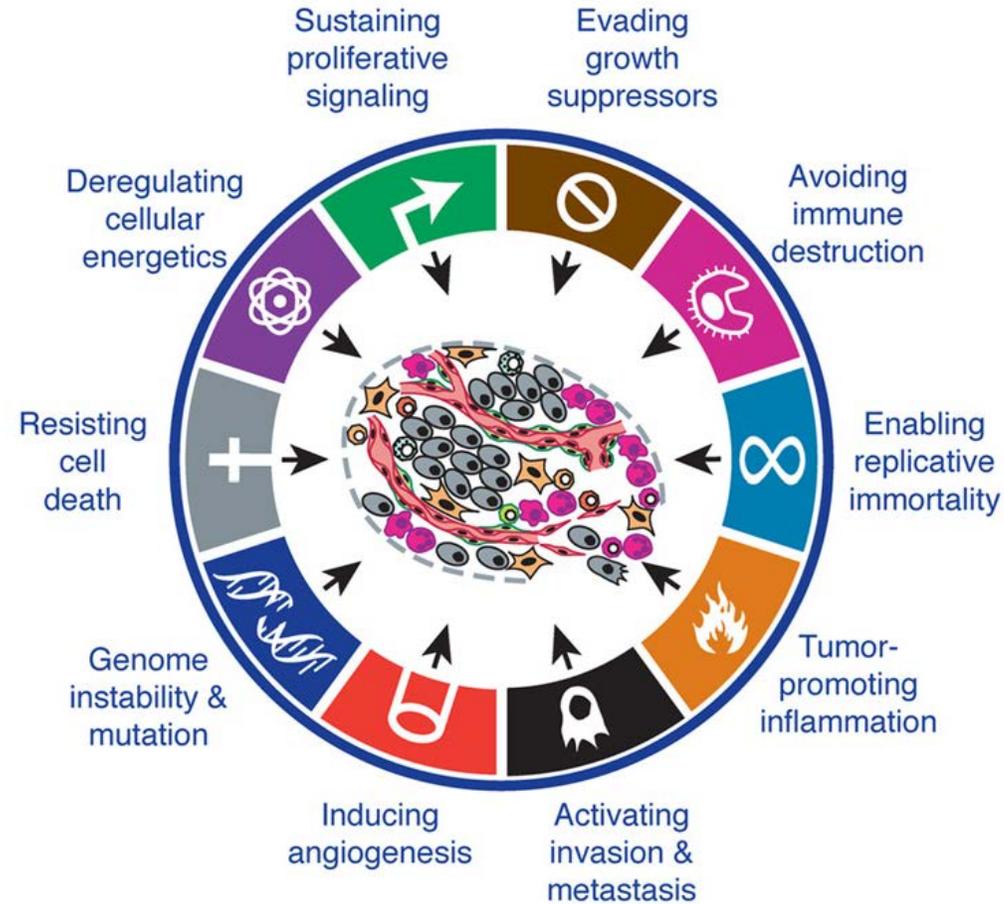
Understanding cancer progression and its control:  
the (im)balance between tissue construction, destruction and reconstruction?

*Conceptual analysis of immune activation in the context of the tumour microenvironment*

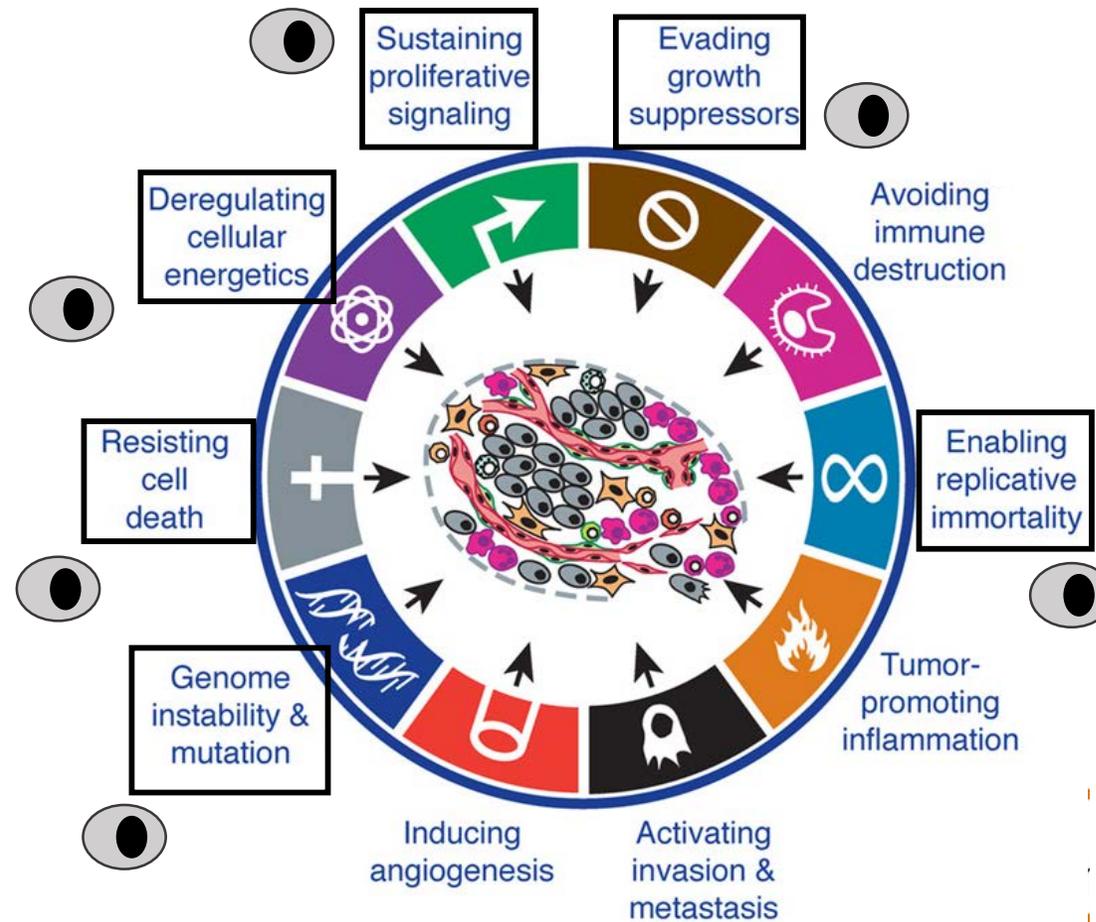
**Elena Rondeau, Thomas Pradeu, Nicolas Larmonier**

*CNRS-UMR5164 ImmunoConcept, University of Bordeaux, France*

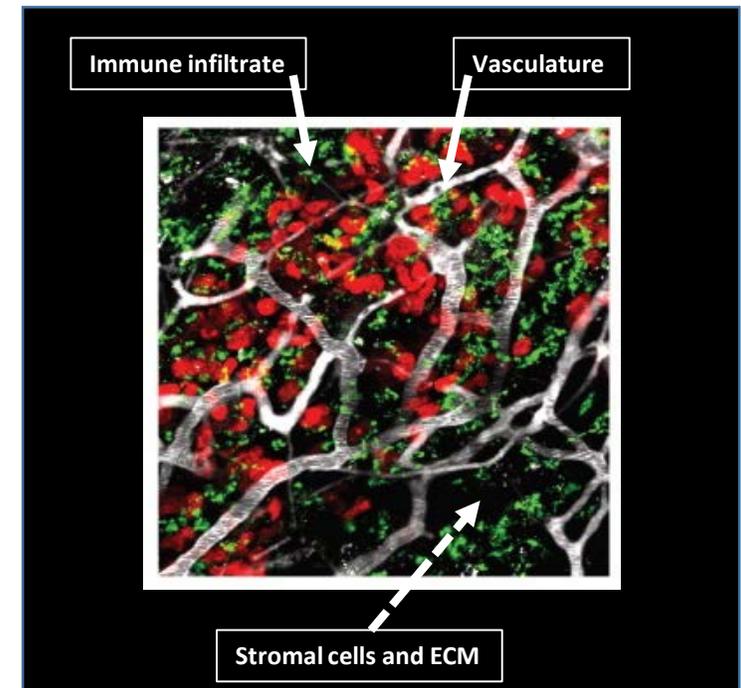
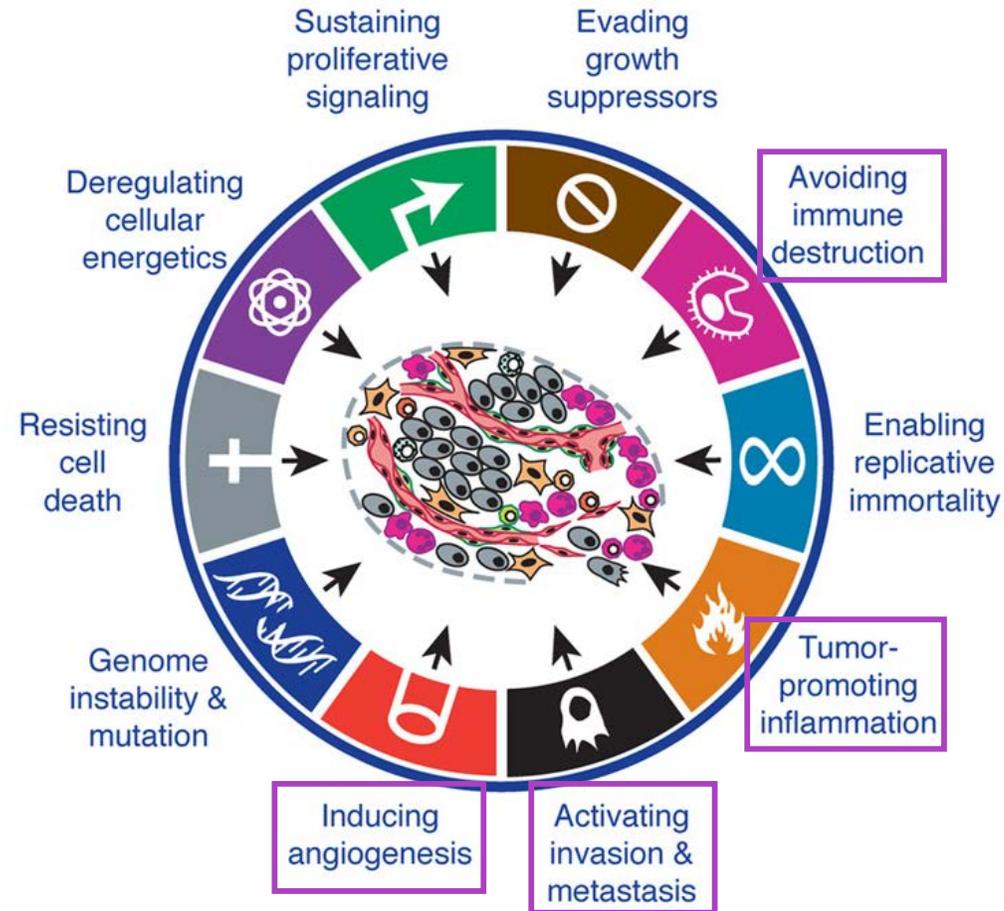
# Cancer: defining characteristics?



# Cancer cell - centered characteristics



# Contextual and environmental characteristics



# Cancer: defining characteristics?

- Cell proliferation and migration
- Angiogenesis
- Epithelial/mesenchymal transitions
- Role of extracellular matrix

- Organ-specific origin of malignant cells
- Differentiation plasticity
- Long-distance communication

- Stroma remodelling
- Inflammation and immune activation
- Vascular alterations

# Two biological analogies for cancer

- Cell proliferation and migration
- Angiogenesis
- Epithelial/mesenchymal transitions
- Role of extracellular matrix

- Organ-specific origin of malignant cells
- Differentiation plasticity
- Long-distance communication

**Organ development?**

- Stroma remodelling
- Inflammation and immune activation
- Vascular alterations

**Tissue repair?**

Organ development?

 Developmental Cell  
**Review**

**Tumors as Organs: Complex Tissues that Interface with the Entire Organism**

**2008**

Mikala Egeblad,<sup>1,\*</sup> Elizabeth S. Nakasone,<sup>1,2</sup> and Zena Werb<sup>3,\*</sup>  
<sup>1</sup>Cold Spring Harbor Laboratory, 1 Bungtown Road, Cold Spring Harbor, NY 11724, USA  
<sup>2</sup>Watson School of Biological Sciences, Cold Spring Harbor Laboratory, 1 Bungtown Road, Cold Spring Harbor, NY 11724, USA  
<sup>3</sup>Department of Anatomy, University of California, 513 Parnassus Avenue, Box 0452, San Francisco, CA 94143, USA  
\*Correspondence: egeblad@cshl.edu (M.E.), zena.werb@ucsf.edu (Z.W.)  
DOI 10.1016/j.devcel.2010.05.012

REVIEWS

**2001**

**PUTTING TUMOURS IN CONTEXT**

*Mina J. Bissell and Derek Radisky*

## Organ development?

**Cell PRESS**

Developmental Cell  
**Review**

### Tumors as **Organs: Complex Tissues** that Interface with the Entire Organism

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### REVIEWS

**2001**

### PUTTING TUMOURS IN CONTEXT

Mina J. Bissell and Derek Radisky

*seminars in CANCER BIOLOGY*, Vol. 11, 2001: pp. 87-95  
doi:10.1006/scbi.2000.0360, available online at <http://www.idealibrary.com> on **IDEAL®**



Tumors are **unique organs** defined by abnormal signaling and context

Derek Radisky, Carmen Hagios and Mina J. Bissell \*

**2001**

**2006**

Of Extracellular Matrix, Scaffolds, and Signaling: Tissue Architecture Regulates Development, Homeostasis, and Cancer

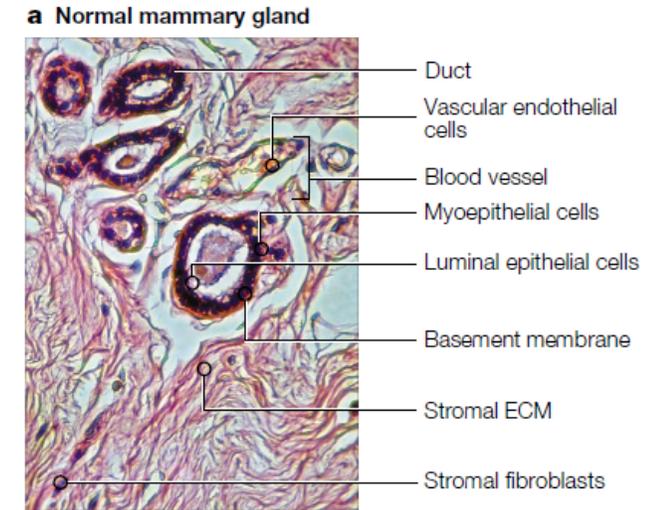
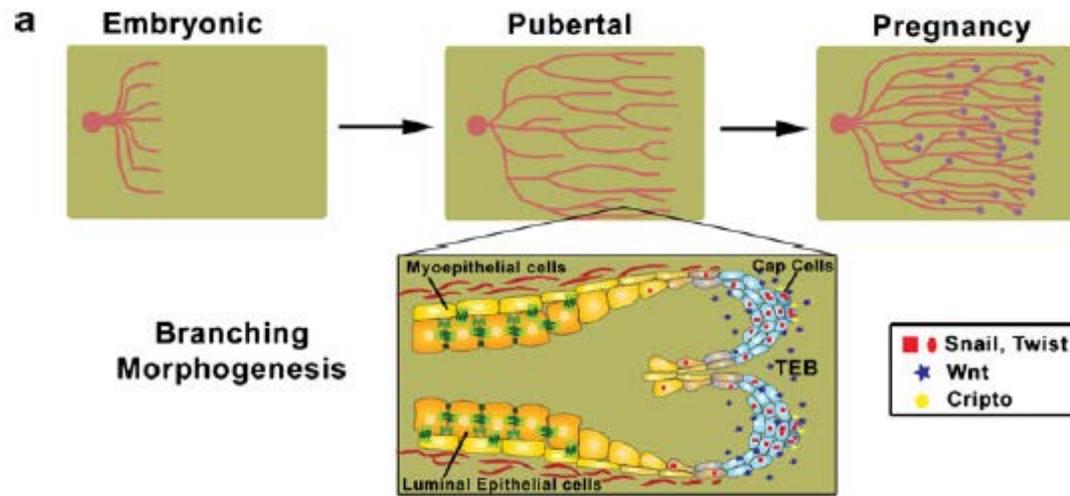
Celeste M. Nelson and Mina J. Bissell

Life Sciences Division, Lawrence Berkeley National Laboratory, Berkeley, California 94720; email: cmnelson@lbl.gov, mjbissell@lbl.gov

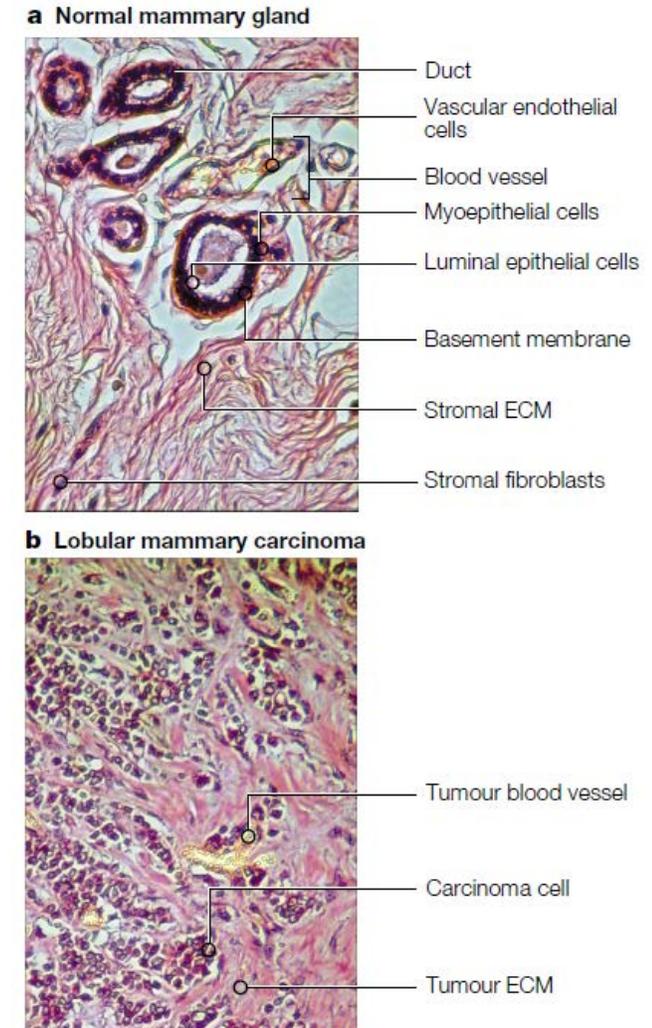
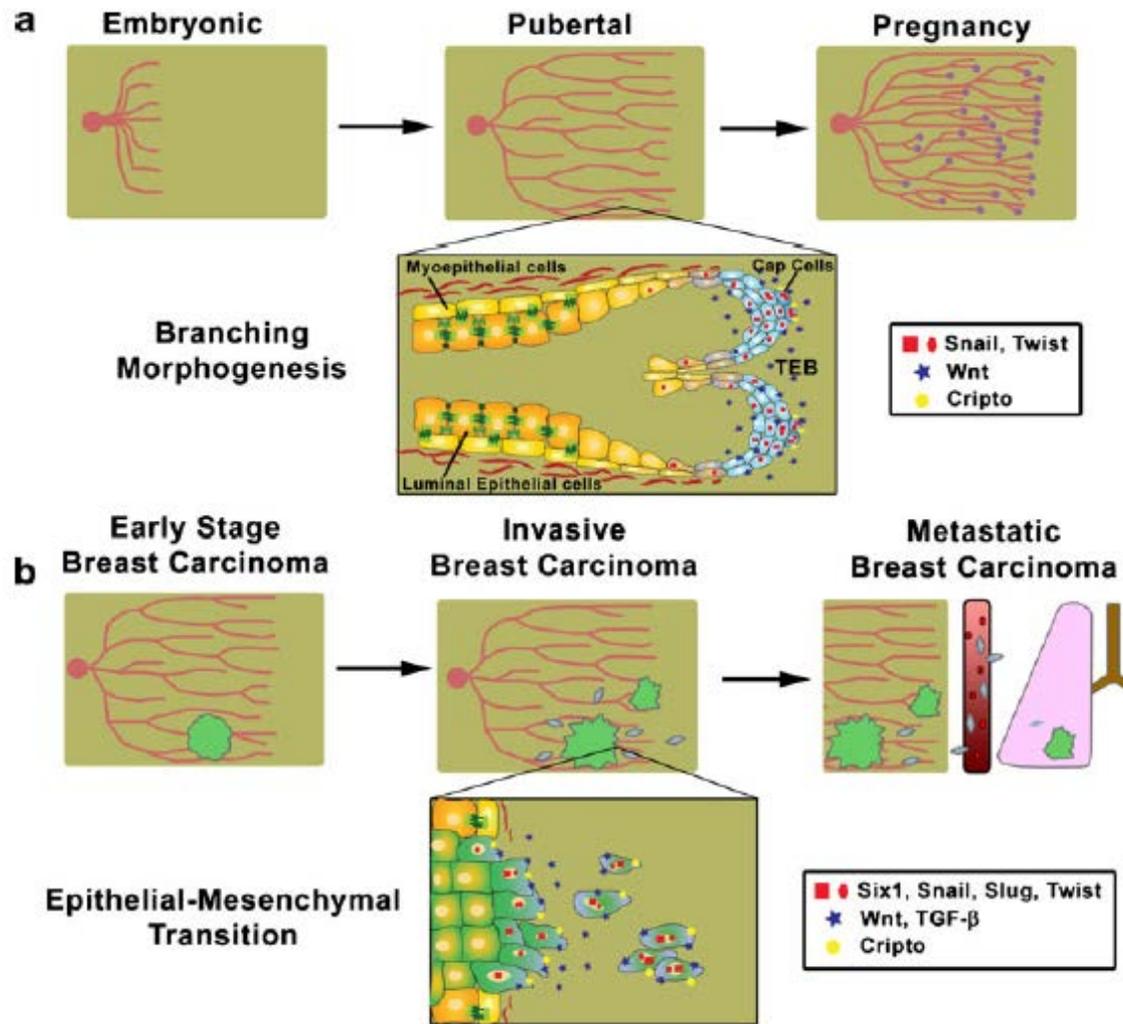
**Return of de-differentiation: why cancer is a developmental disease** **2001**

Luís Filipe Teixeira da Costa, PhD

# Cancer as a developmental process?

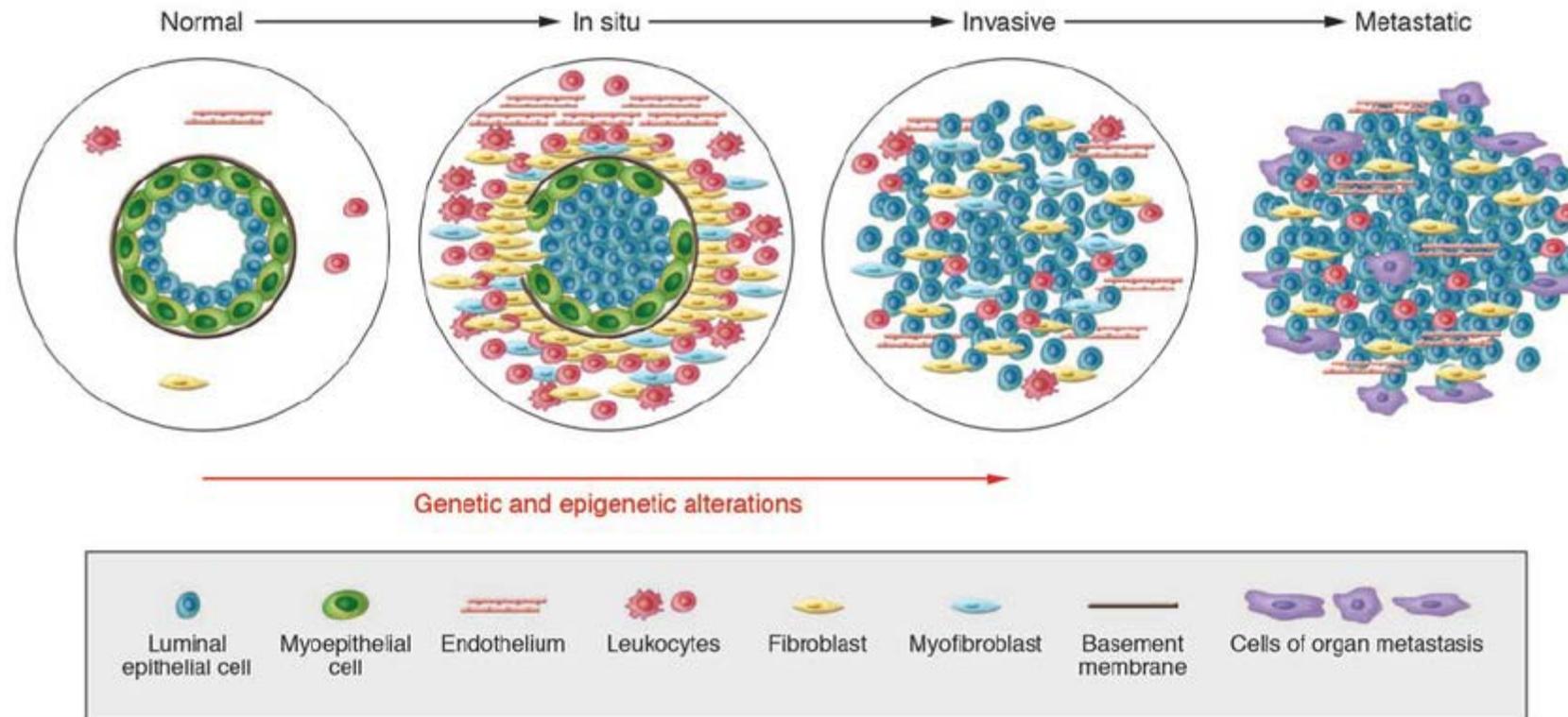


# Cancer as a developmental process?



# Cancer as a dysregulated developmental process?

Disorganisation, evasion and functional isolation from other tissues?



SEMINARS IN MEDICINE  
OF THE  
BETH ISRAEL HOSPITAL, BOSTON



1986

JEFFREY S. FLIER, M.D., *Editor*  
LISA H. UNDERHILL, *Assistant Editor*

**TUMORS: WOUNDS THAT DO NOT HEAL**  
**Similarities between Tumor Stroma Generation  
and Wound Healing**  
HAROLD F. DVORAK, M.D.

Tissue repair?

REVIEWS

2008

Cancer as an **overhealing wound:**  
an old hypothesis revisited

*Matthias Schäfer and Sabine Werner*

2015

Masters of Immunology

**Tumors: Wounds That Do Not Heal—Redux** 

Harold F. Dvorak

Cancer  
Immunology  
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Harold F. Dvorak

Cancer Immunology Research

INSIGHT REVIEW

NATURE|Vol 454|24 July 2008|doi:10.1038/nature07205

**Cancer-related inflammation** 2008

Alberto Mantovani<sup>1,2</sup>, Paola Allavena<sup>1</sup>, Antonio Sica<sup>3</sup> & Frances Balkwill<sup>4</sup>

Published OnlineFirst November 3, 2009; DOI: 10.1158/1078-0432.CCR-09-1126

**Imaging, Diagnosis, Prognosis**

**Activation of Host Wound Responses in Breast Cancer Microenvironment** 2009

Melissa A. Troester,<sup>1,2</sup> Myung Hee Lee,<sup>5</sup> Matthew Carter,<sup>6</sup> Cheng Fan,<sup>2</sup> David W. Cowan,<sup>2</sup> Erick Roman Perez,<sup>1</sup> Jason R. Pirone,<sup>2</sup> Charles M. Perou,<sup>2,3,4</sup> D. Joseph Jerry,<sup>6,7</sup> and Sallie Smith Schneider<sup>6</sup>

Published online: July 1, 2015

Article

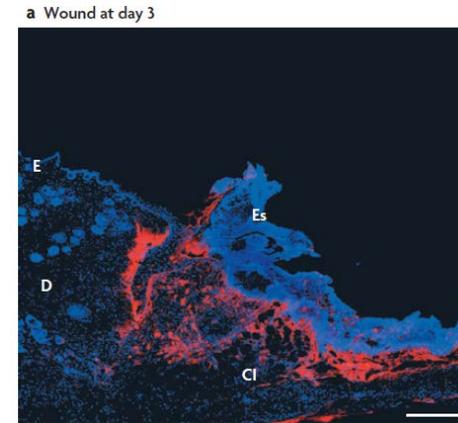
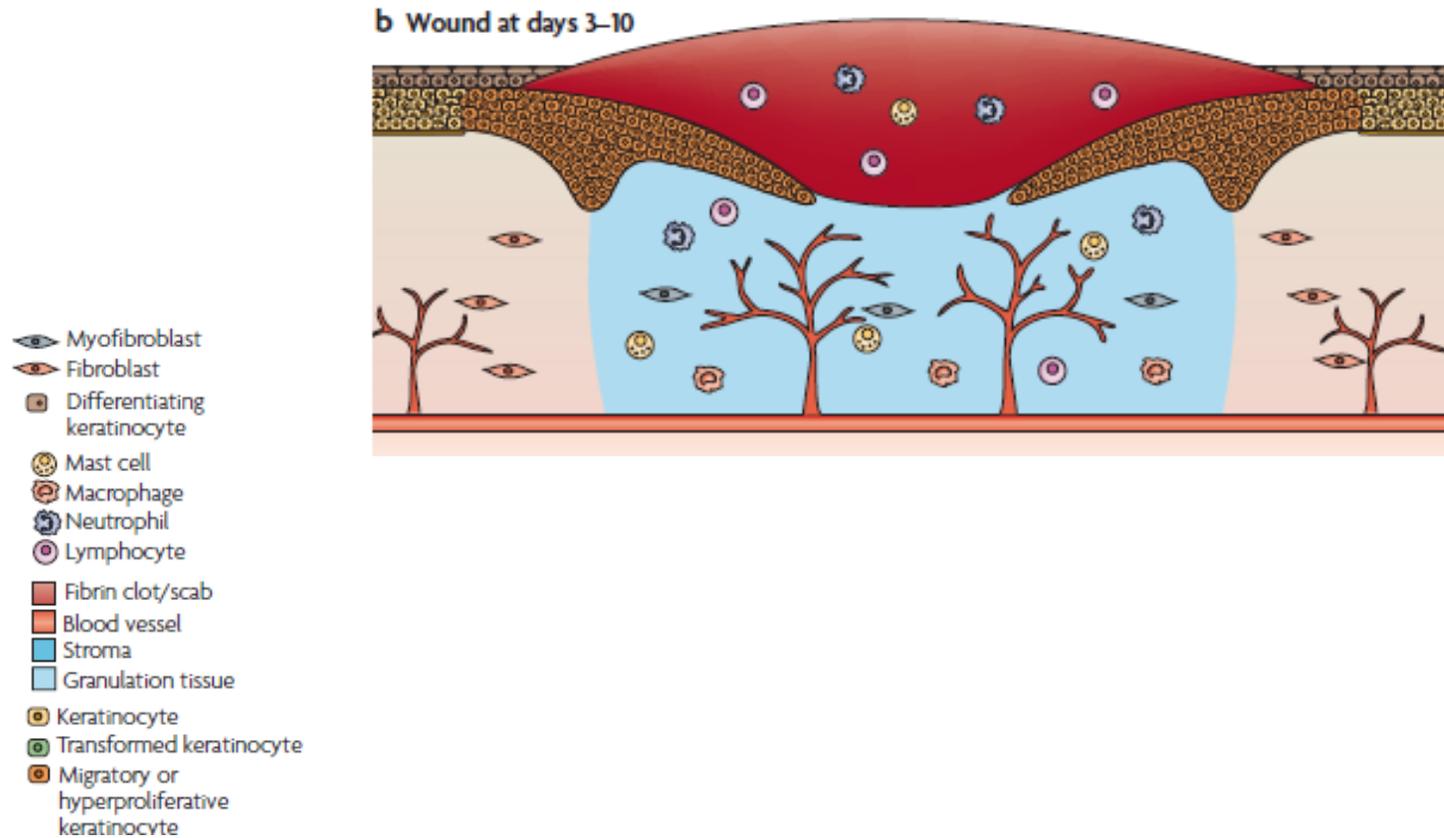
TRANSPARENT PROCESS OPEN ACCESS

THE EMBO JOURNAL

**The wound inflammatory response exacerbates growth of pre-neoplastic cells and progression to cancer** 2015

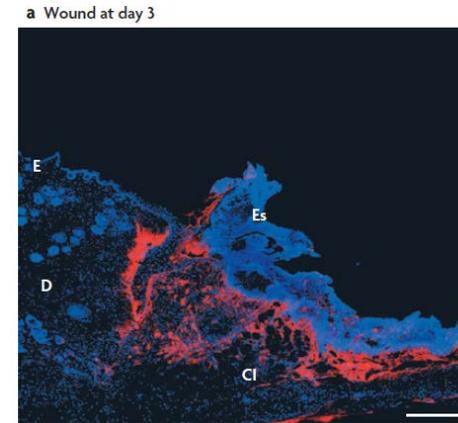
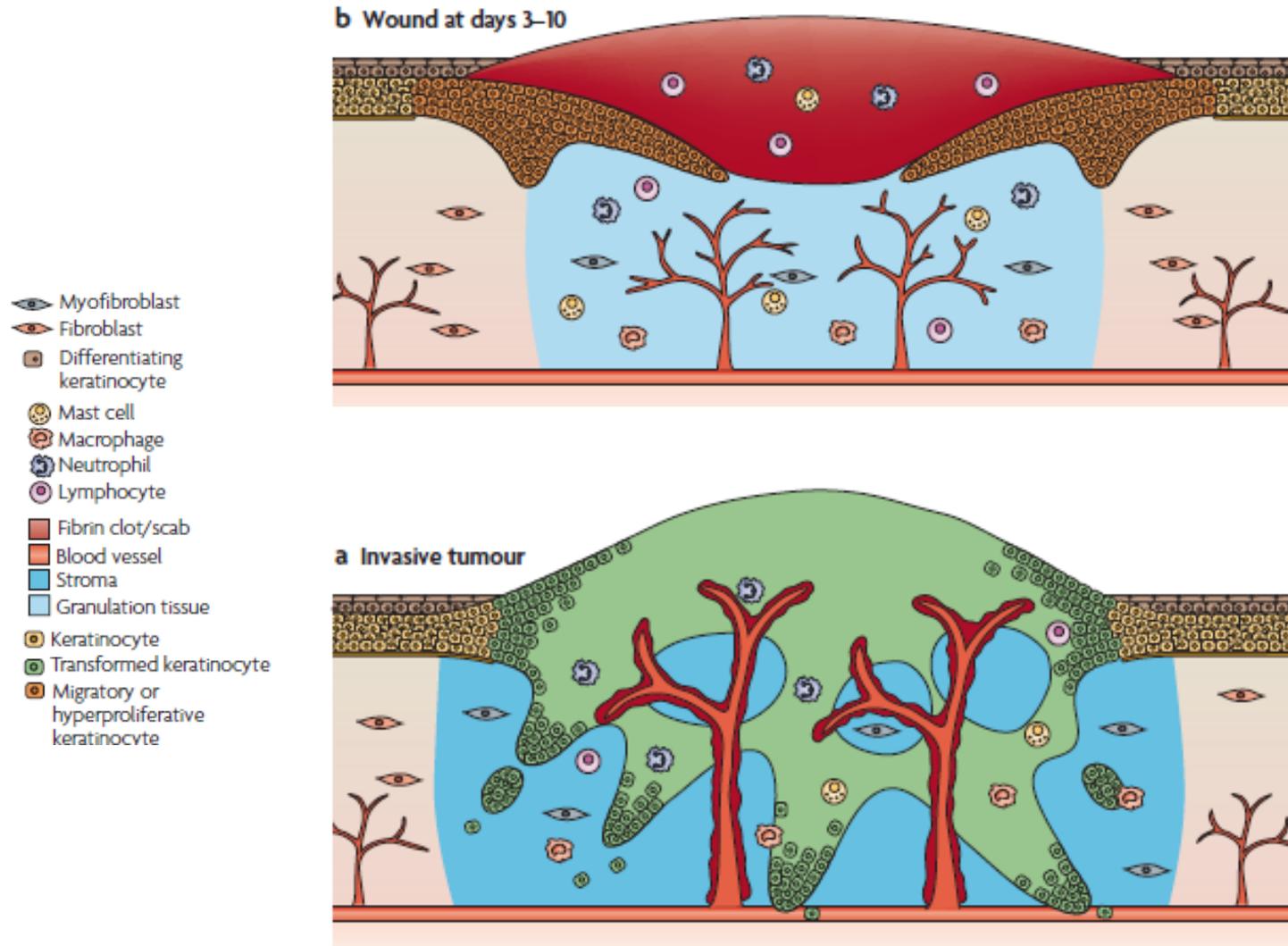
Nicole Antonio<sup>1,†</sup>, Marie Louise Bønnelykke-Behmdtz<sup>2,3,†</sup>, Laura Chloe Ward<sup>4,†</sup>, John Collin<sup>4</sup>, Ib Jarle Christensen<sup>5</sup>, Torben Steiniche<sup>6,7</sup>, Henrik Schmidt<sup>7,8,\*</sup>, Yi Feng<sup>9\*\*\*</sup> & Paul Martin<sup>1,4,10\*\*\*\*</sup>

# Cancer as a repair process?

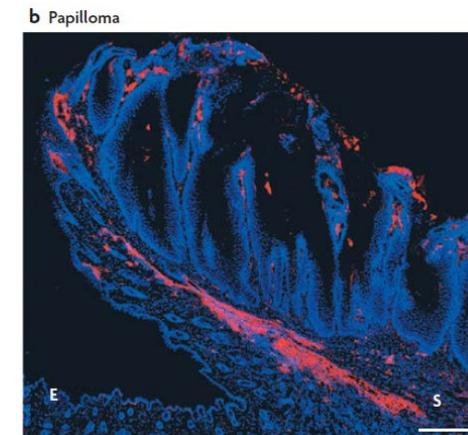


*Fibrin deposition in the stroma*

# Cancer as a repair process?

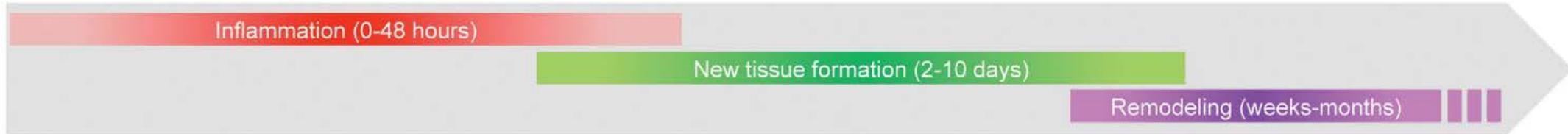


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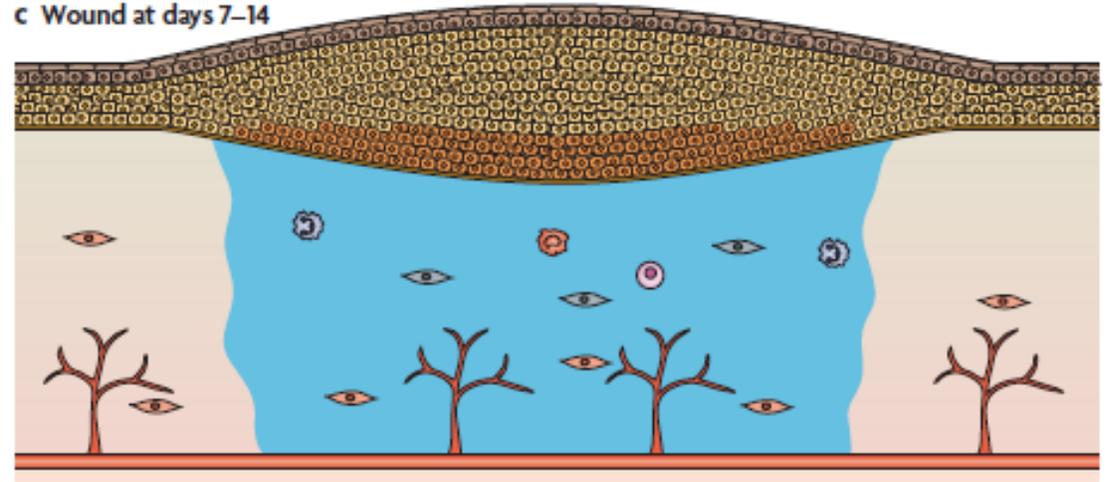


# Cancer as a dysregulated repair process?

## Stages of tissue repair

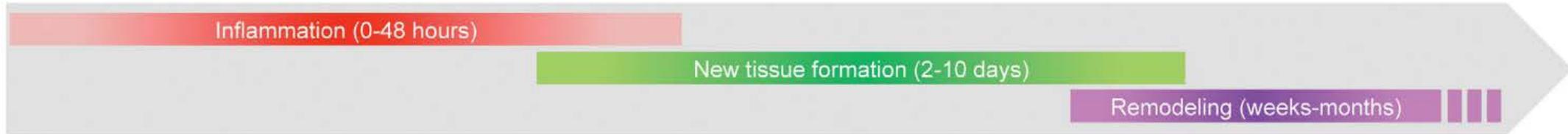


c Wound at days 7-14



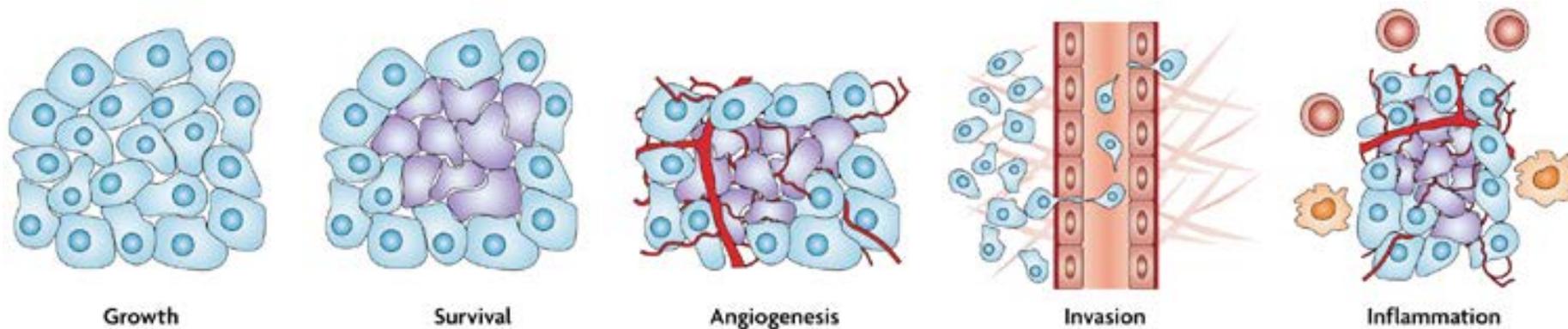
# Cancer as a dysregulated repair process?

## Stages of tissue repair



**Alteration and/or amplification of healing mechanisms?**

## Stages of cancer progression



Nature Reviews | Cancer

# Understanding cancer progression and its control

## Development

Tumour as an abnormal organ?

## Tissue repair

Tumour as dysfunctional healing?

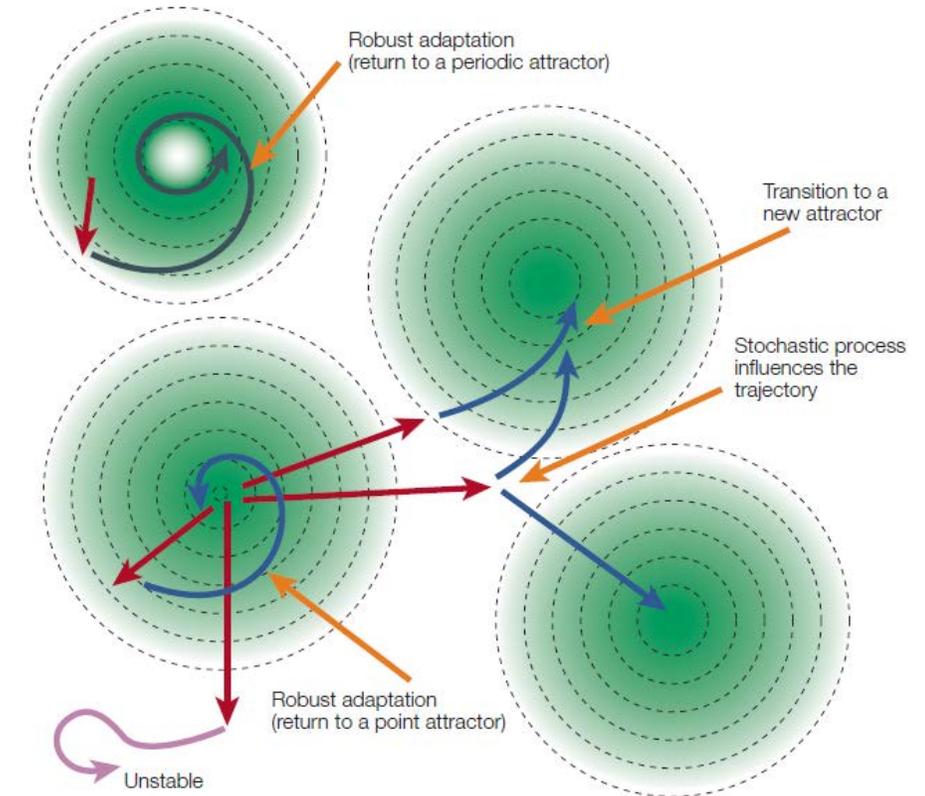
*“Cancer cells reactivate a latent behavioural programme that is usually confined to **embryonic development and tissue repair**, although in cancer cells it occurs in an **exaggerated and uncontrolled manner**” (Schäfer and Werner, 2008)*

**Understanding cancer progression and its control: the (im)balance  
between tissue construction, destruction and reconstruction?**

# Understanding cancer progression and its control

## Conceptual link with the notion of robustness?

Robustness as an active and ubiquitous property of functional persistence



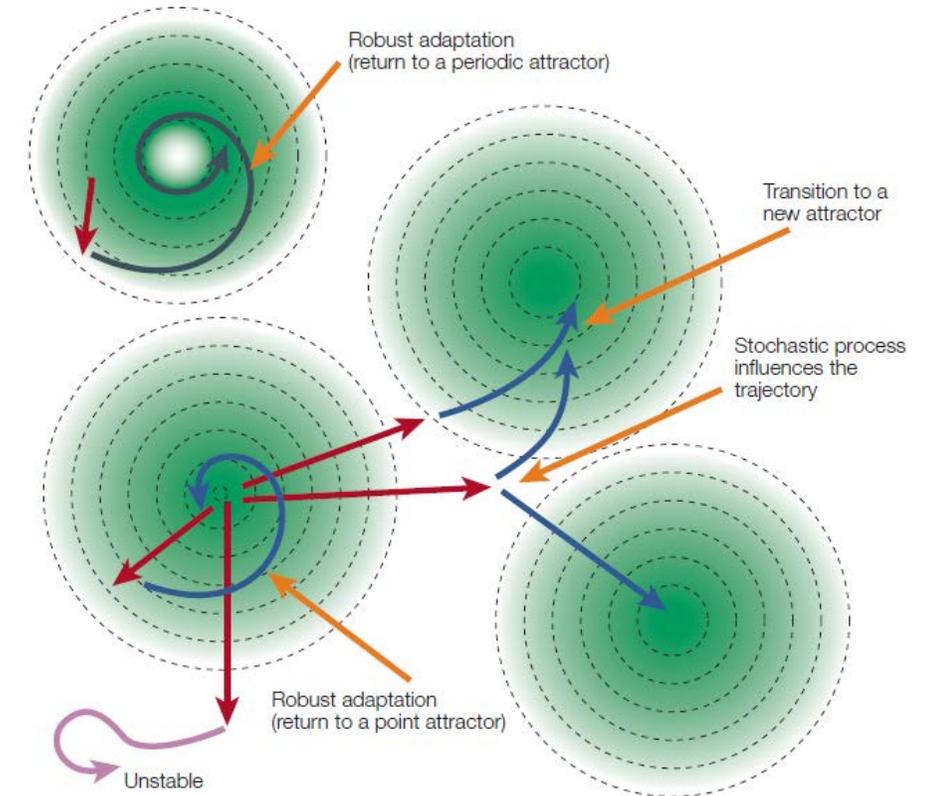
Kitano, H. (2004). Biological robustness. *Nature Reviews Genetics*, 5(11), 826.

# Understanding cancer progression and its control

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- “Complex biological systems must be robust against environmental and genetic perturbations to be evolvable” (Kitano, 2004)
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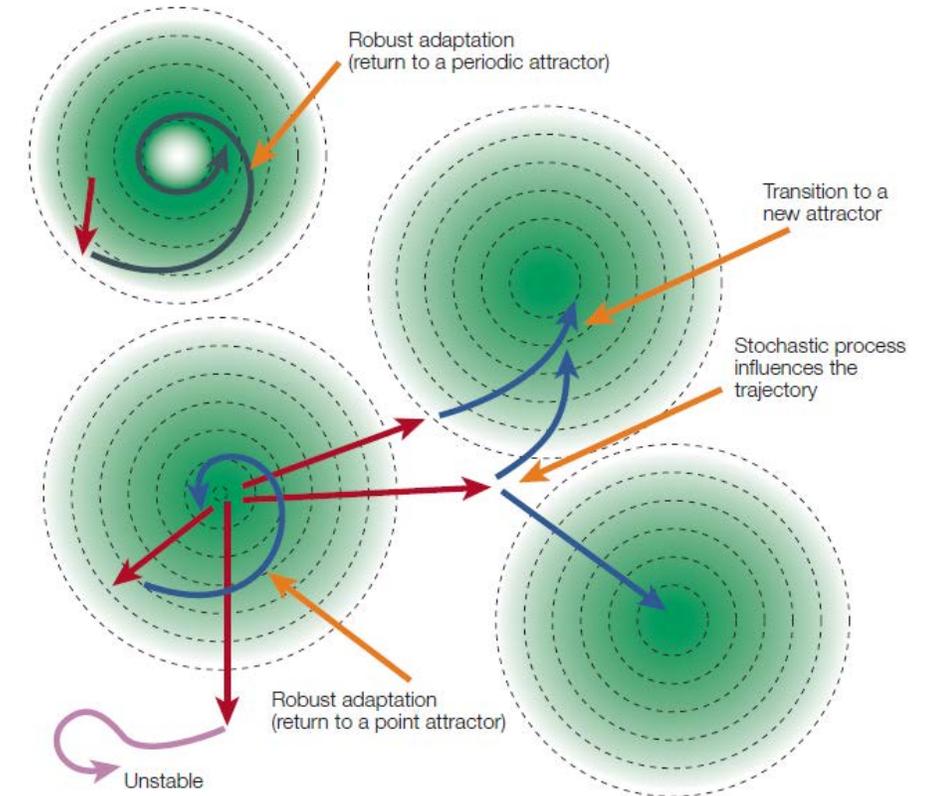
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→ Disease as a failure/rupture of robustness?



Kitano, H. (2004). Biological robustness. *Nature Reviews Genetics*, 5(11), 826.

# Understanding cancer progression and its control

## **Cancer as a robust system?**

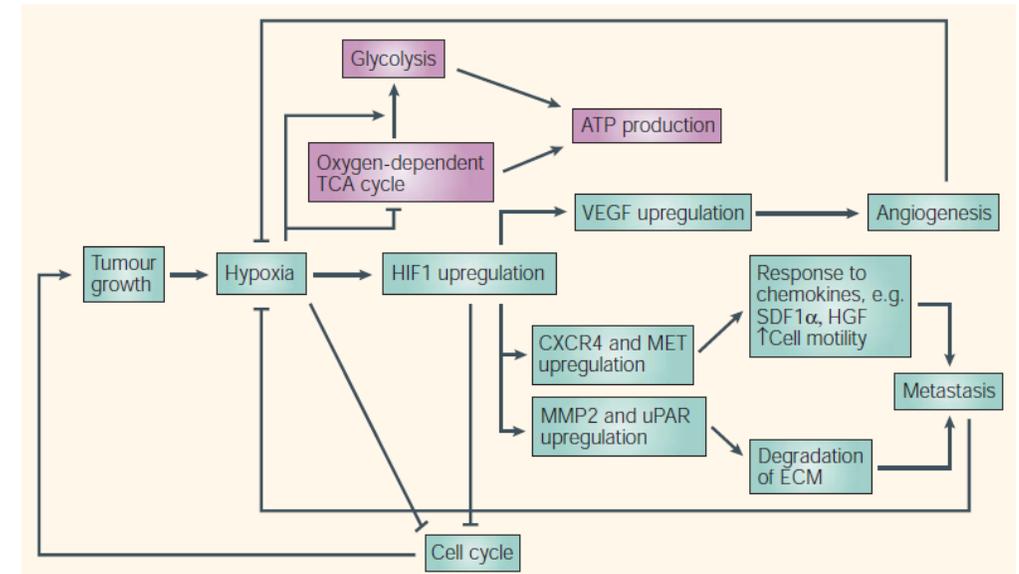
Cancer robustness as the maintenance of tumour cell proliferation potential despite genetic and environmental perturbations (Kitano, 2004)

# Understanding cancer progression and its control

## Cancer as a robust system?

Cancer robustness as the maintenance of tumour cell proliferation potential despite genetic and environmental perturbations (Kitano, 2004)

- Functional redundancy through cellular heterogeneity
- Feedback control through complex interaction loops
- Sensing signals and constraints
- Response to stress and adaptability



Kitano, H. (2004). Cancer as a robust system: implications for anticancer therapy. *Nature Reviews Cancer*, 4(3), 227.

# Understanding cancer progression and its control

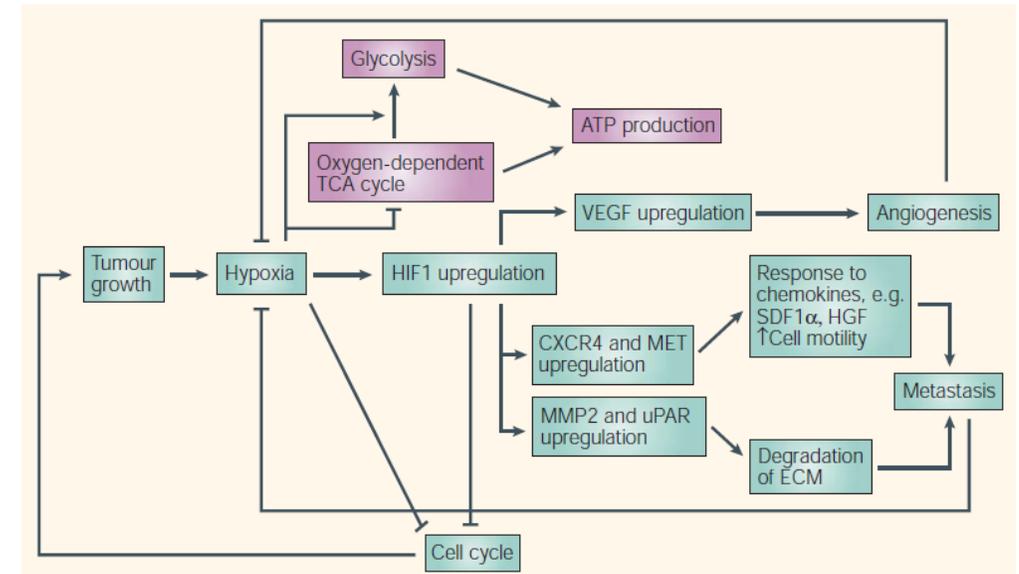
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### → Definitional requirements:

- Precise nature of actors: “system”, “functions”, “perturbations”?
- Questioning the “gradual degradation of function in response to damage”?



# Cancer as a robust system?

## **Fragility trade-offs and implications for cancer therapy**

“there are trade-offs between robustness, fragility, performance and resource demands, which explain system behaviour, including the patterns of failure” (Kitano, 2004)

# Cancer as a robust system?

## **Fragility trade-offs and implications for cancer therapy**

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- Lessons from the “highly optimized tolerance” (HOT) theory (Carlson and Doyle)
- Focus on the cell cycle, growth and apoptosis
- Reducing heterogeneity and minimizing selective pressure

# Cancer as a robust system?

## Fragility trade-offs and implications for cancer therapy

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- Focus on the cell cycle, growth and apoptosis
- Reducing heterogeneity and minimizing selective pressure

→ Therapeutic strategies based on the control of cellular dynamics

“robustness can be controlled by carefully selecting modulation targets and the systematic use of multiple drugs”

+ question of applicability *in vivo* and management of tumour resistance?

# Cancer as a robust system?

## **Open questions inspired by the tissue (re)construction analogies:**

- Exploring the spatial and temporal levels of cancer robustness

# Cancer as a robust system?

## **Open questions inspired by the tissue (re)construction analogies:**

- Exploring the spatial and temporal levels of cancer robustness
  - Who is robust? (malignant cells / tumour microenvironment / cancer vs organism)
  - Where and when? (tumour site(s) and dissemination, stages of cancer progression)
  - How much change is allowed/tolerated?
  - Cancer typology and degrees of robustness?

# Cancer as a robust system?

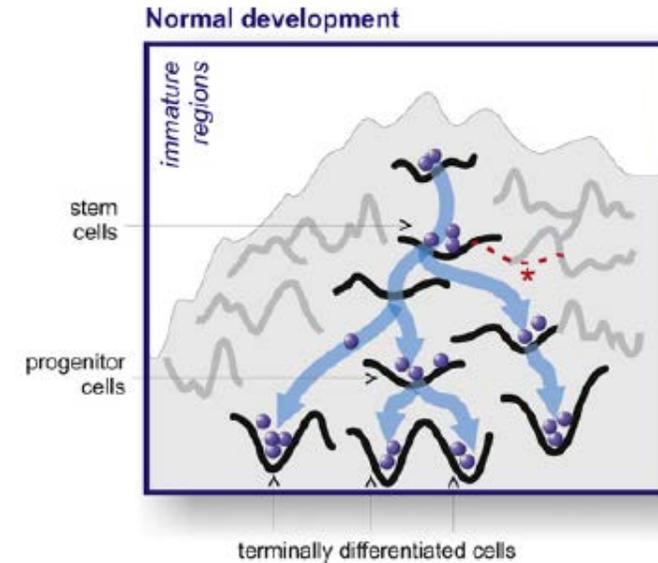
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  - How much change is allowed/tolerated?
  - Cancer typology and degrees of robustness?
- Is cancer progression and control a matter of conflicting robustness between tumour and host?
- How can tumour cell migration and metastasis causality be better understood in terms of cancer adaptability to change?
- Investigating the notions of (in)stability, homeostasis, fitness, evolvability

# Cancer as a robust system?

## Cancer robustness in dysregulated development?

- Robustness in normal development and morphogenesis



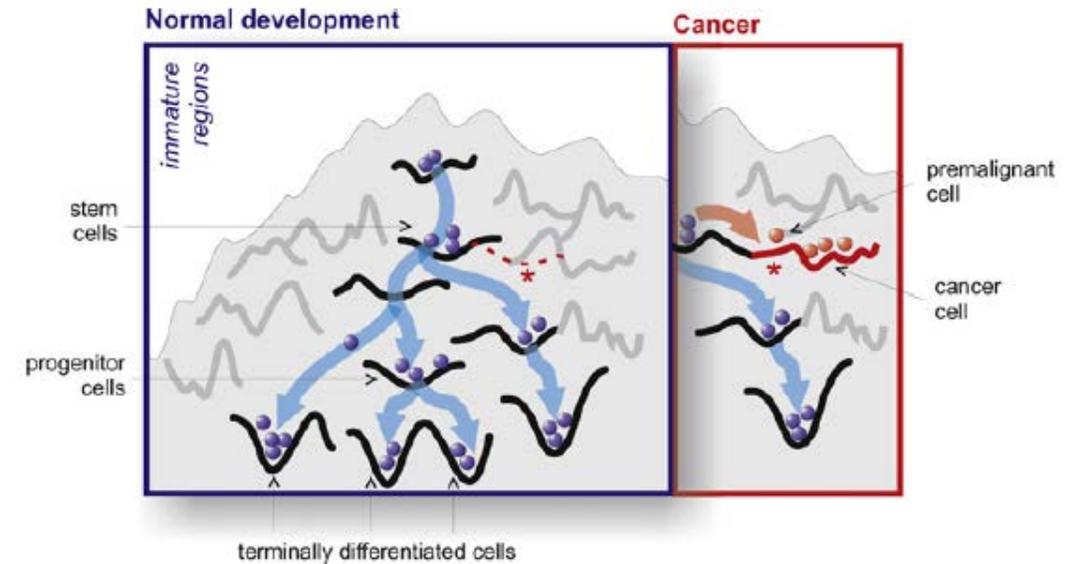
*Attractors as "distinct, self-stabilizing gene expression patterns that encode a particular relatively stable phenotype" (Huang, 2011)*

Huang, S. (2011, June). On the intrinsic inevitability of cancer: from foetal to fatal attraction. In *Seminars in cancer biology* (Vol. 21, No. 3, pp. 183-199). Academic Press.

# Cancer as a robust system?

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- Robustness in normal development and morphogenesis
- Cancer: enabling role of mutations
- Status of “cancer stem cells”?



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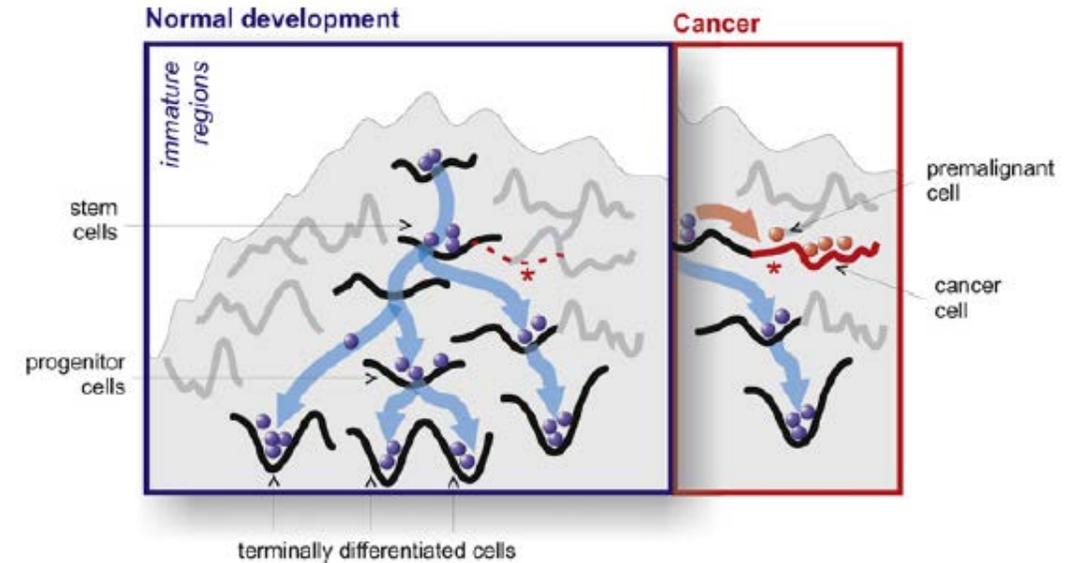
# Cancer as a robust system?

## Cancer robustness in dysregulated development?

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### Broader questions:

- Embryonic vs post-natal development (and robustness of other communication systems?)
- Clonal evolution and “populational” robustness



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# Cancer as a robust system?

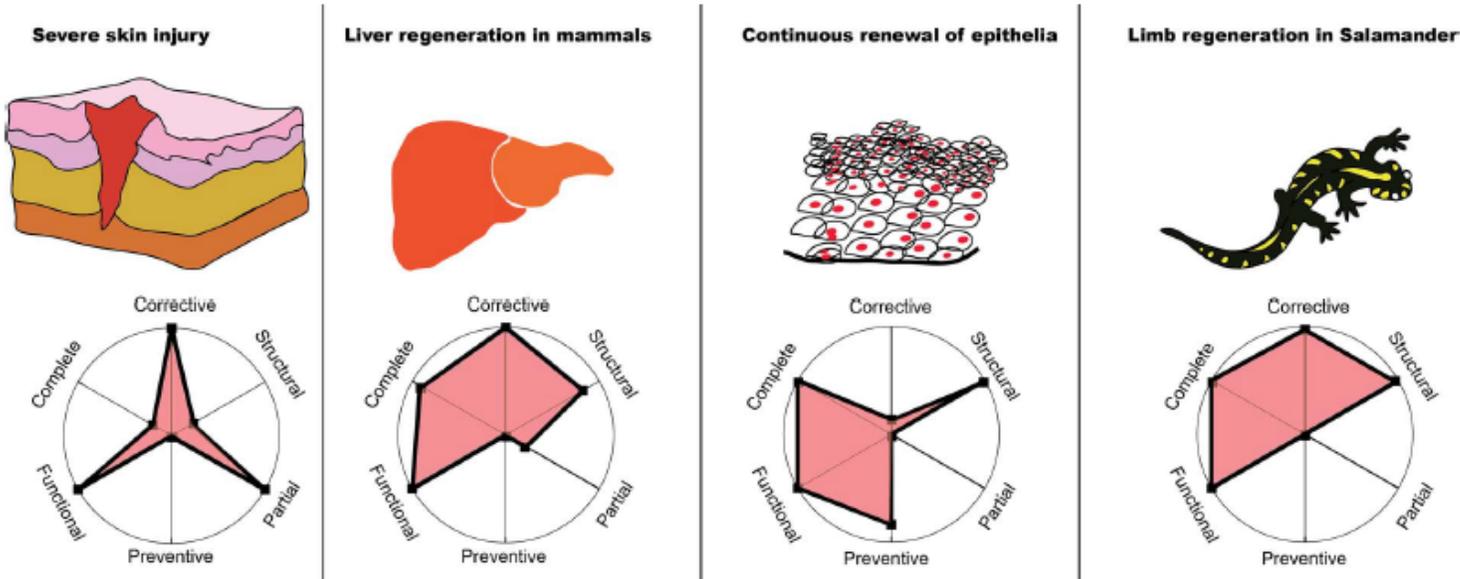
## Cancer robustness in dysregulated repair?

*“Robustness allows changes in the structure and components of the system owing to perturbations, but the key idea is that robustness leads to the maintenance of specific functions” (Truchetet and Pradeu, 2018)*

Truchetet, M. E., & Pradeu, T. (2018, March). Re-thinking our understanding of immunity: Robustness in the tissue reconstruction system. In *Seminars in immunology*. Academic Press.

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→ Nature and kinetics of robustness in cancer?

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# Cancer as a robust system?

## Cancer robustness in dysregulated repair?

| TRS robustness        | Cancer (hijacking of TRS robustness)  |
|-----------------------|---|
| Plasticity            | <ul style="list-style-type: none"><li>- MET/EMT with the tumor-initiating ability required for metastatic colonization [130]</li><li>- Plasticity between the epithelial and the mesenchymal states rather than a fixed phenotype [131]</li><li>- UPR in macrophage polarization and plasticity with shift to M1-like profile [121]</li></ul>   |
| Functional redundancy | <ul style="list-style-type: none"><li>- IL-6 and glycoprotein 130 in the pathophysiology of multiple myeloma [123]</li></ul>  |
| Constant surveillance | <ul style="list-style-type: none"><li>- TRMs in human non-small cell lung tumor tissue [125]</li><li>- Role of amphiregulin in orchestrating responses to tumors [136]</li></ul>  |
| Restraint             | <ul style="list-style-type: none"><li>- TAMs recruitment in triple negative breast cancer [124]</li><li>- Tregs in tumor progression [138]</li><li>- Tregs and cancer cell clearance [139]</li><li>- Tregs and cancer immunotherapies with IL-2 [140]</li><li>- To target immune checkpoints such as CTLA4, PD1 or TIGIT to both interfere with Treg function and enhance effector responses at the same time [141]</li></ul> |
| Dynamic adjustment    | <ul style="list-style-type: none"><li>- Cancer cells and use of the dynamic potential of neutrophils [126]</li><li>- CCL26 in colorectal cancer cells invasion by inducing TAM infiltration [142]</li><li>- Inhibitors of the receptor tyrosine kinase c-MET and impairment of the mobilization and recruitment of neutrophils into tumors [143]</li></ul>  |

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→ Robustness as a *dysfunction* or *dysfunctional robustness*?

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→ Robustness as a *dysfunction* or *dysfunctional robustness*?

**Crucial role of the immune system**

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| Restraint             | <ul style="list-style-type: none"><li>– TAMs recruitment in triple negative breast cancer [124]</li><li>– Tregs in tumor progression [138]</li><li>– Tregs and cancer cell clearance [139]</li><li>– Tregs and cancer immunotherapies with IL-2 [140]</li><li>– To target immune checkpoints such as CTLA4, PD1 or TIGIT to both interfere with Treg function and enhance effector responses at the same time [141]</li></ul> |
| Dynamic adjustment    | <ul style="list-style-type: none"><li>– Cancer cells and use of the dynamic potential of neutrophils [126]</li><li>– CCL26 in colorectal cancer cells invasion by inducing TAM infiltration [142]</li><li>– Inhibitors of the receptor tyrosine kinase c-MET and impairment of the mobilization and recruitment of neutrophils into tumors [143]</li></ul>  |

Truchetet, M. E., & Pradeu, T. (2018, March). Re-thinking our understanding of immunity: Robustness in the tissue reconstruction system. In *Seminars in immunology*. Academic Press.

# Cancer as a robust system?

**Cancer robustness in tumour immunity?**



# Cancer as a robust system?

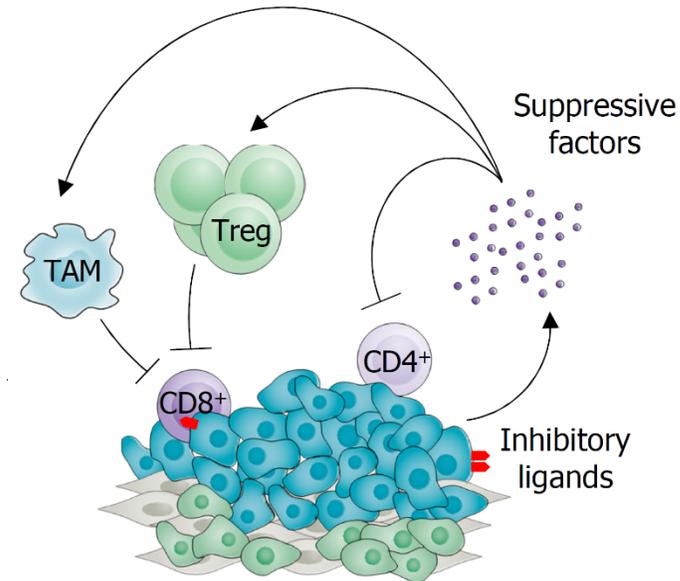
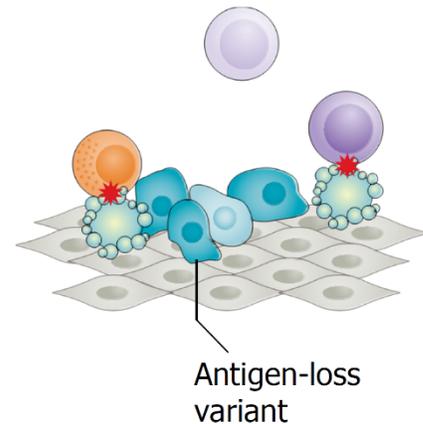
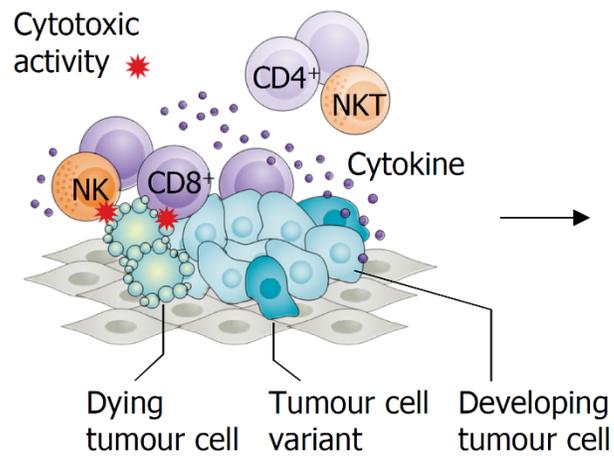
## Cancer robustness in tumour immunity?



Elimination phase

Equilibrium phase

Escape phase



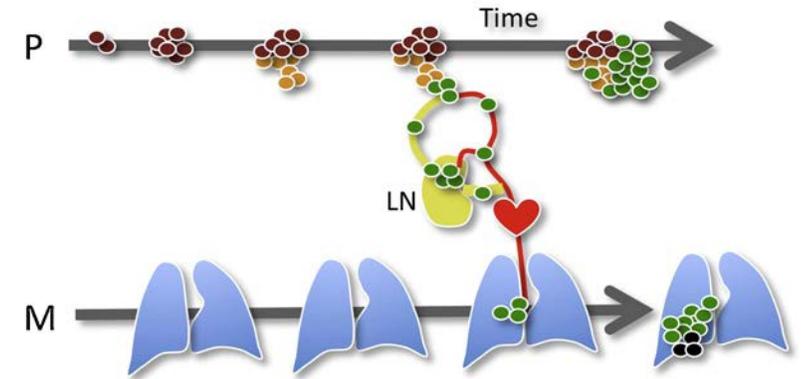
- Genetic instability and tumour heterogeneity
- Immune selection

# Cancer as a robust system?

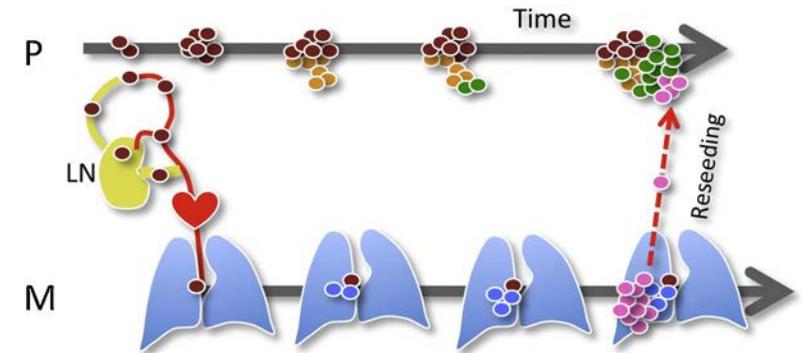
## Cancer robustness in metastasis?



Linear model



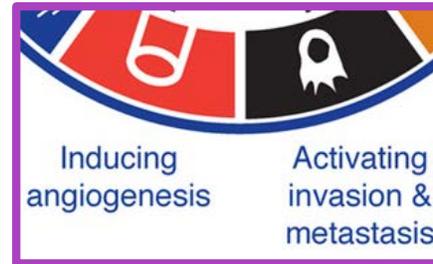
Parallel model



Lorusso, G., and Rüegg, C. (2012). New insights into the mechanisms of organ-specific breast cancer metastasis. *Semin. Cancer Biol.* 22, 226–233.

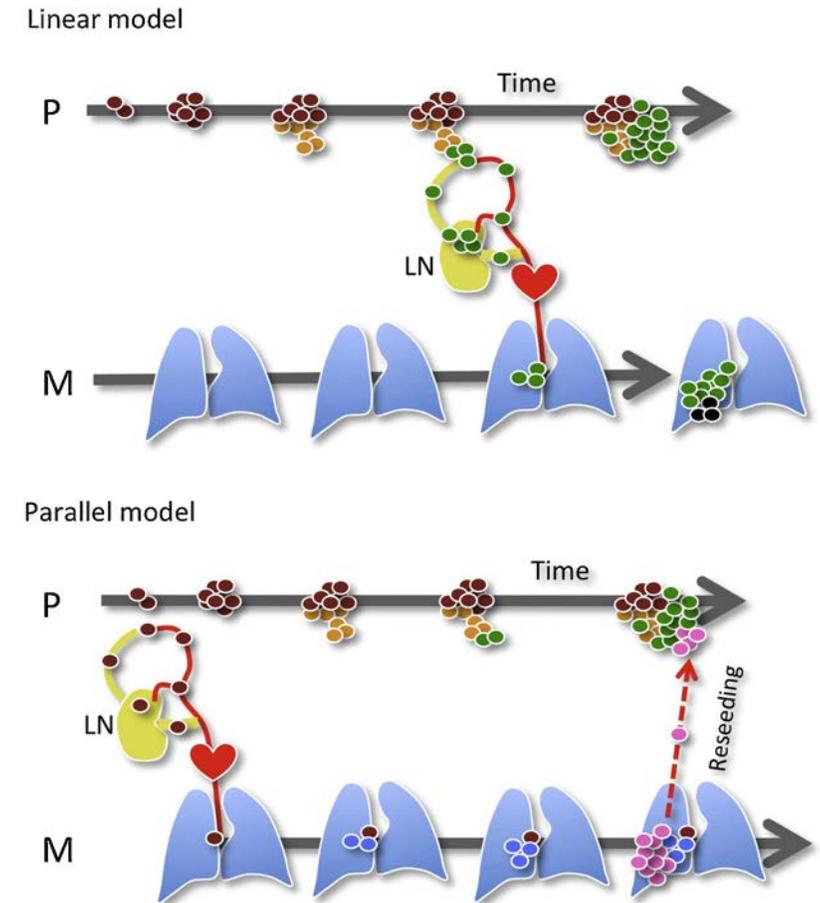
# Cancer as a robust system?

## Cancer robustness in metastasis?



“When the environment is not optimal [...] tumour-cell survival can be assured by adaptive changes, responses that change the environment, or migration to a new environment” (Kitano, 2004)

- Cancer dissemination as an adaptation?
- Link with causality and tropism of metastasis?



Lorusso, G., and Rüegg, C. (2012). New insights into the mechanisms of organ-specific breast cancer metastasis. *Semin. Cancer Biol.* 22, 226–233.

# Understanding cancer progression and its control