Robustness workshop, Bordeaux, June 19, 2018

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Robustness in the tissue reconstruction system:

Immunity from defence to repair

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ImmunoConcEpT
Immunologie conceptuelle expérimentale translationnelle

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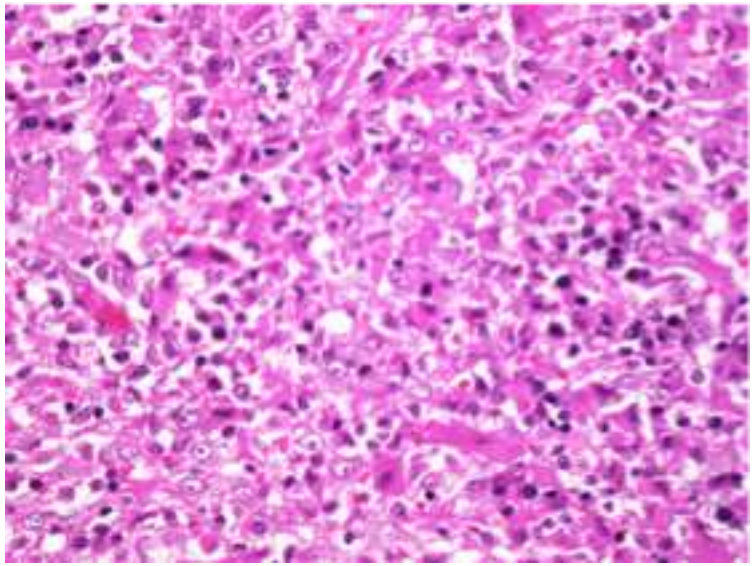
Re-thinking our understanding of immunity: Robustness in the tissue reconstruction system

Marie-Elise Truchetet[a,b], Thomas Pradeu[b,*]

➔ Special issue on “Redundancy and Robustness in Immunity”

Introduction: Robustness, immunity, and tissue repair



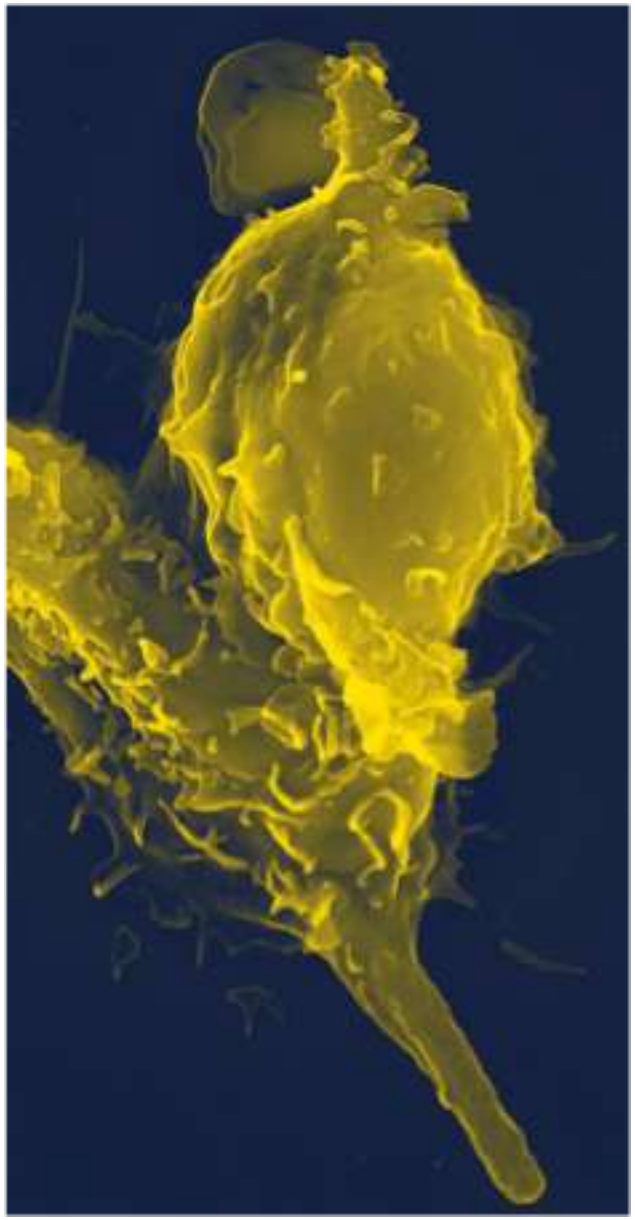
➔ **Two motivations:**

- Discussions on **robustness** often general & abstract
- Growing realization that the **immune system** plays a crucial role in **tissue repair** and **regeneration.**

➔ **Main problem:**

- **Robustness -> Repair?**
- **Repair -> robustness?**

Outline



1. Defining the tissue-reconstruction system (TRS) and robustness
2. Mechanisms of tissue reconstruction
3. Robustness and dysfunctions of the TRS
4. Conceptual consequences

1. Defining the tissue-reconstruction system (TRS) and robustness

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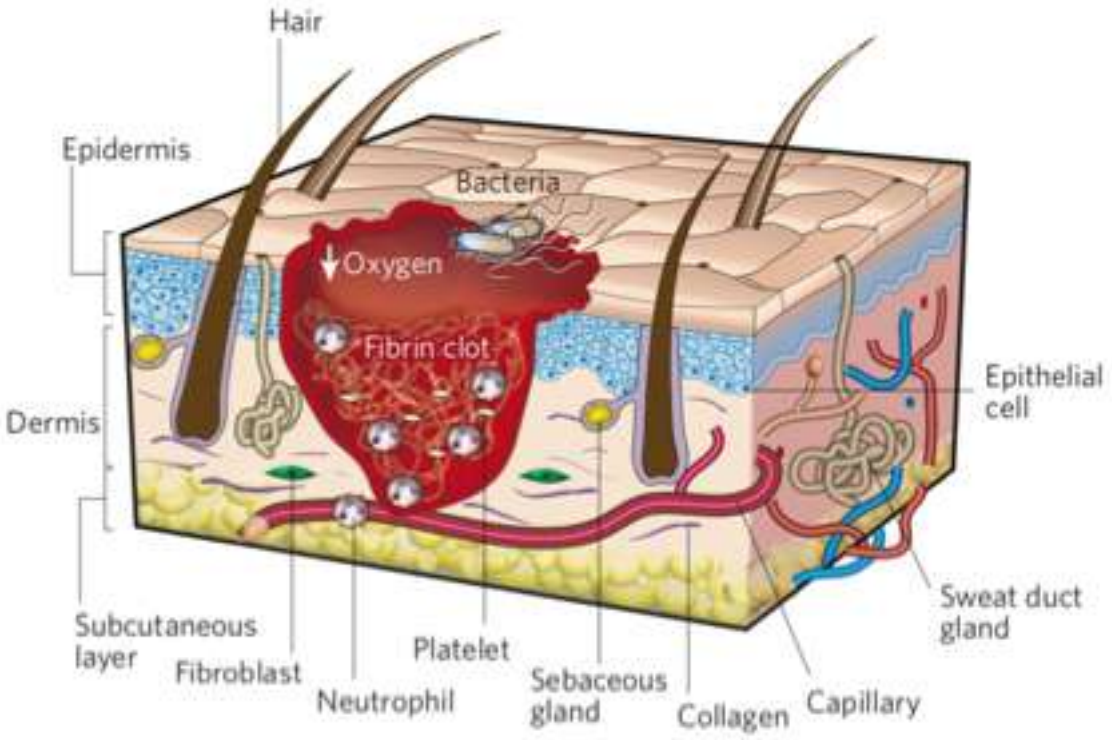
What do we mean by “tissue reconstruction system” (TRS)?



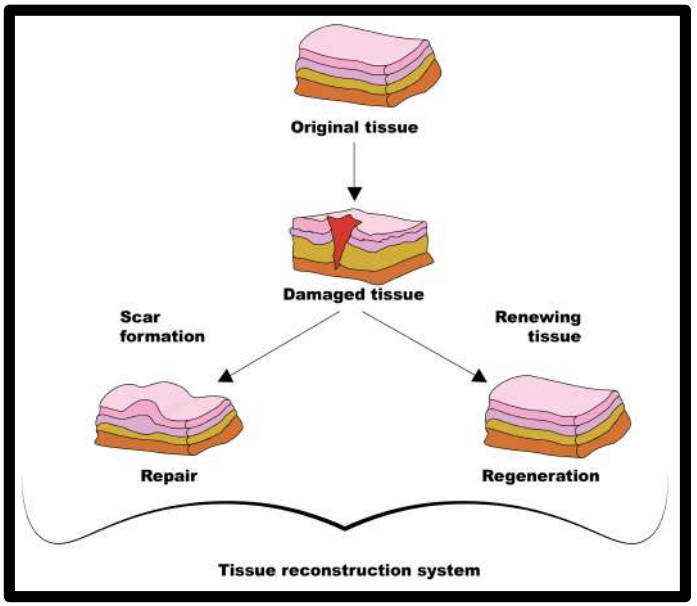
Gurtner et al. Wound repair and regeneration, *Nature* (2008)

- **Tissue repair**: a horde of components and pathways, including **structural** and **immunological**.
- (TRS)
- **Repair** essential, and occurs constantly.
- Many pathological states associated with **dysfunctional repair** (fibrosis, ulcers, also cancer, etc.)

Continuum repair-regeneration?

- Continuum, but with **distinct poles**.
- **Regeneration**: capacity to regrow complex organs entirely, generally with the implication of several cell types.
- **Immune system** crucial in all these processes.

S.A. Eming, T.A. Wynn, P. Martin, Inflammation and metabolism in tissue repair and regeneration, *Science* (2017)



Robustness and its four mechanisms

- **Robustness** = maintenance of specific functionalities of a given system against internal and external perturbations.
- Kitano (2004): **4 main mechanisms**:
- **System control** (negative and positive feed-backs)
- **Alternative mechanisms** (multiple routes to achieve a given function)
  - Redundancy (identical or nearly identical components can realize a given function)
  - Diversity (heterogeneous components can realize a given function)
- **Modularity** (flexible sets of components that collectively realize a given function)
- **Decoupling** (prevention of undesired connection between low-level variations and high-level functionalities)
- R in immunology: some (but not many) reflections. (Mantovani 1999).

2. Mechanisms of tissue reconstruction

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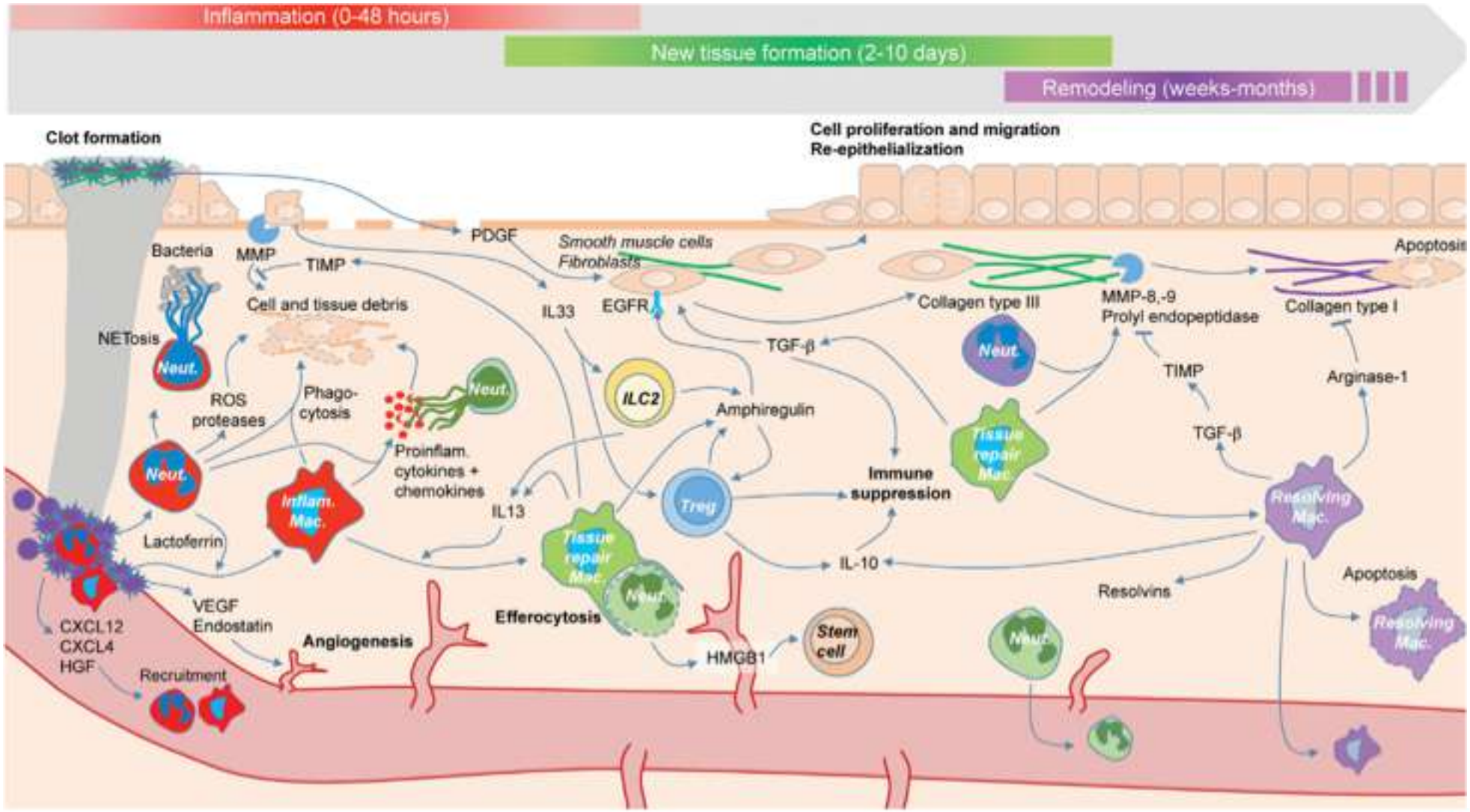
The mechanisms that mediate tissue reconstruction

- ***TRS is a complex and dynamic process***



Laurent P, et al. Immune-Mediated Repair: A Matter of Plasticity. Front Immunol. 2017 Apr 24;8:454.

The mechanisms that mediate tissue reconstruction

The TRS exhibits five key features that participate in robustness

- ➔ Plasticity
- ➔ Functional redundancy
- ➔ Constant surveillance
- ➔ Restraint
- ➔ Dynamic adjustment

The mechanisms that mediate tissue reconstruction

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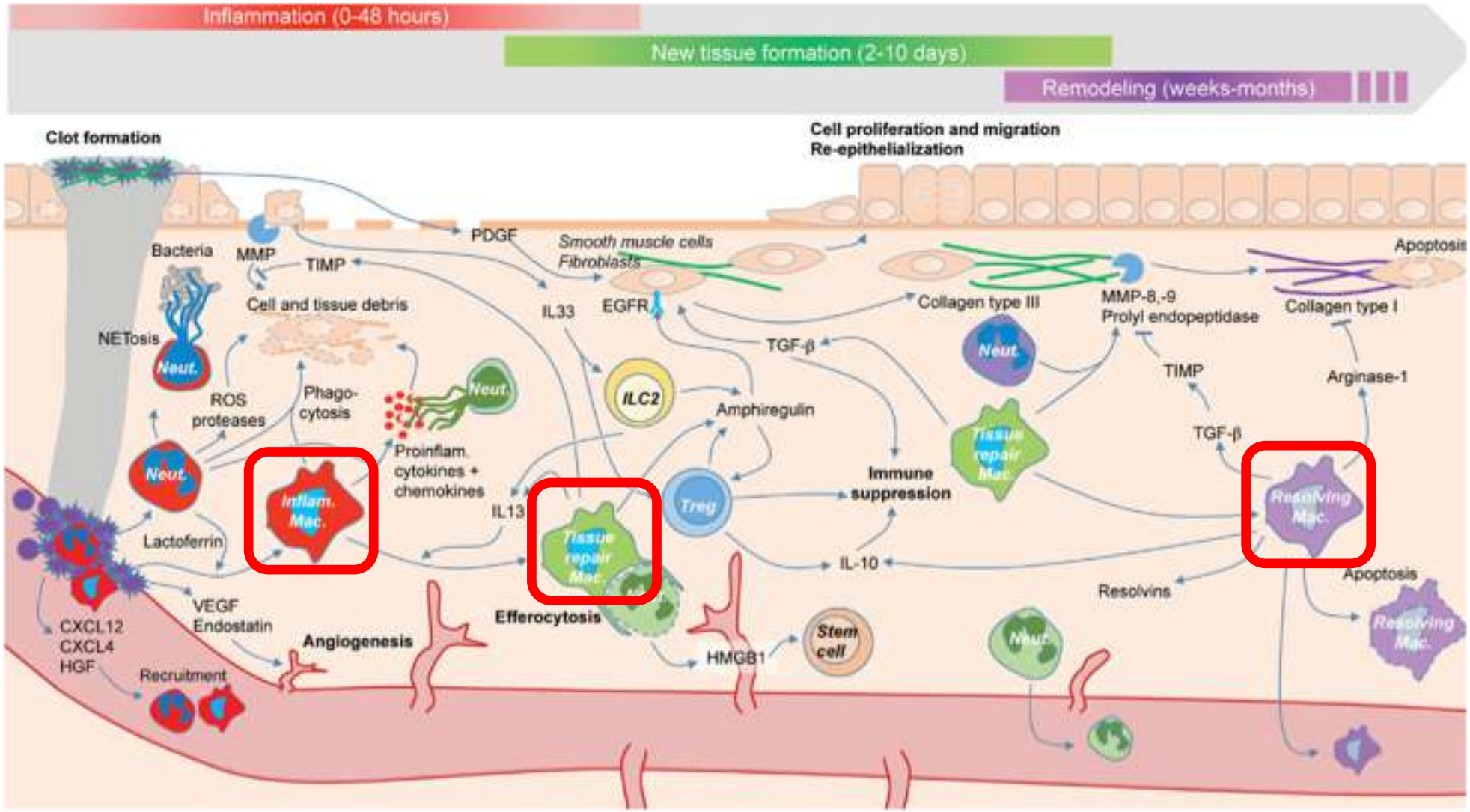
The mechanisms that mediate tissue reconstruction

- ***Plasticity***



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The mechanisms that mediate tissue reconstruction

- ***Plasticity***

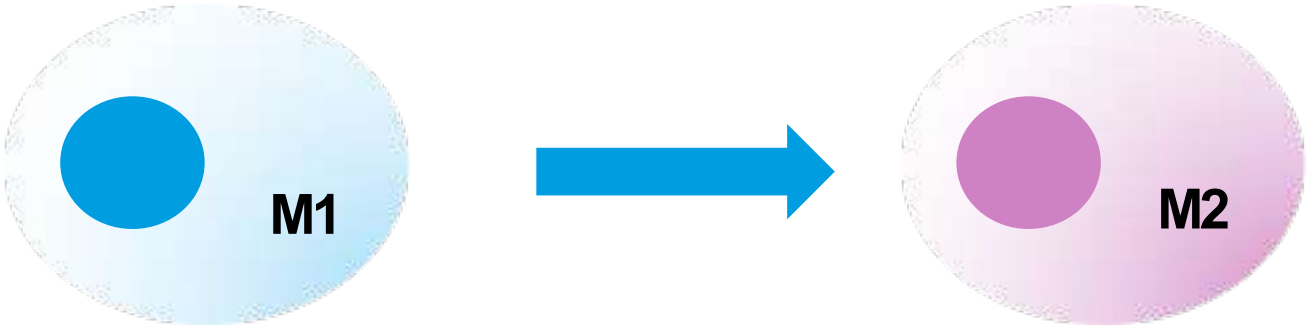
→ Intra-lineage cell plasticity

→ Trans-lineage cell plasticity

The mechanisms that mediate tissue reconstruction

➢ ***Plasticity***

➔ Intra-lineage cell plasticity / Functional plasticity

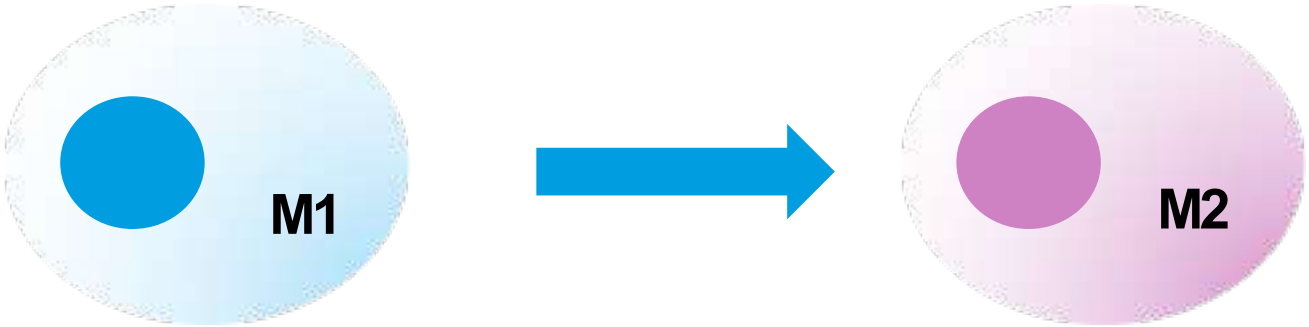


➔ Trans-lineage cell plasticity

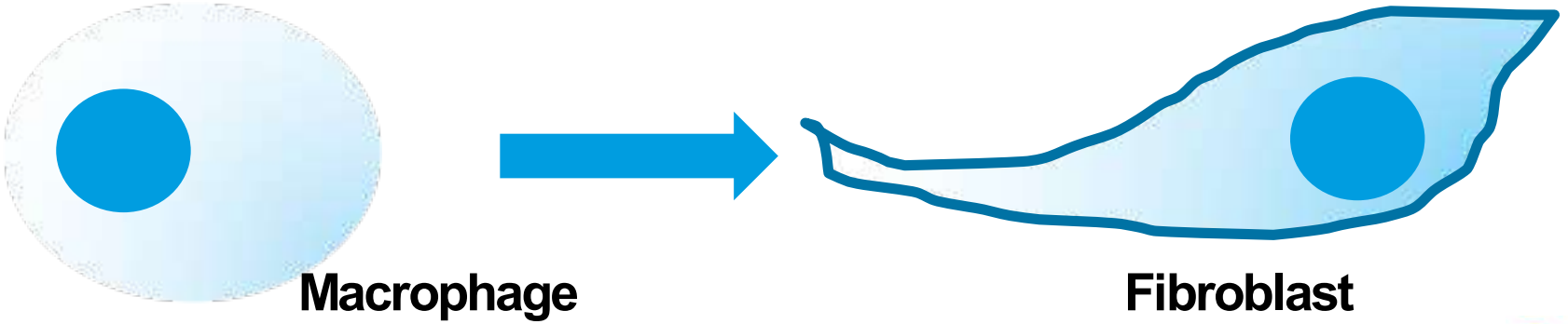
The mechanisms that mediate tissue reconstruction

➢ ***Plasticity***

➔ Intra-lineage cell plasticity / Functional plasticity

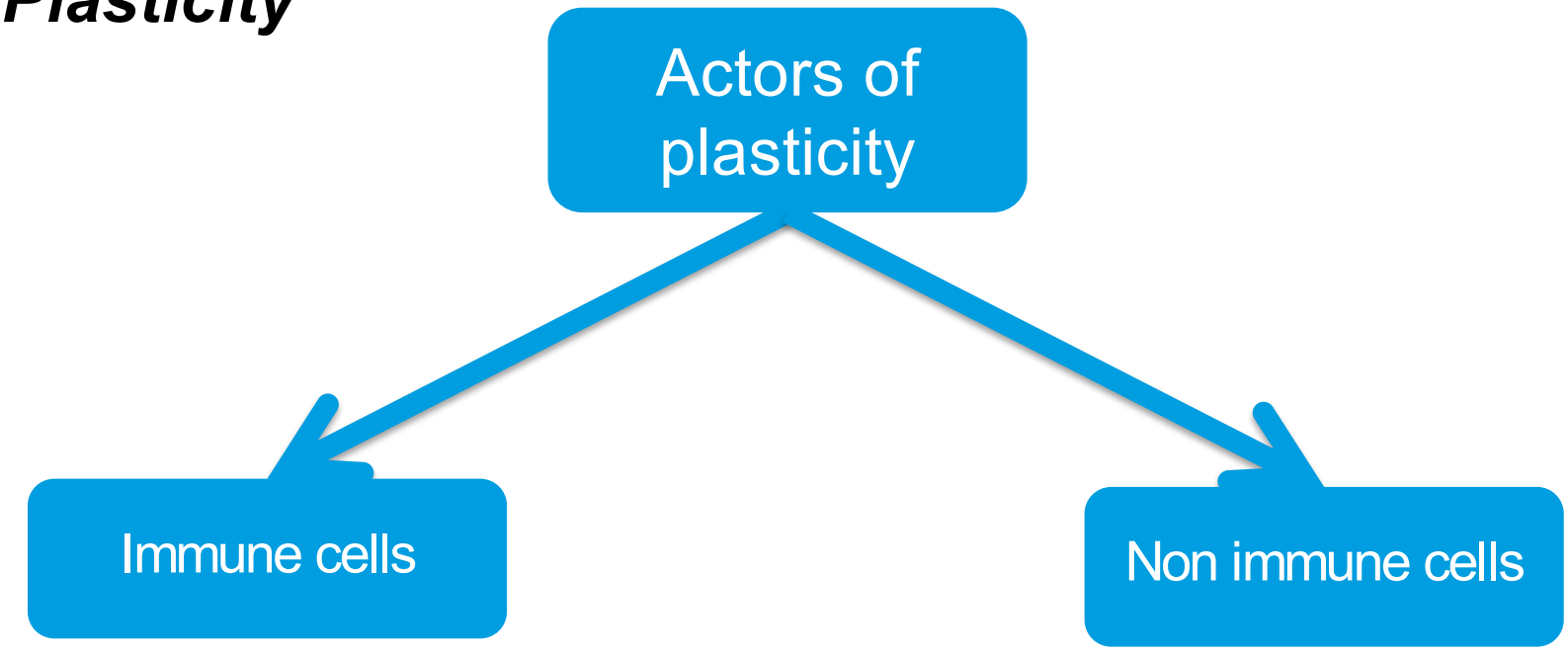


➔ Trans-lineage cell plasticity / Transdifferentiation, reprogramming



The mechanisms that mediate tissue reconstruction

- ***Plasticity***

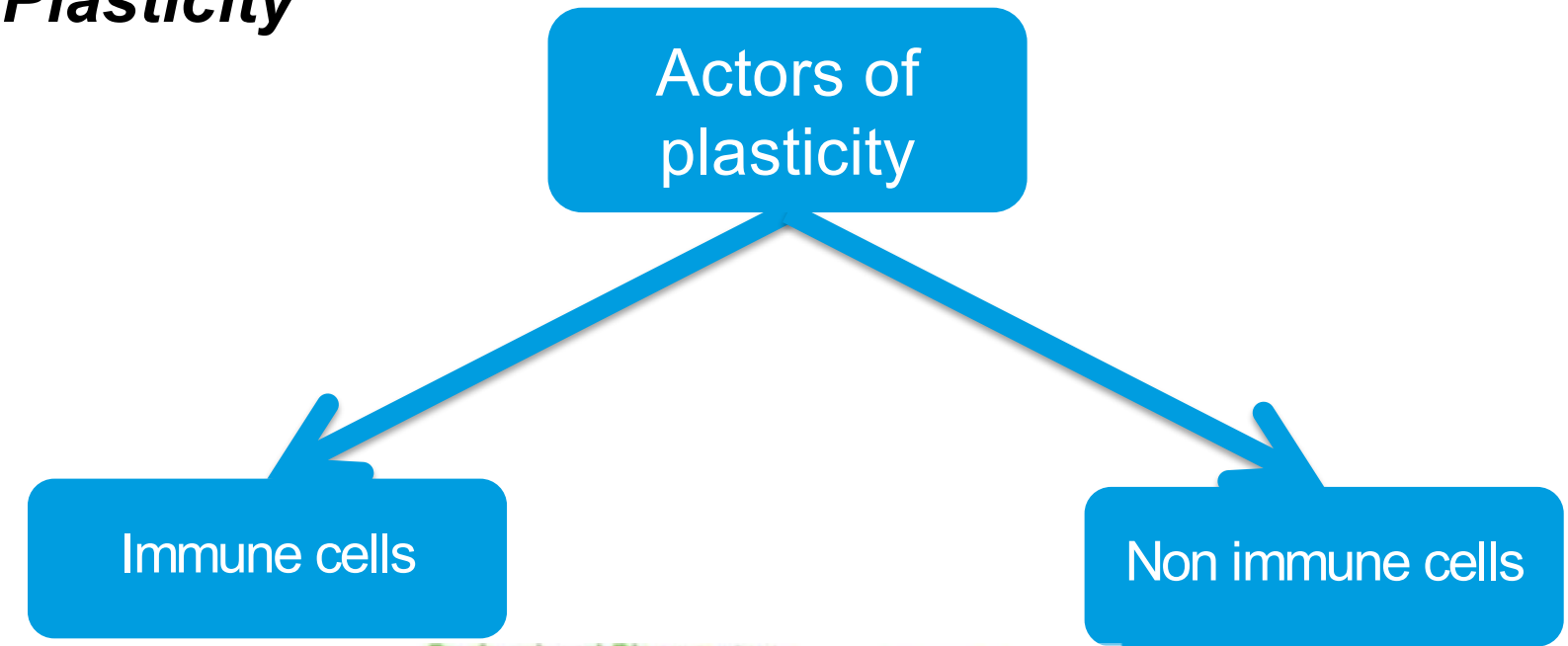


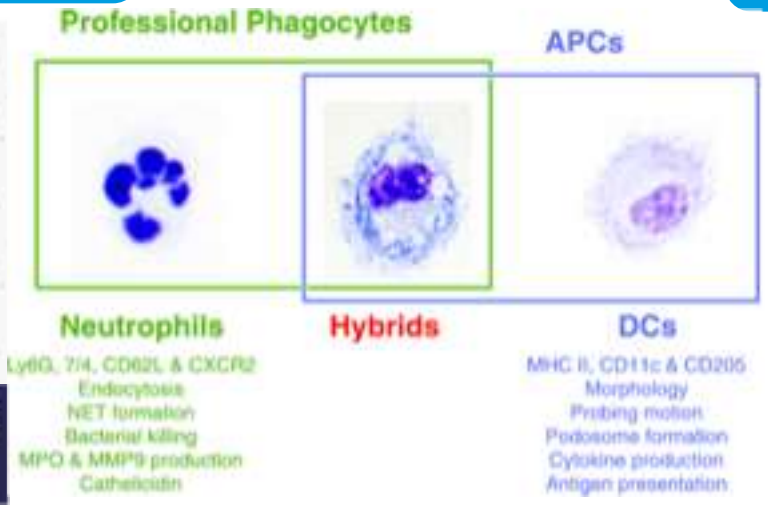
Mishalian I et al. The diversity of circulating neutrophils in cancer. Immunobiology. 2017 Jan;222(1):82-88.

Yang F. et al., The diverse biological functions of neutrophils, beyond the defense against infections, Inflammation 40 (2017) 311–323

The mechanisms that mediate tissue reconstruction

- ***Plasticity***





Matsushima H. et al., Neutrophil differentiation into a unique hybrid population exhibiting dual phenotype and functionality of neutrophils and dendritic cells, Blood 121 (2013) 1677–1689,

The mechanisms that mediate tissue reconstruction

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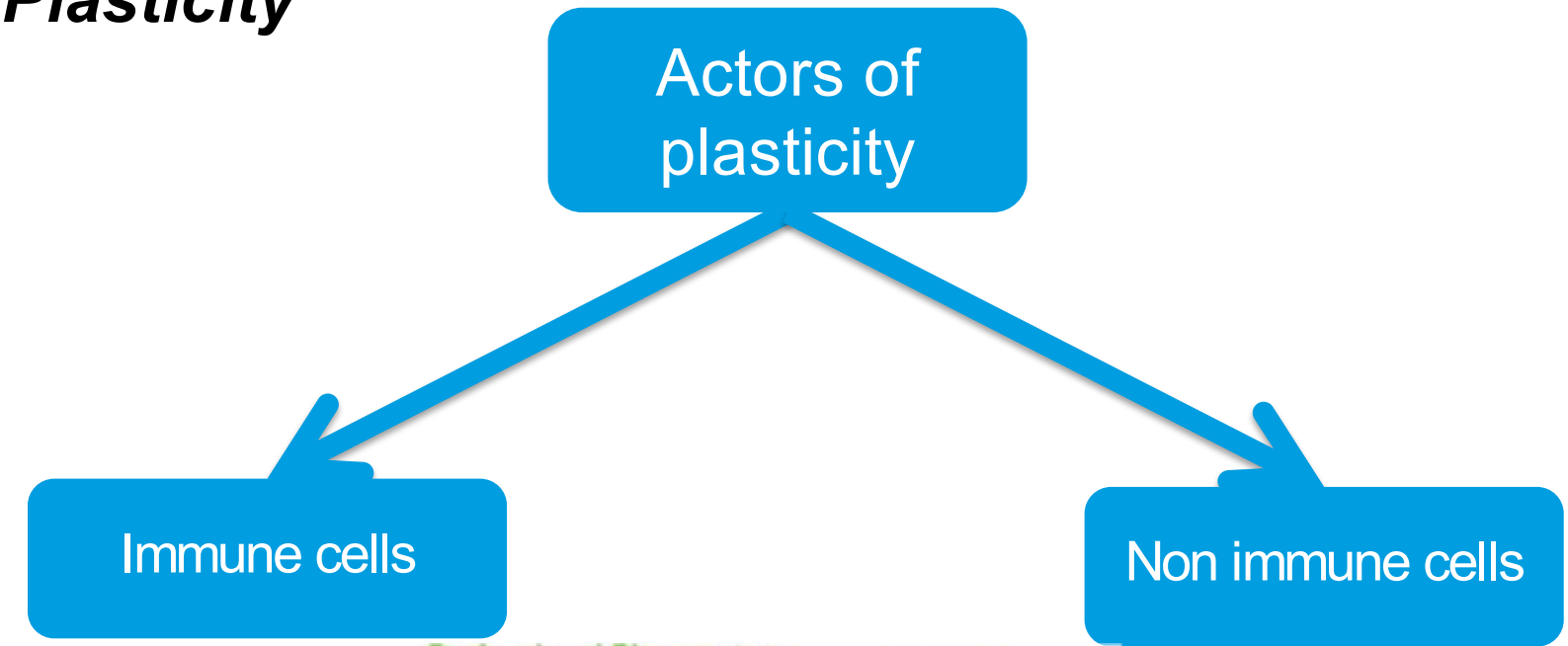

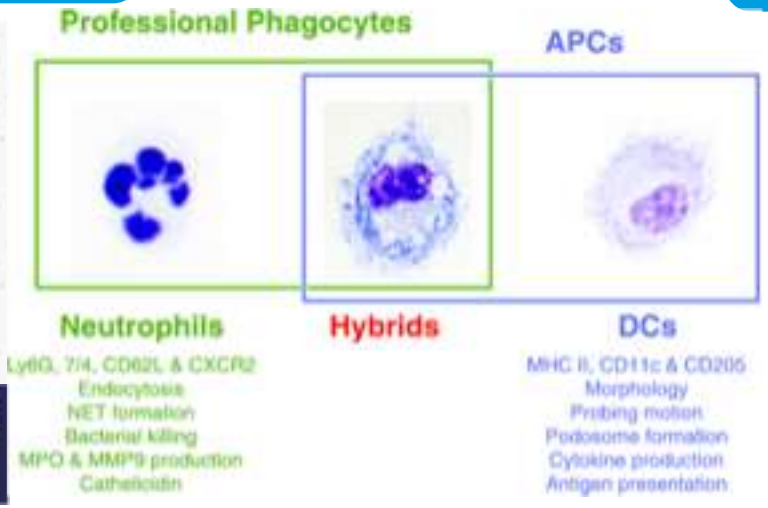

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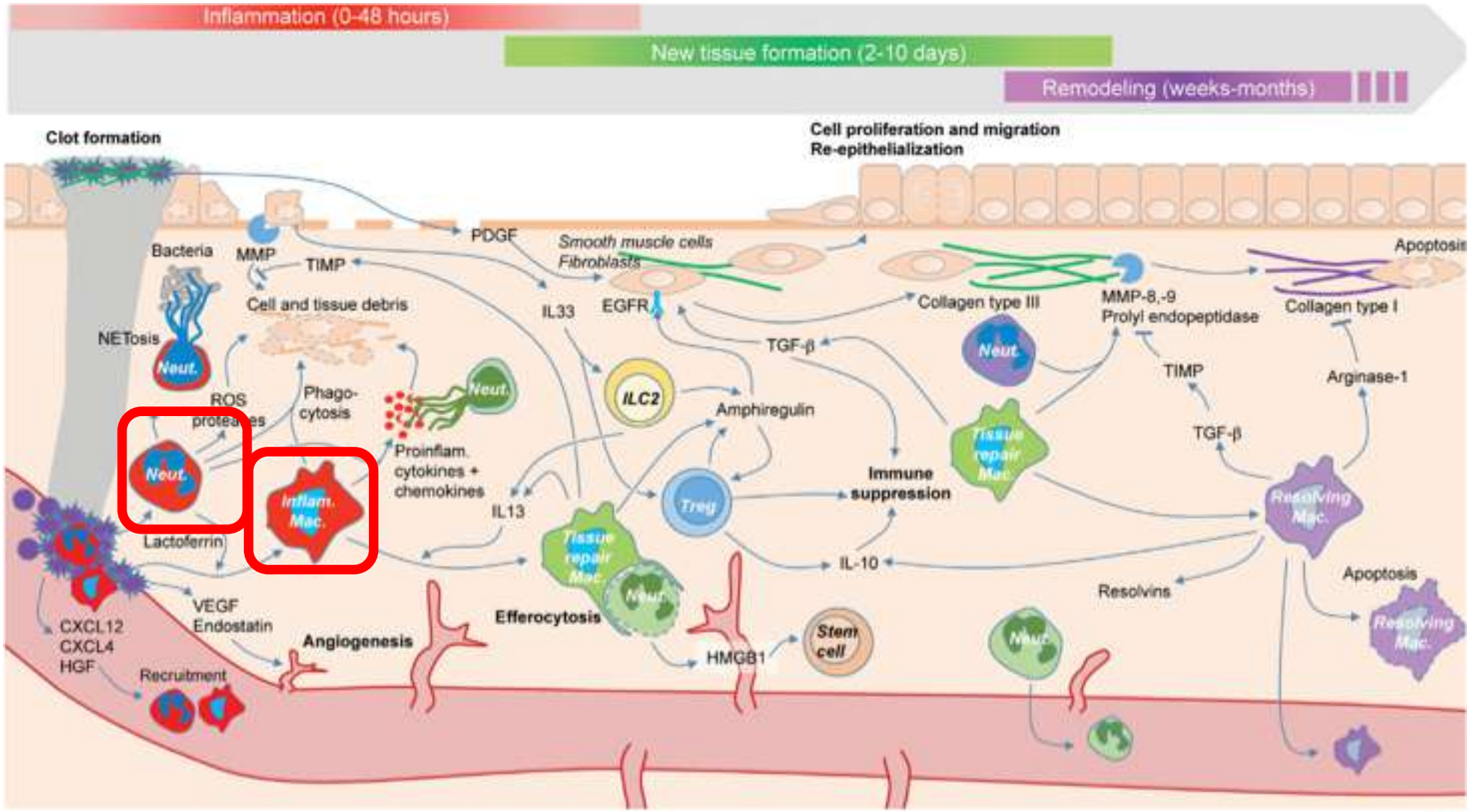
- ➔ Dynamic adjustment

The mechanisms that mediate tissue reconstruction

- ***Functional redundancy***



Laurent P, et al. Immune-Mediated Repair: A Matter of Plasticity. Front Immunol. 2017 Apr 24;8:454.

The mechanisms that mediate tissue reconstruction

- ***Functional redundancy***

➔ TRS: characterized by a high level of redundancy, even though some components and pathways seem to be pivotal in the reconstruction process

➔ And **degeneracy**:

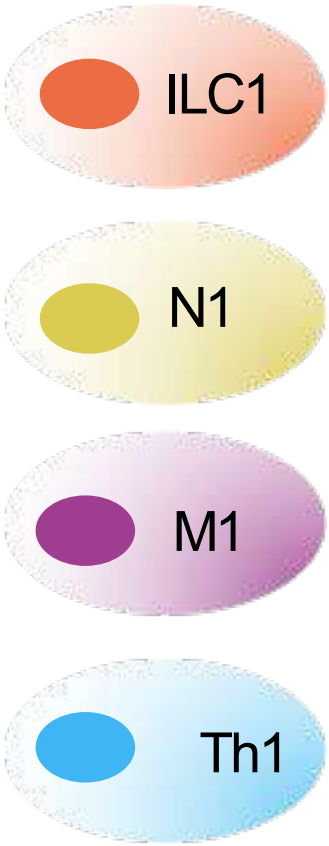
› **the ability of elements that are structurally different to perform the same function or yield the same output**

G.M. Edelman, J.A. Gally, Degeneracy and complexity in biological systems, Proc. Natl. Acad. Sci. 98 (2001) 13763–13768

The mechanisms that mediate tissue reconstruction

➢ ***Functional redundancy***

➔ Type I response



➔ Functional reponse

Inflammation

Tissue repair

Resolving

L.C. Rankin, et al. Complementarity and redundancy of IL-22-producing innate lymphoid cells, Nat. Immunol. 17 (2016) 179–186,

The mechanisms that mediate tissue reconstruction

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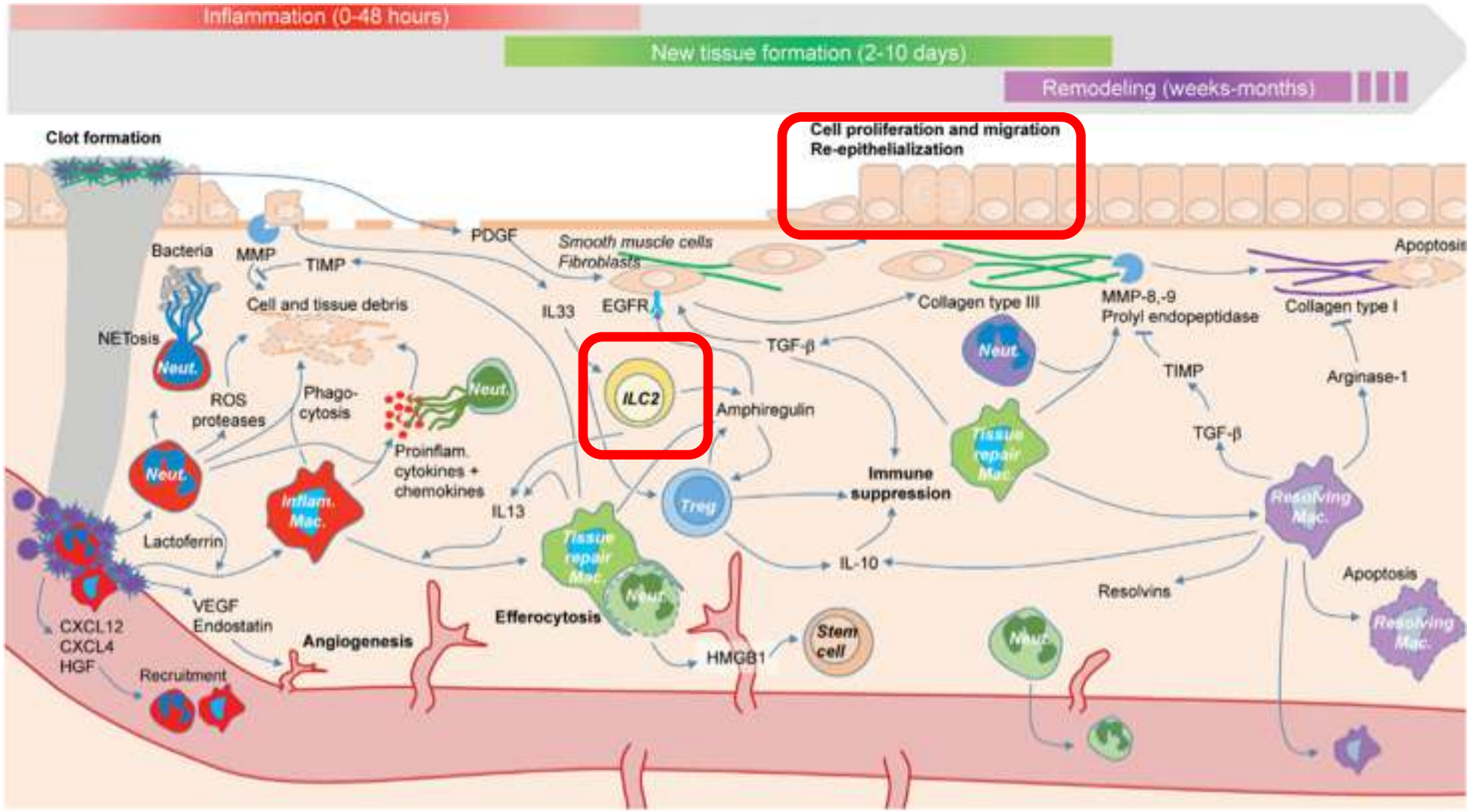
The mechanisms that mediate tissue reconstruction

- ***Constant surveillance***



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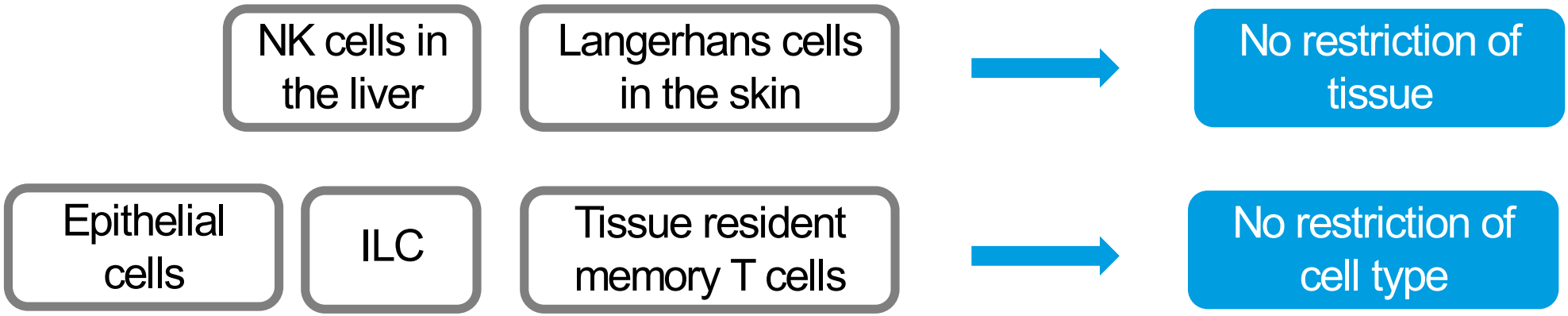
The mechanisms that mediate tissue reconstruction

➢ ***Constant surveillance***

➔ Crucial importance of tissue-resident sentinel cells, as they are present and on standby before any damages.

➔ Maintaining the integrity of the barriers

➔ Crosstalk with the microenvironment



Dalessandri T et al. Beneficial autoimmunity at body surfaces –immune sur- veillance and rapid type 2 immunity regulate tissue homeostasis and cancer, Front. Immunol. 5 (2014)

The mechanisms that mediate tissue reconstruction

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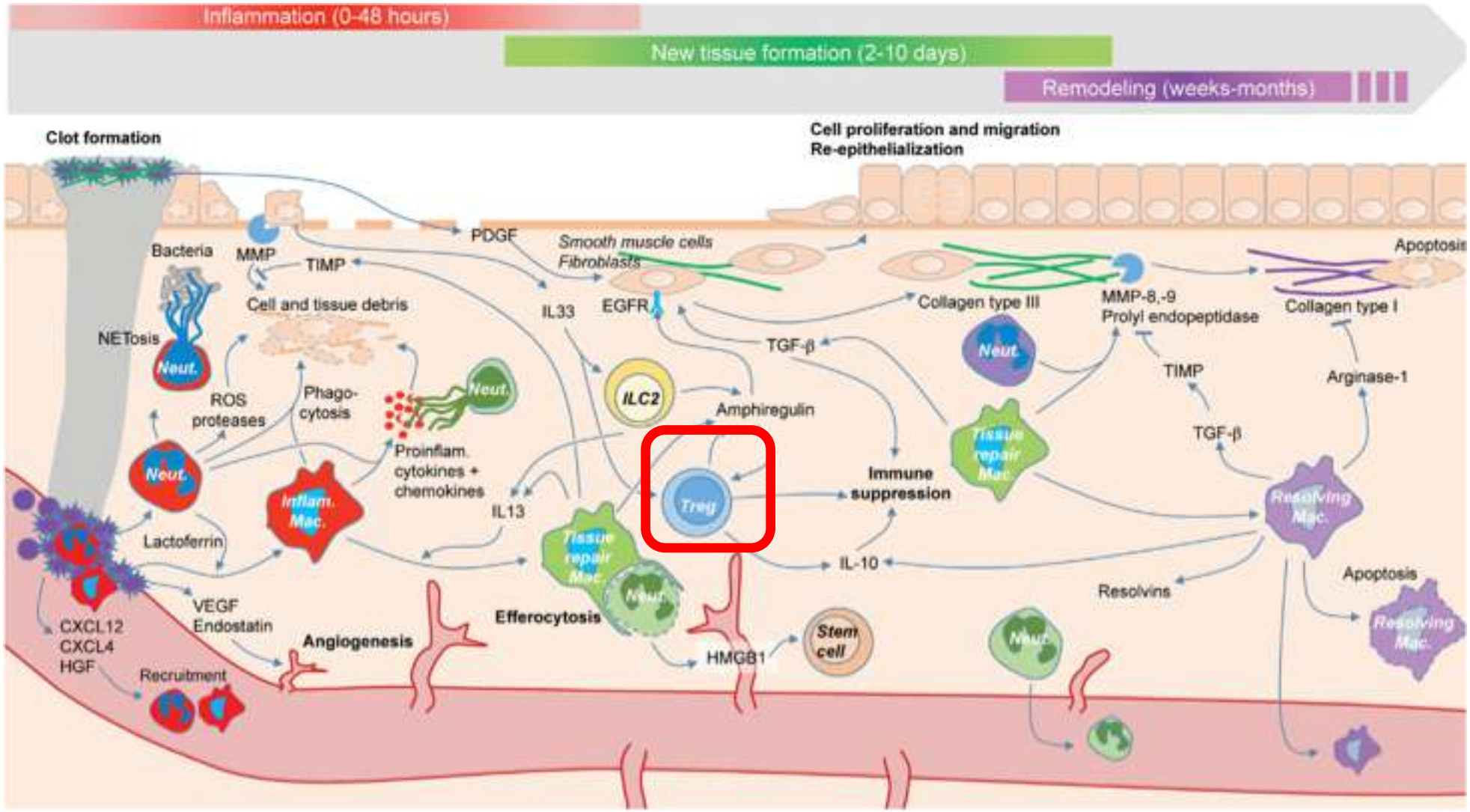
The mechanisms that mediate tissue reconstruction

- ***Restraint***



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The mechanisms that mediate tissue reconstruction

- ***Restraint***
  - The TRS is always on alert, ready to be triggered
  - Potential threat for the organism ➔ inflammation, tissue formation, and tissue remodelling can all go awry, with potentially dramatic consequences
  - Constantly under control

Pro-resolving phase of the process

The mechanisms that mediate tissue reconstruction

- ***Restraint***
  - ➔ The TRS is always on alert, ready to be triggered
  - ➔ Potential threat for the organism ➔ inflammation, tissue formation, and tissue remodelling can all go awry, with potentially dramatic consequences
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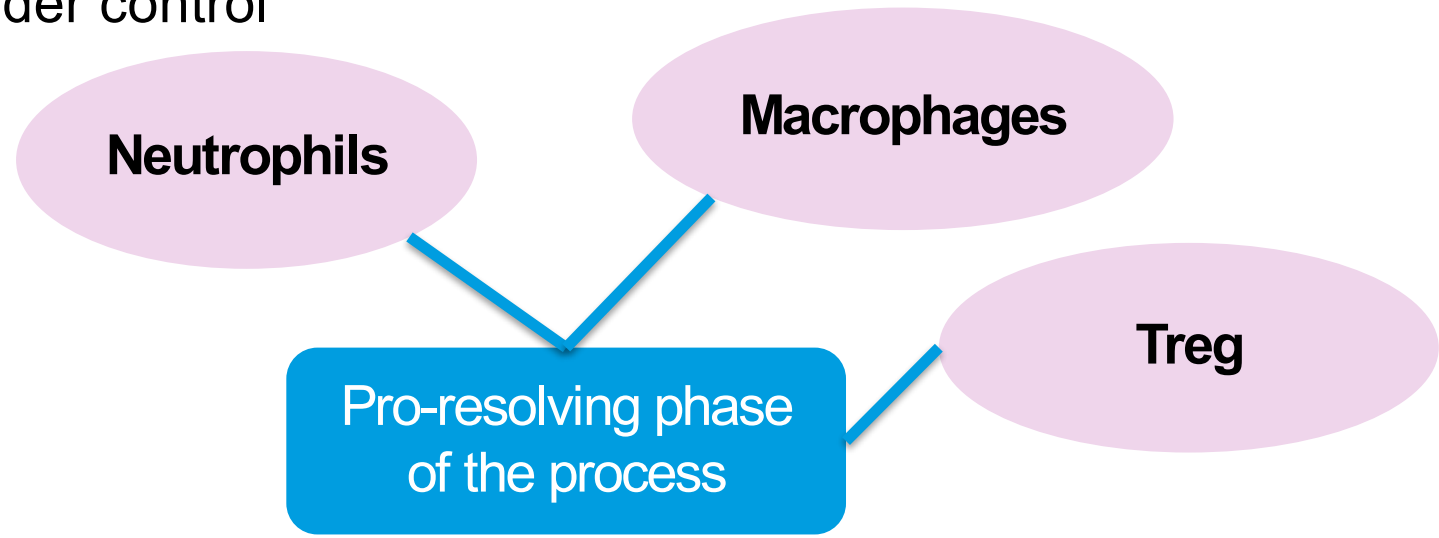

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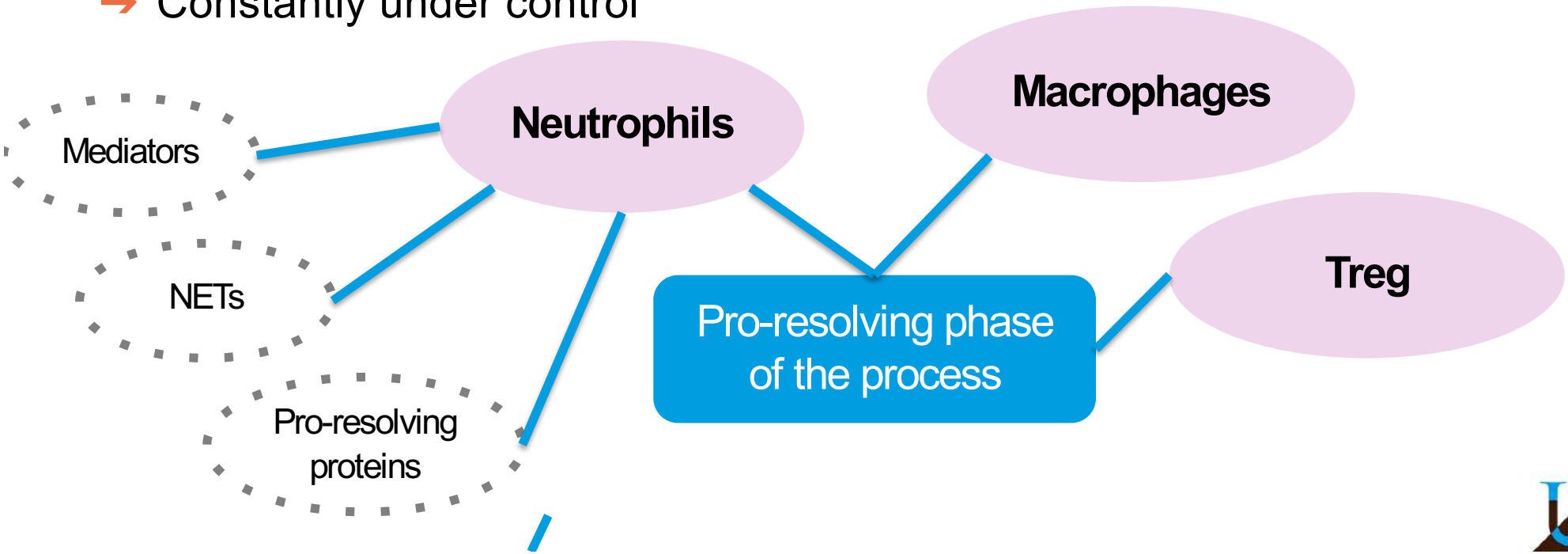

The mechanisms that mediate tissue reconstruction

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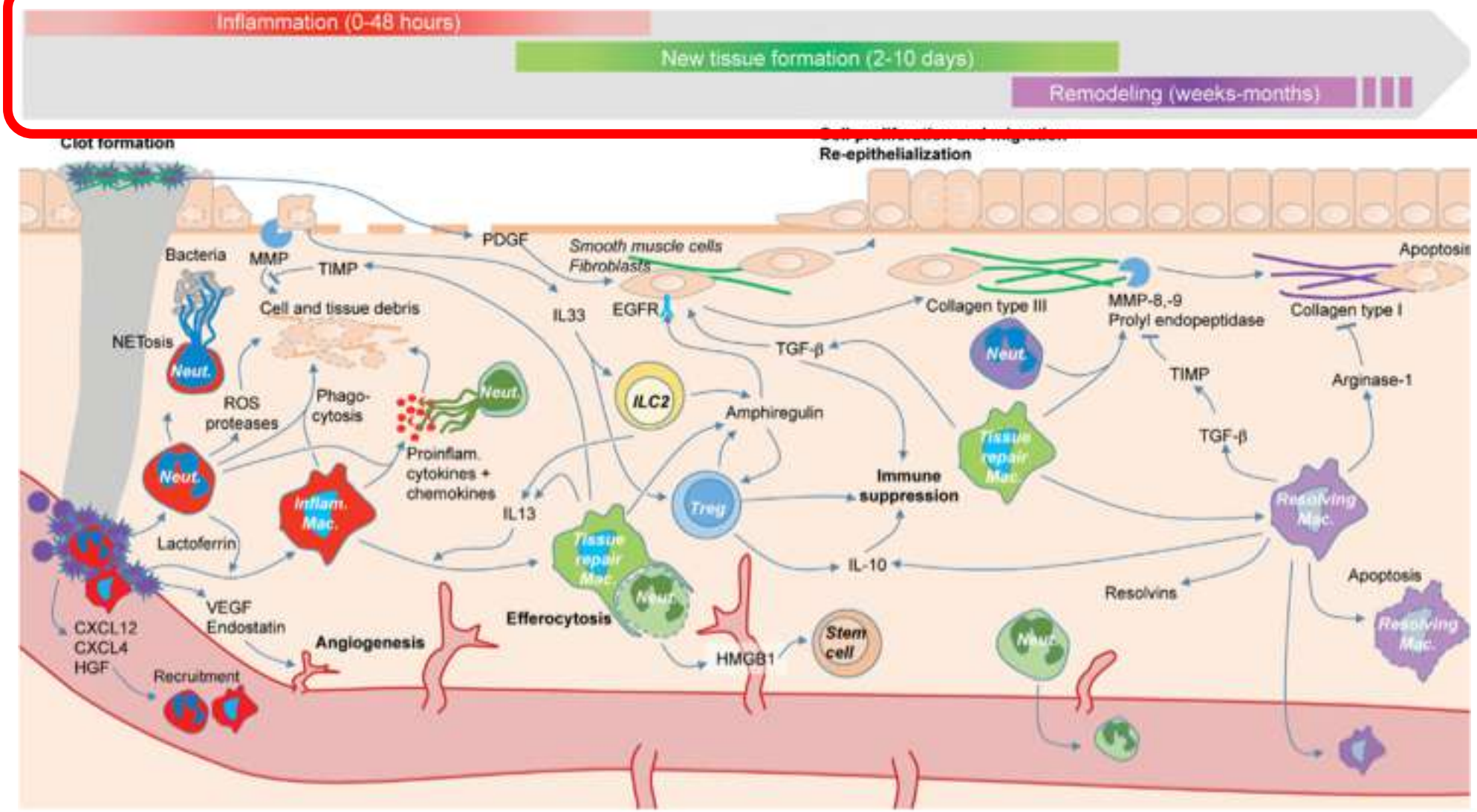
The mechanisms that mediate tissue reconstruction

- ***Dynamic adjustment***



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The mechanisms that mediate tissue reconstruction

- ***Dynamic adjustment***
  - Highly dynamic process
  - Recruitment of various cells
  - Movements in a tri-dimensional matrix
  - Many back and forth between different steps
  - Overlap
  - Also for resident cells

The mechanisms that mediate tissue reconstruction

- ***Dynamic adjustment***
  - Highly dynamic process
  - Recruitment of various cells
  - Movements in a tri-dimensional matrix
  - Many back and forth between different steps
  - Overlap
  - Also for resident cells

  - Velocity of migration partly regulated by the microenvironment

3. Robustness and dysfunctions of the TRS

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Dysfunctions of the tissue reconstruction system

- ➔ the concept of robustness can shed light on certain pathological processes
- ➔ Mechanisms that mediate tissue reconstruction to ensure robustness are constantly challenged…
- ➔ …and sometimes overwhelmed

Dysfunctions of the tissue reconstruction system

- ➔ the concept of robustness can shed light on certain pathological processes
- ➔ Mechanisms that mediate tissue reconstruction to ensure robustness are constantly challenged…
- ➔ …and sometimes overwhelmed

Rupture of robustness

Excess of robustness

Hijacking of robustness

Dysfunctions of the tissue reconstruction system

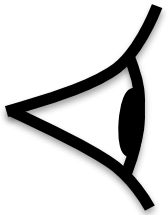
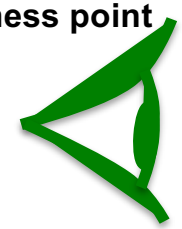
- ➔ the concept of robustness can shed light on certain pathological processes
- ➔ Mechanisms that mediate tissue reconstruction to ensure robustness are constantly challenged…
- ➔ …and sometimes overwhelmed

Rupture of robustness	**Excess of robustness**	**Hijacking of robustness**
Ulcers	**Fibrosis**	**Cancer**

Dysfunctions of the tissue reconstruction system

Rupture of robustness

Ulcers

	Pathological situation	Biological traduction	Therapeutic consequence
Classical view 	Wound	Not enough wound healing	To add wound healer
From the robustness point of view 			

Dysfunctions of the tissue reconstruction system

Rupture of robustness

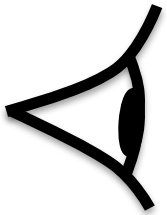
Ulcers

Pathological situation

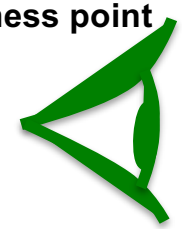
Biological traduction

Therapeutic consequence

Classical view



From the robustness point of view

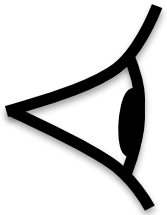
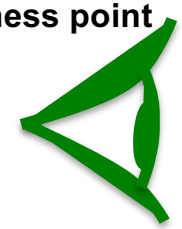


Not enough wound healing

Dysfunctions of the tissue reconstruction system

Rupture of robustness

Ulcers

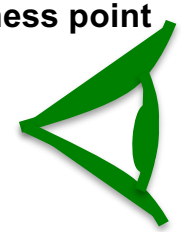
	Pathological situation	Biological traduction	Therapeutic consequence
Classical view 	Wound	Not enough wound healing	To add wound healer
From the robustness point of view 	Wound	Break in robustness	To increase robustness

Dysfunctions of the tissue reconstruction system

Rupture of robustness

Ulcers

From the robustness point of view



Wound

Break in robustness

To precisely identify vulnerabilities, which vary depending on the clinical situation

To increase robustness

To work out innovative therapeutic strategies

➔ Each mechanism underlying the robustness of the TRS can be affected

Dysfunctions of the tissue reconstruction system

Rupture of robustness

Ulcers

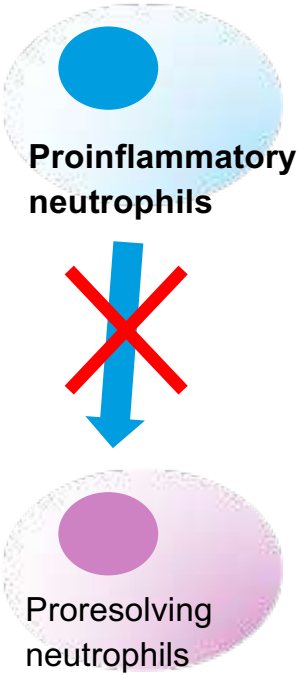
Plasticity

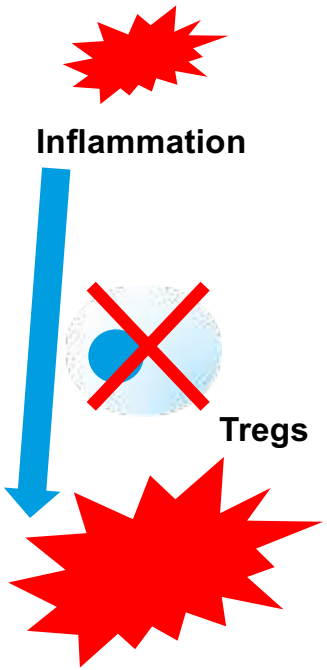
Redundancy

Restraint

Constant surveillance

Dynamic adjustement





Dysfunctions of the tissue reconstruction system

Rupture of robustness

Ulcers

Plasticity	Redundancy	Restraint	Constant surveillance	Dynamic adjustement
Reintroduction of very plastic cells	Favouring the resolving phase	Pro-Treg therapeutics	Targeting sentinels	Promoting cell migration
Adipose tissue-derived stem cells	Resolving compounds	Low-dose IL2		Chemokines

Dysfunctions of the tissue reconstruction system

Excess of robustness

Fibrosis

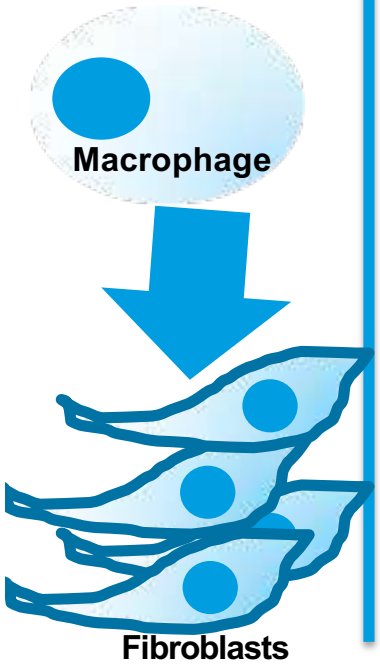
Plasticity

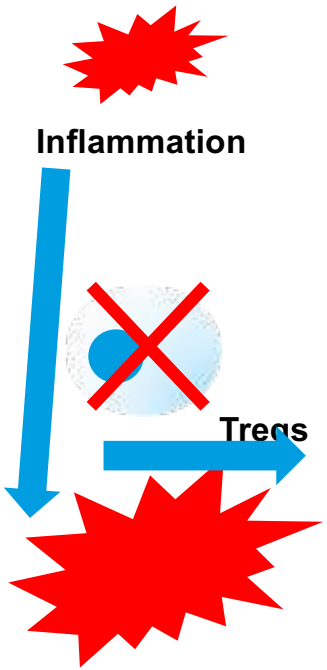
Redundancy

Restraint

Constant surveillance

Dynamic adjustement





Dysfunctions of the tissue reconstruction system

Excess of robustness

Fibrosis

Plasticity	Redundancy	Restraint	Constant surveillance	Dynamic adjustement
To limit the plasticity		Restore Treg functionality	Limiting the sensitivity of resident cells	Limiting cell migration
Infusion of **stabilized** pro-resolving macrophages				Anti-CXCL12 and fibrocytes (peptide R1R2)

Dysfunctions of the tissue reconstruction system

Hijacking of robustness

Cancer

« Wounds that do not heal? »

The cancerous tumor hijacks some properties of the TRS that normally ensure robustness in physiological conditions

Plasticity	Redundancy	Restraint	Constant surveillance	Dynamic adjustement
Epithelial-mesenchymal transition		Tumor associated macrophages (TAM)	Use and destruction of immunosurveillance	Use of chemotactics pathway
Migratory, invasive, and stem-like properties			Resident memory CD8 + T cells	Neutrophil migration and recruitment precedes metastatic cascade

Dysfunctions of the tissue reconstruction system

Hijacking of robustness

Cancer

Plasticity	Redundancy	Restraint	Constant surveillance	Dynamic adjustement
To limit the EMT	Not at the cell level	To decrease the tolerance	Increasing the surveillance	Limiting cell migration
To increase SCAI/ targeting macrophage polarization	To promote the local immune responses in the tumor microenvironment	To switch of M2 TAMs into antitumor M1 macrophages	Vaccines to increase resident memory CD8 + T cells	

4. Conceptual consequences

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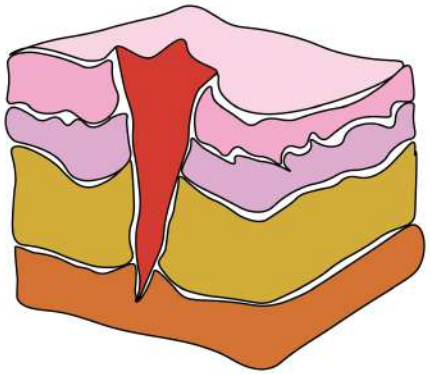
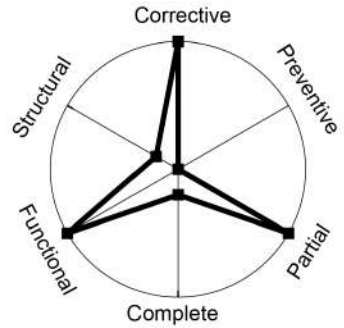
3 main conceptual consequences

- Different **robustness-promoting mechanisms** (system control, alternative mechanisms, modularity, decoupling) = a **useful conceptual framework to better describe the TRS** and its **dysfunctions** in pathological situations.
- (In turn) Example of the **TRS** -> crucial conceptual distinctions about robustness.
  - Functional vs. structural robustness
  - Partial vs. complete robustness
  - Corrective vs. preventive robustness
- A **redefinition of immunity**: from defence to repair, development, housekeeping. Maintains the cohesiveness of the organism.

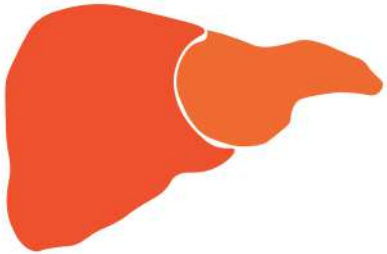
Different types (or dimensions) of robustness

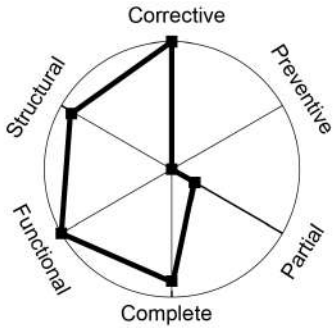
Severe skin injury



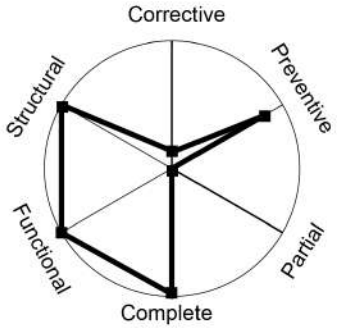


Liver regeneration in mammals

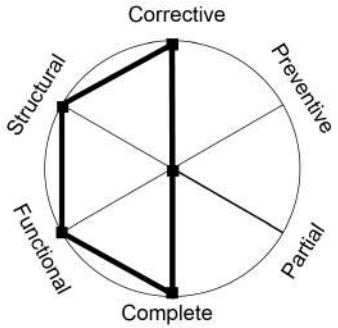




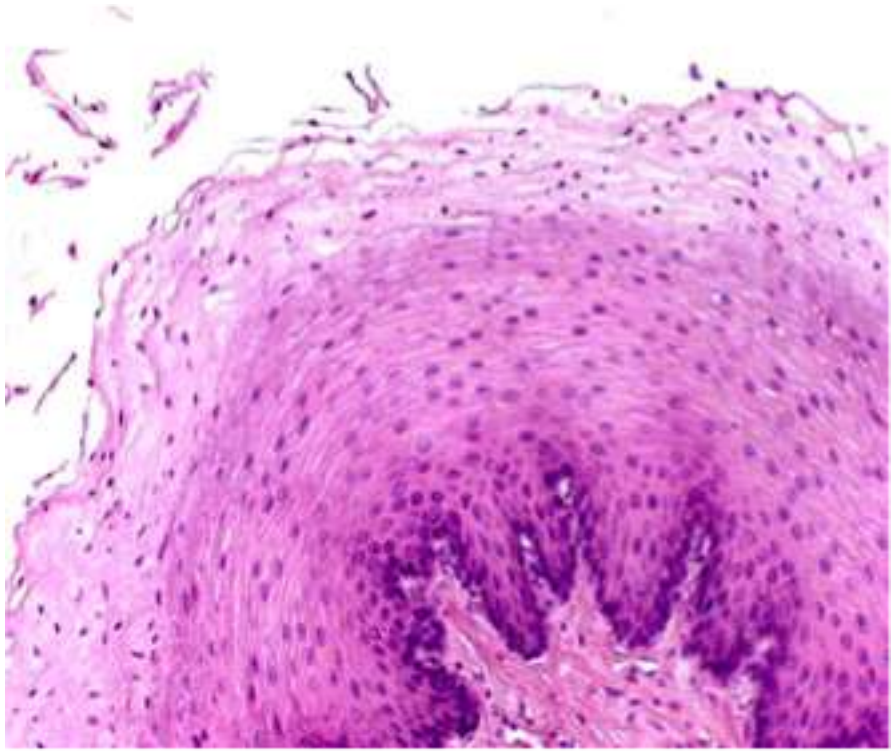
Continuous renewal of epithelia



Member regeneration in Salamander



Conclusions



- **TRS** is a **good test-case** for showing the fruitfulness of robustness talk, especially: multidimensionality and degrees.
- Robustness concept will be enriched by a **multiplication of examples, including clinically relevant ones**, and the comparison between them. E.g., **repair** and **cancer**.
- TRS helps **re-define immunity** as maintaining of cohesiveness.

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