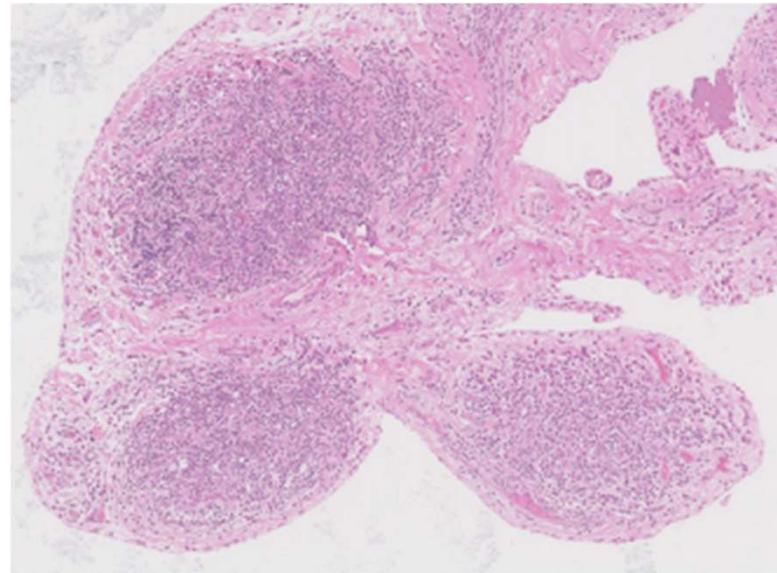
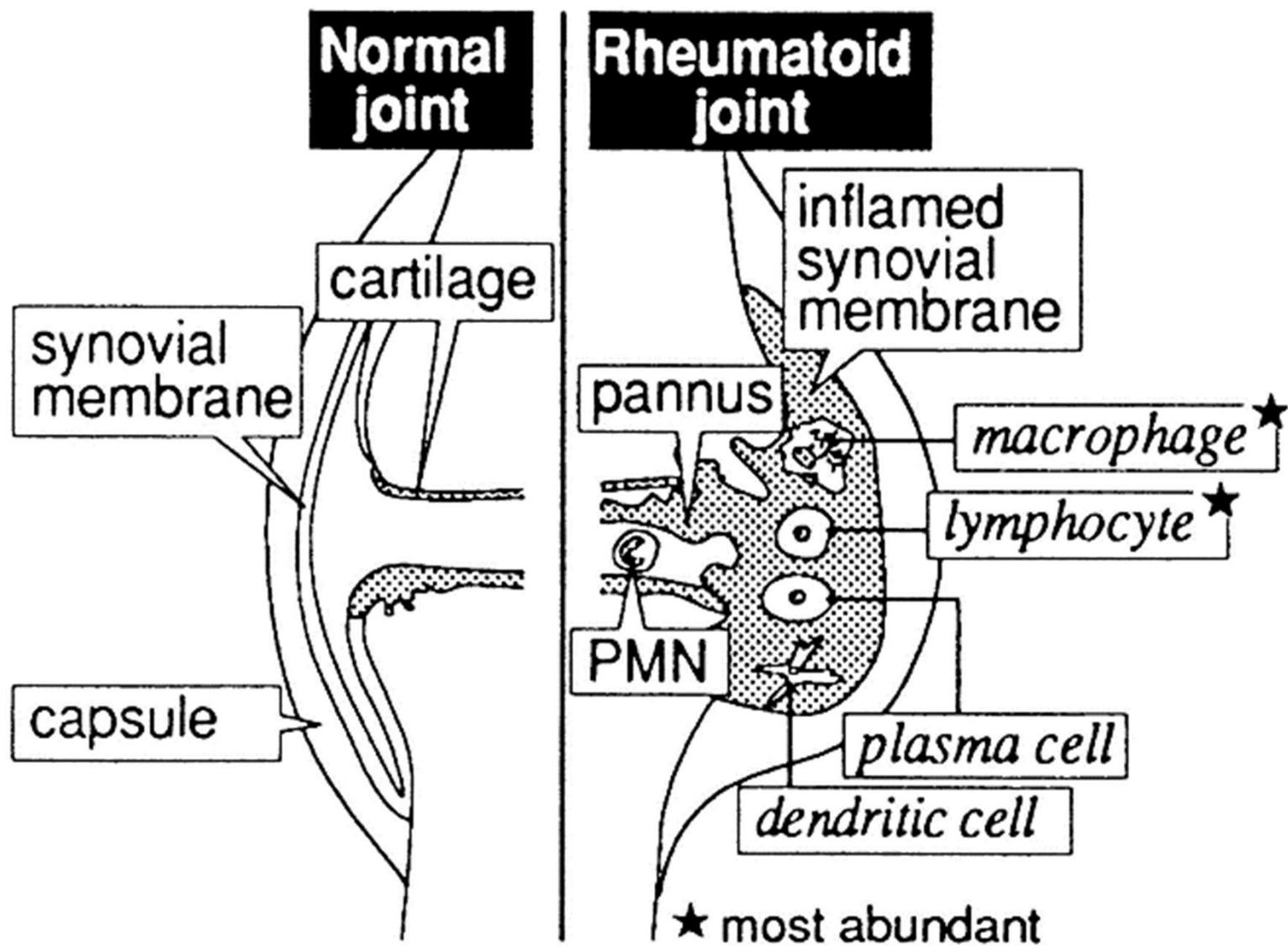
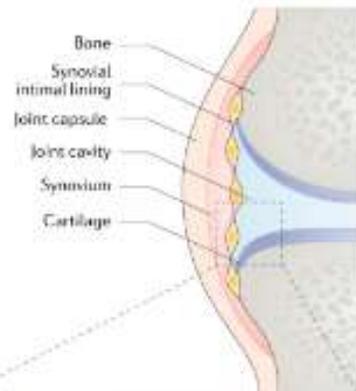


Communications intercellulaires dans la PR

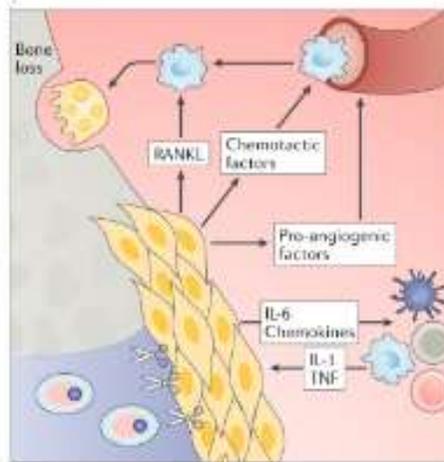
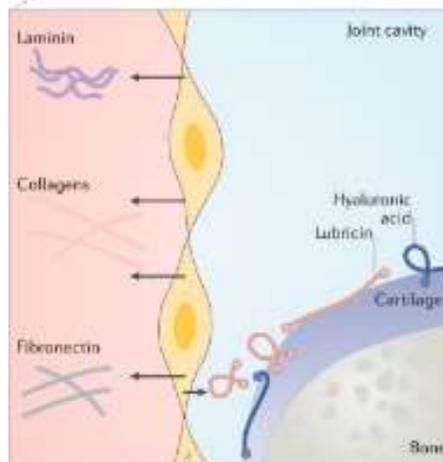
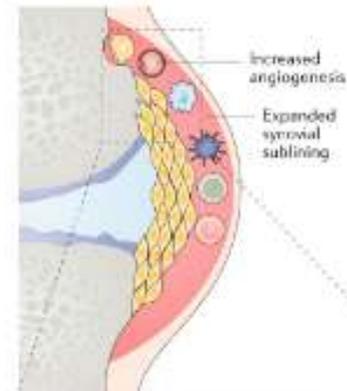




a Healthy



b Rheumatoid arthritis



FLS in healthy joints:

- Shape and maintain the ECM
- Produce joint lubricants
- Provide structure between synovium and the joint cavity

FLS in the joints in RA:

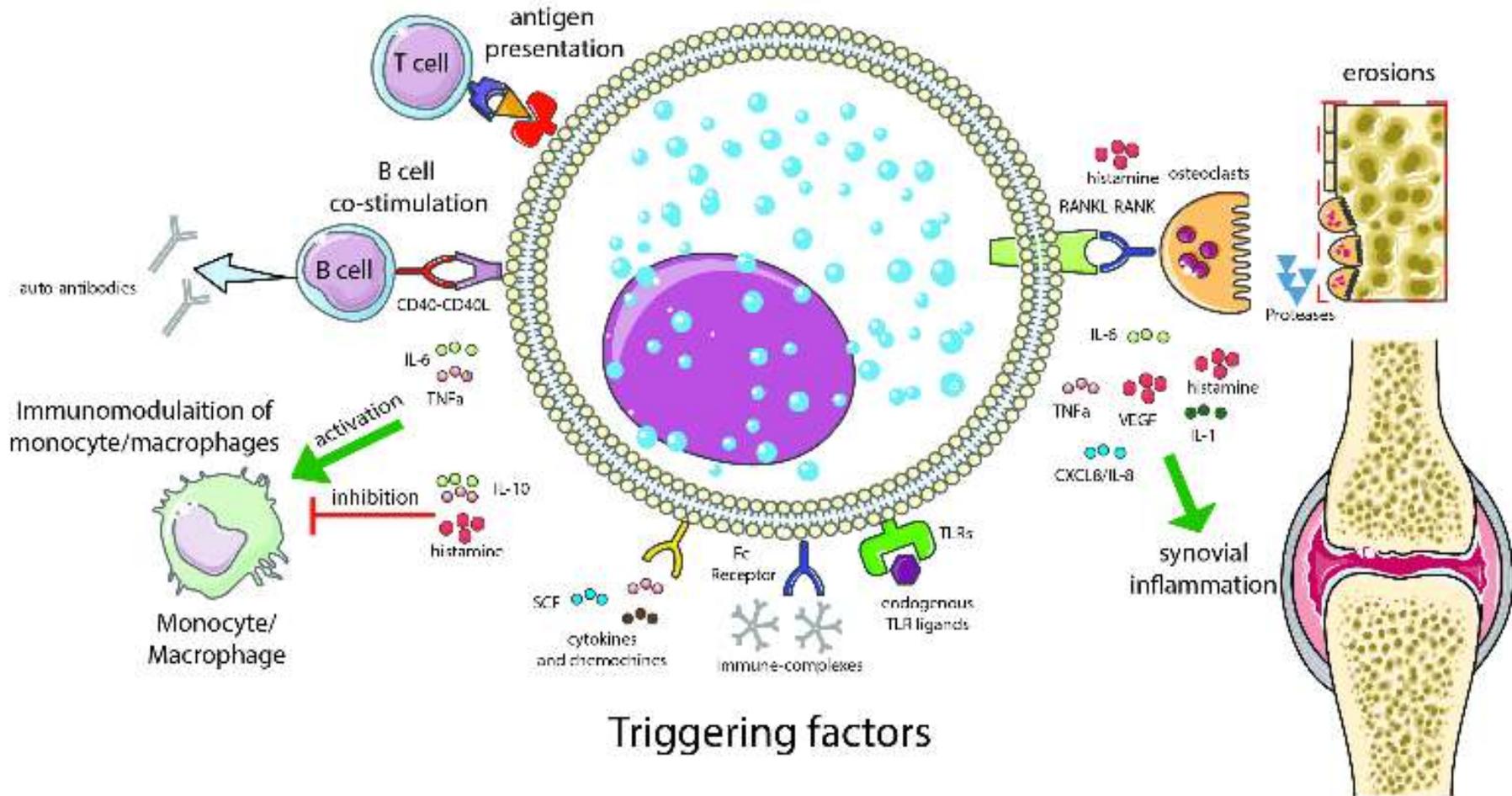
- Marked increase in number
- Important role in cartilage destruction
- Produce inflammatory cytokines and chemokines
- Facilitate the influx, proliferation and survival of immune cells
- Delay the resolution of inflammation
- Contribute to bone erosion and interfere with bone repair
- Stimulate angiogenesis



Synovial Mast Cells

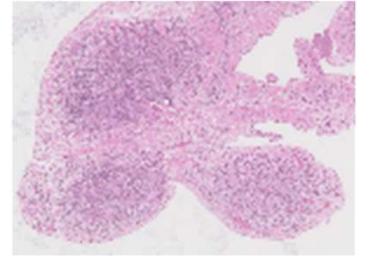
Cellular interactions

Effector functions

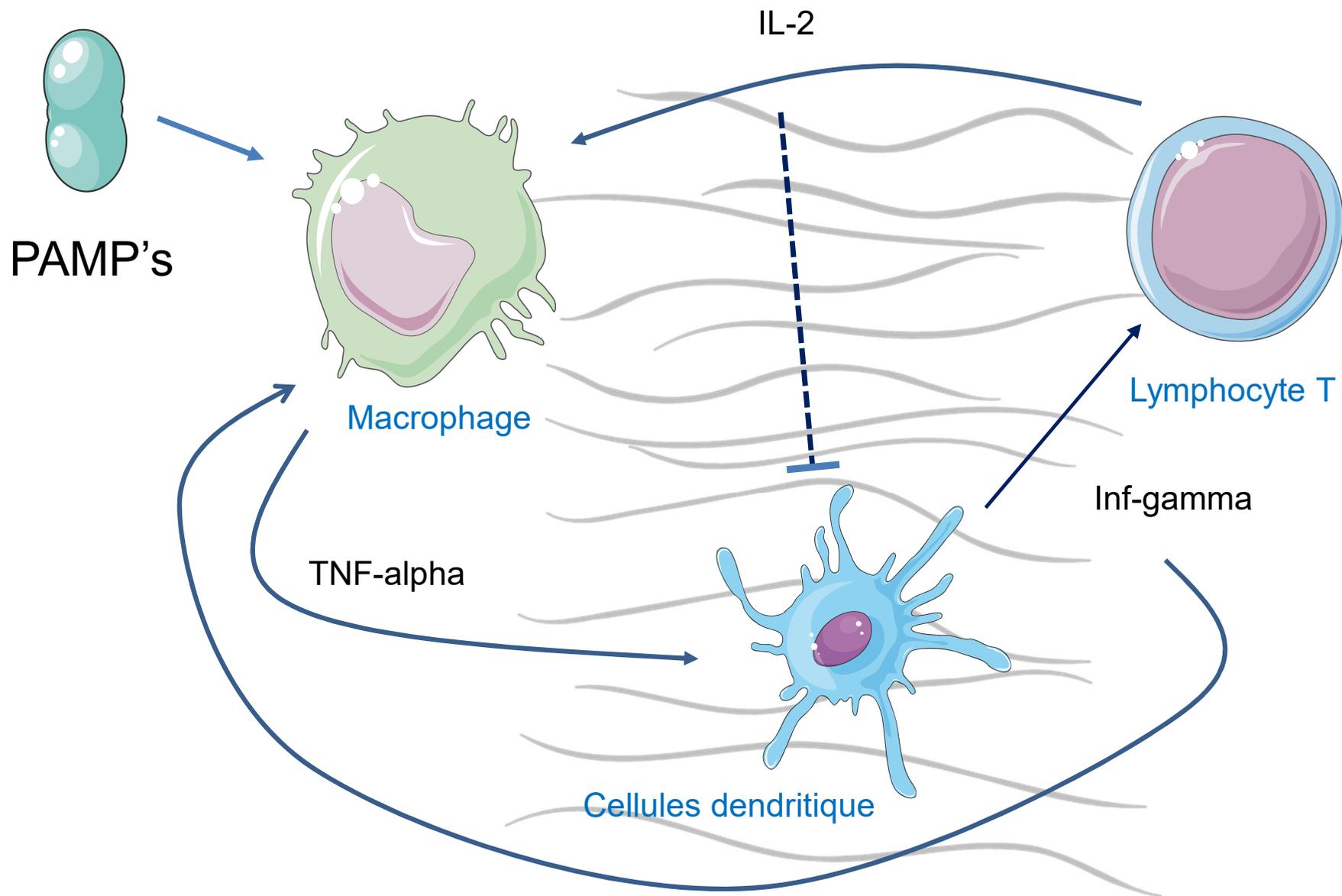


Tous ces modèles sont faux !

Systeme complexe adaptatif

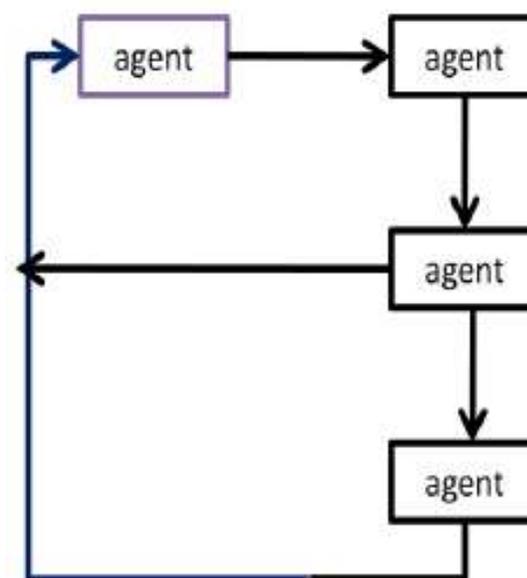


- **Systeme** : un complexe d'elements en interaction
- **Complexe** :
 - Actions/rétroactions
 - Phénomènes d'émergence
- **Adaptatif**
 - Sensible à son environnement



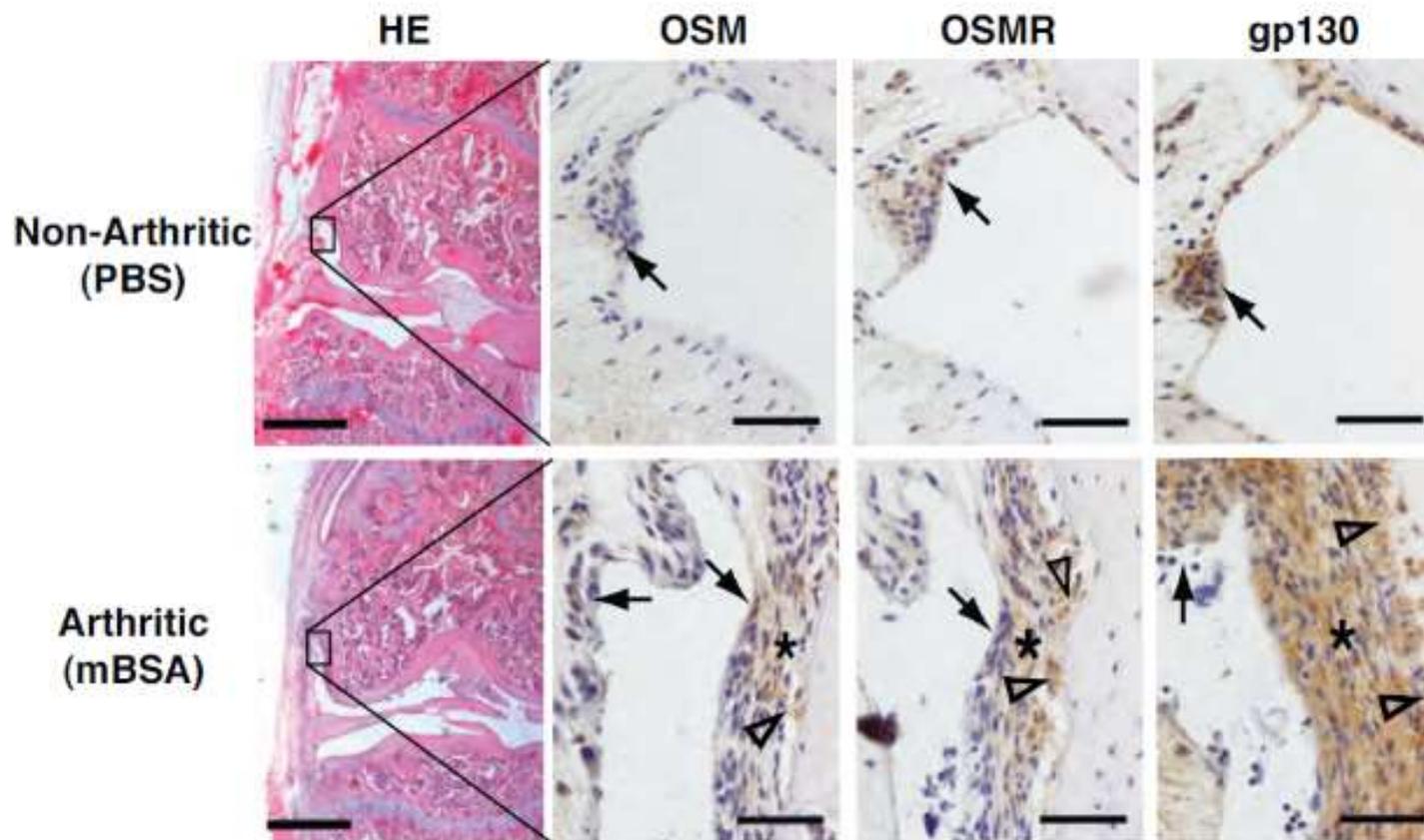
Importance des rétroactions

- Il y a rétroaction lorsqu'un **agent reçoit des stimuli influencés par les stimuli qu'il a émis**
- Multiplicité des réseaux d'interactions bouclés avec des rétroactions **négatives et positives** (feedback).



Boucles d'interactions

Rôle de l'OSM dans la synoviale de PR



Le Goff, 2010

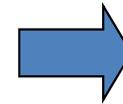
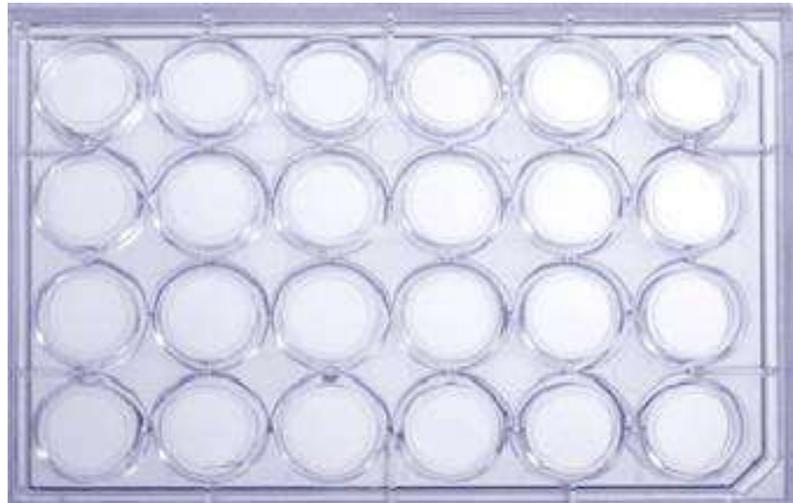
20 weeks old
OSM-R KO or WT



Digestion 2H with
Collagenase IV

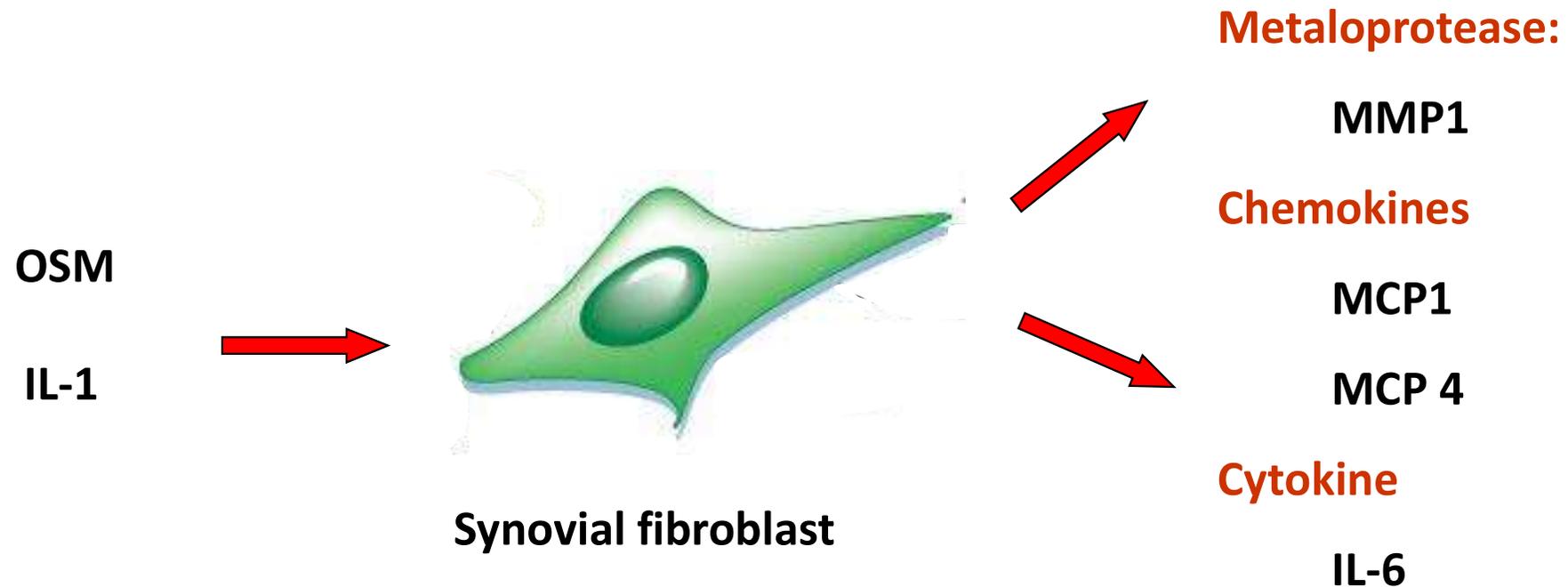


Culture in DMEM, 10% FBS

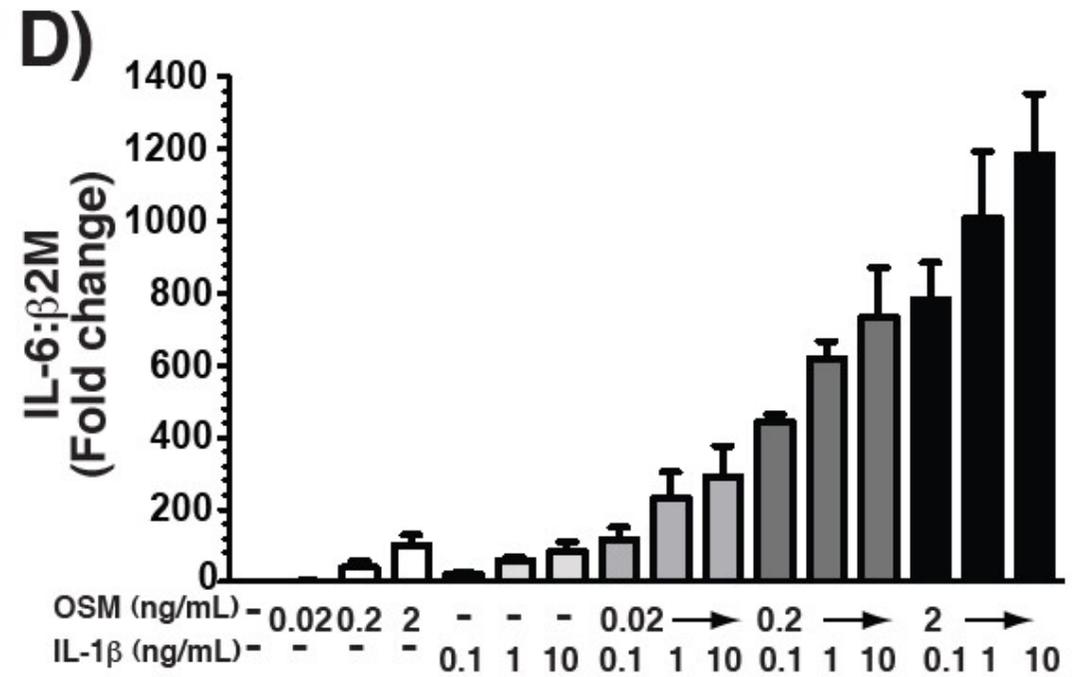
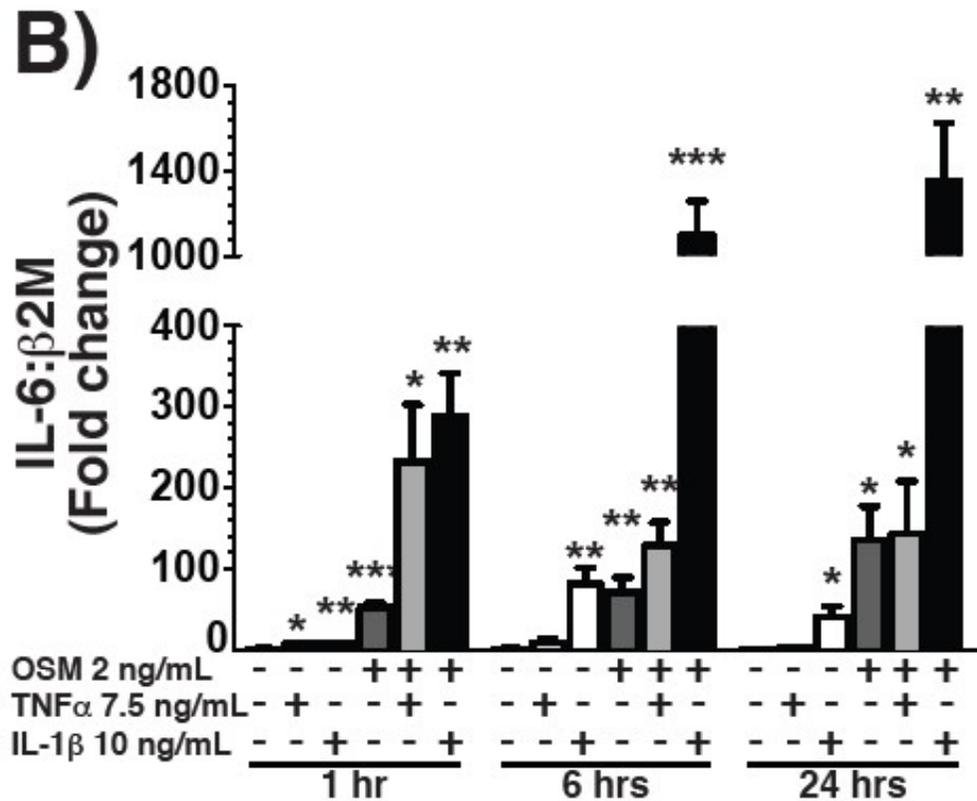


RNA extraction
qPCR analysis

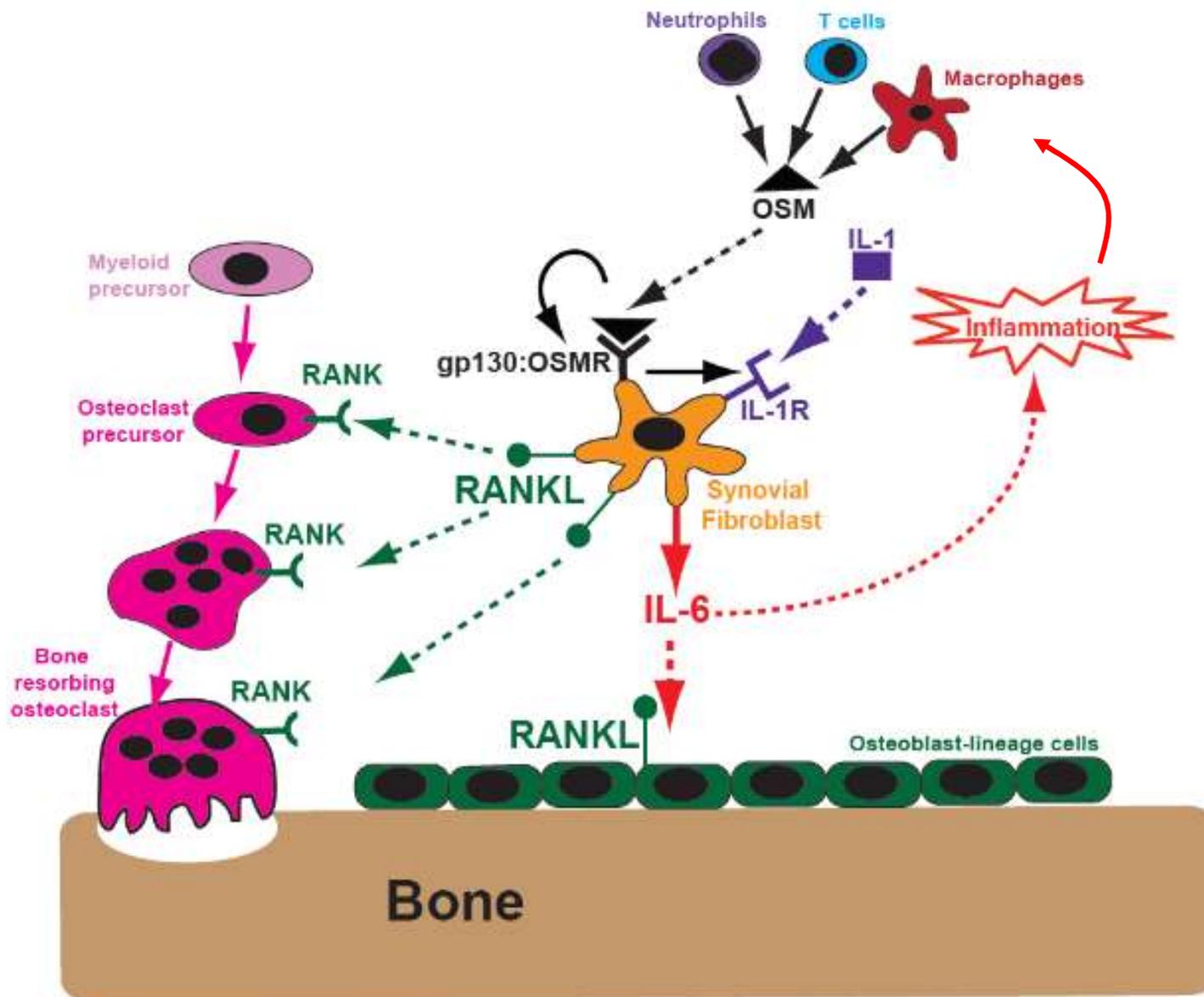
Stimulation des fibroblastes synoviaux



Synergie entre OSM et IL-1 sur l'expression d'IL-6



Le Goff, 2010



Le Goff, 2010

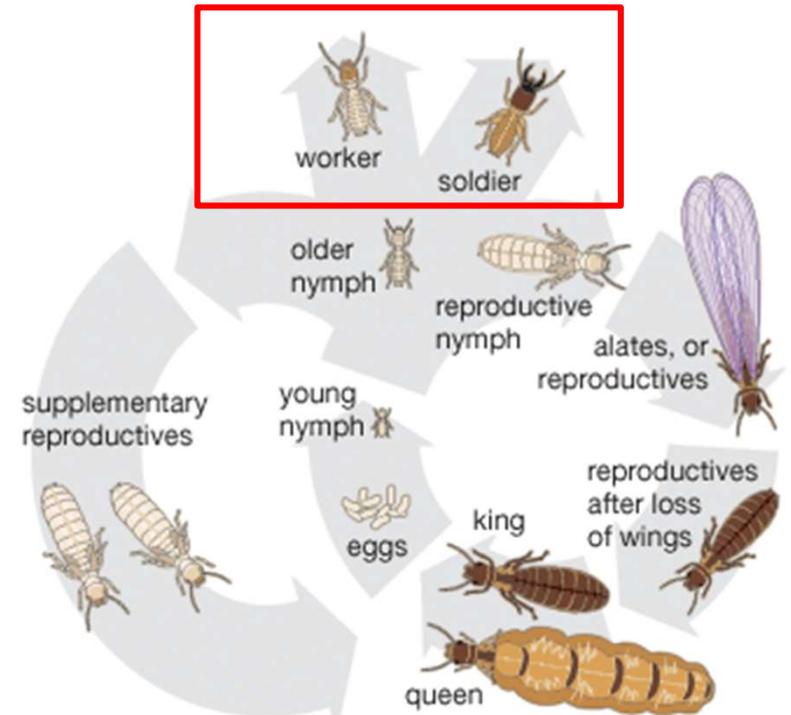
Conséquences des rétroactions

- Engendrent les propriétés fondamentales des systèmes complexes :
 - Holisme
 - **Synergie**
 - Dynamique cyclique
 - Bifurcations
 - Basculements
 - Évolution
 - Adaptation
 - Émergence
 - **Auto-organisation ...**





1. La Termitière (photo)
2. Cheminée principale
3. La Meule
4. Galeries permettant le renouvellement de l'air, reliant la partie basse du nid à l'extérieur
5. Puits profonds



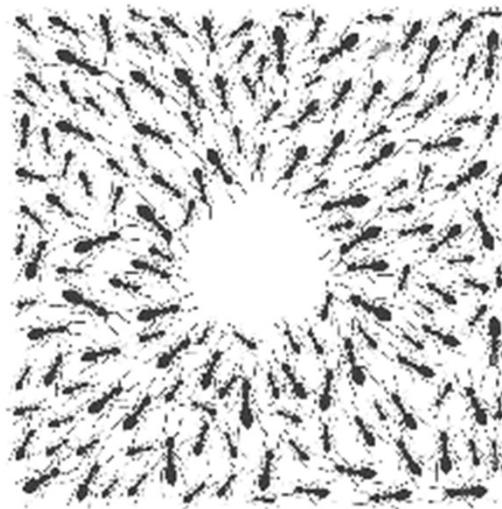
© 2008 Encyclopædia Britannica, Inc.



Emergence

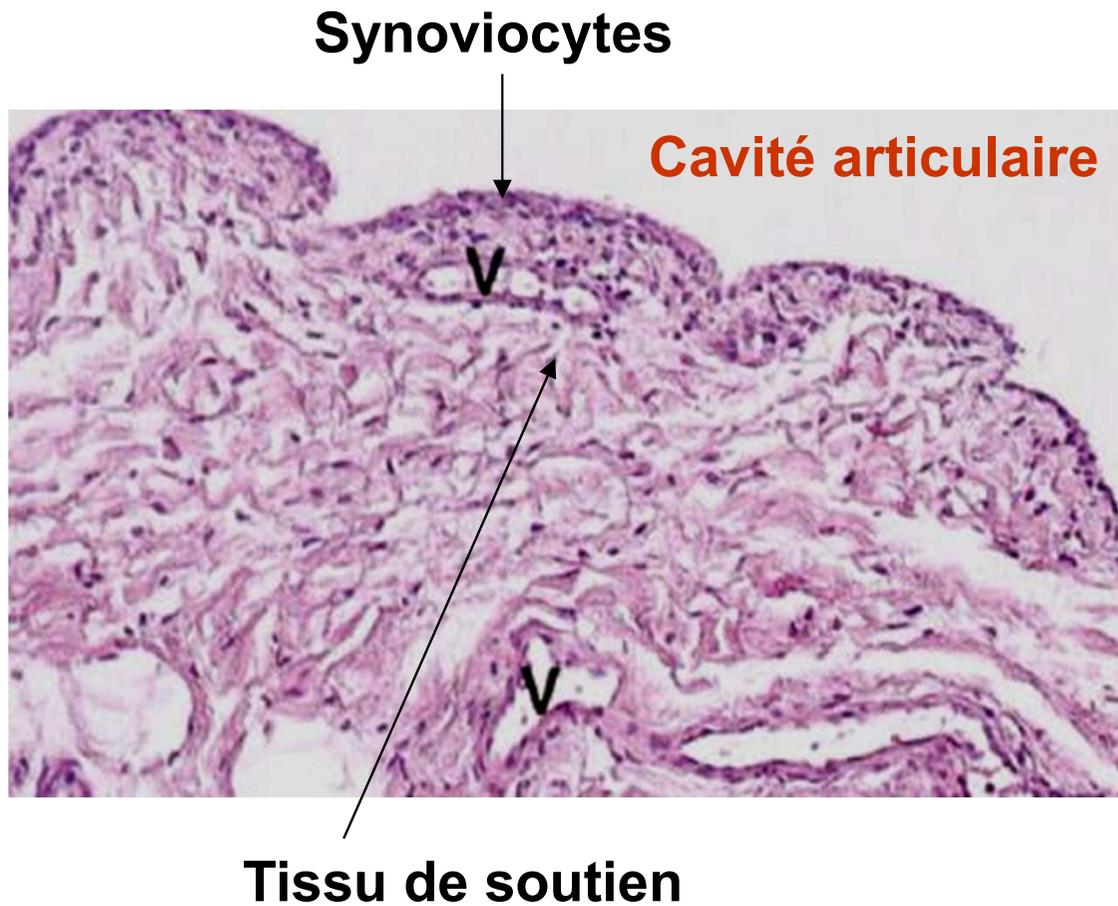


Macro-niveau : structure globale complexe émergente

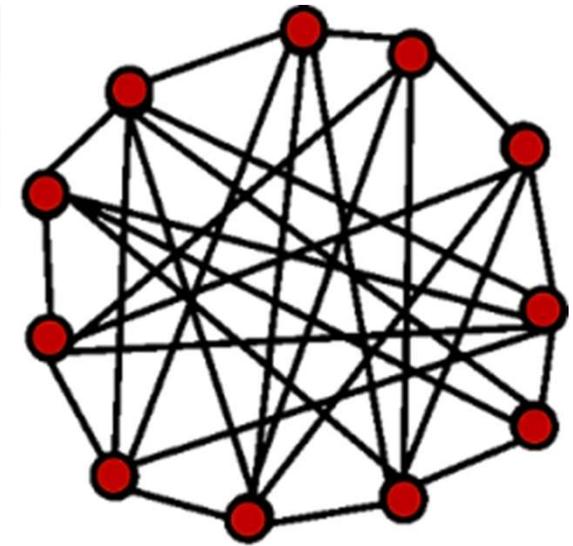
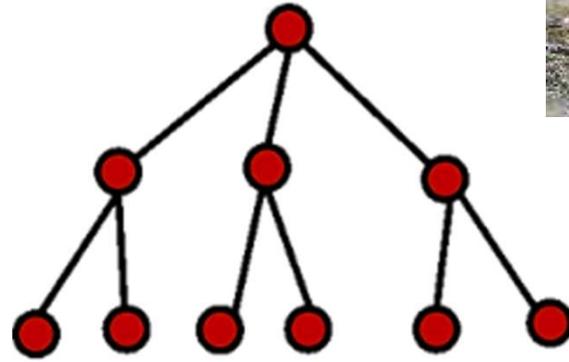


Micro-niveau : règles d'interaction entre les éléments du système

Tissu synovial normal



- ➔
- Lubrification
 - Nutrition cartilage
 - Élimination des déchets



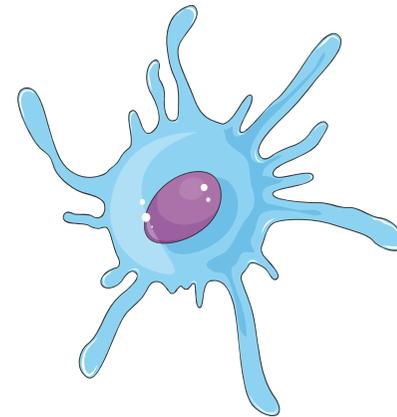
“Top-down”

“Bottom-up”



Emergence

« Comment des choses **stupides** deviennent **intelligentes** ensemble »



« Comment des choses **intelligentes** deviennent **stupides** ensemble? »



SOCIÉTÉ DE
RHUMATOLOGIE
DE L'OUEST



« Comment des choses **stupides** deviennent **encore plus stupides** ensemble? »



Modélisation des systèmes complexes adaptatifs

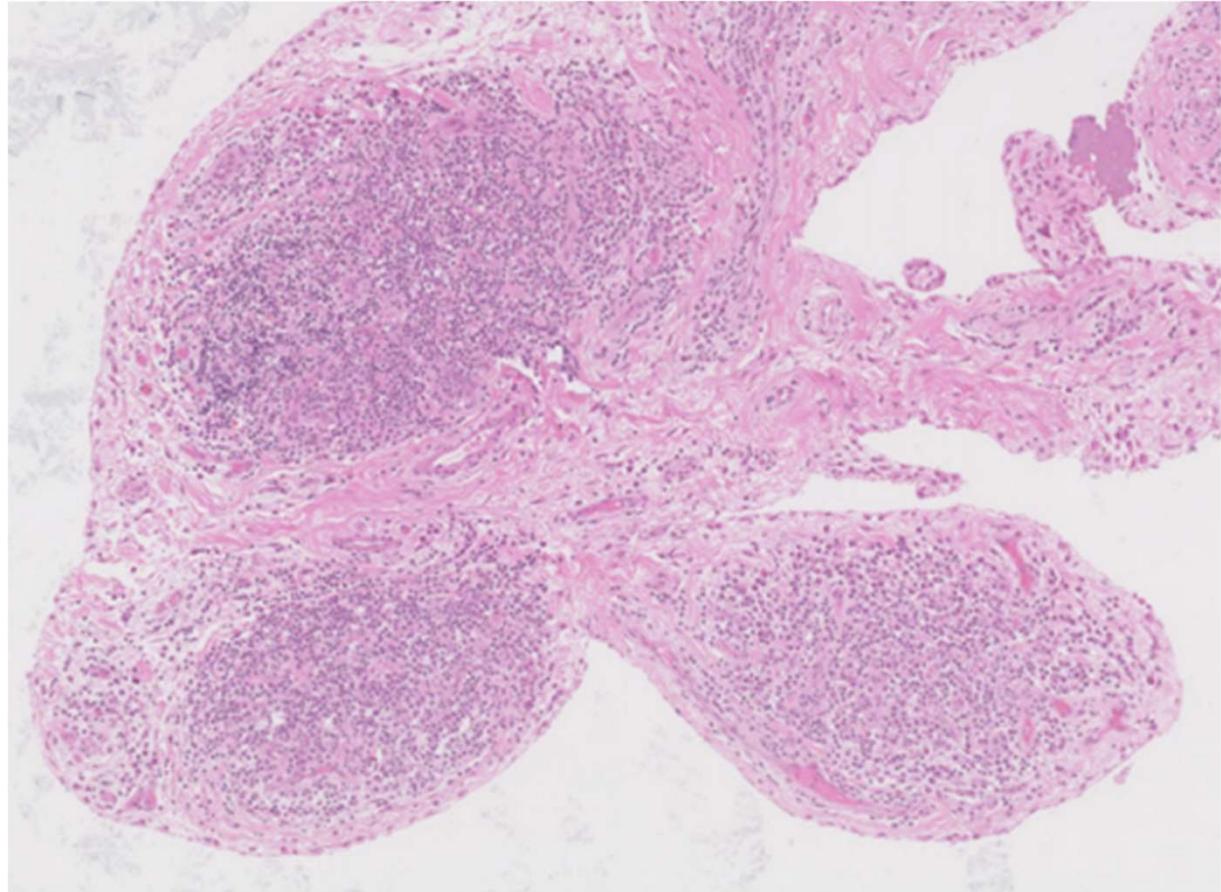
- **Imprévisibles** = impossible de définir l'ensemble des variables avec la précision requise pour une prévision
- **Incertitude des causes** ... étude des conséquences
- Comportement **chaotique**
 - **Dynamique** : le comportement du système à un moment donné influence son comportement futur
 - **Non linéaire** : obéissent à des relations exponentielles plutôt qu'additives

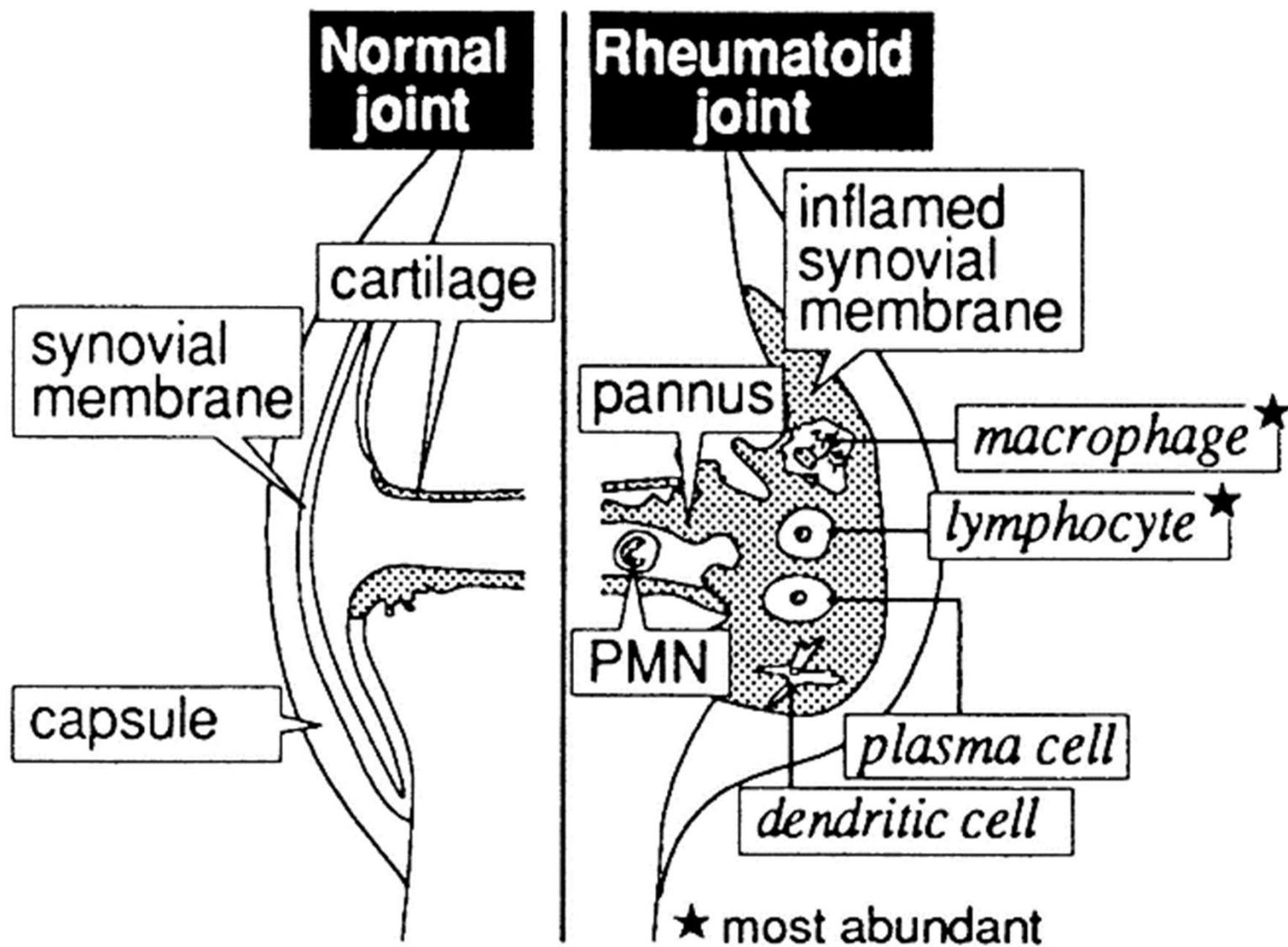


La synovite rhumatoïde ...

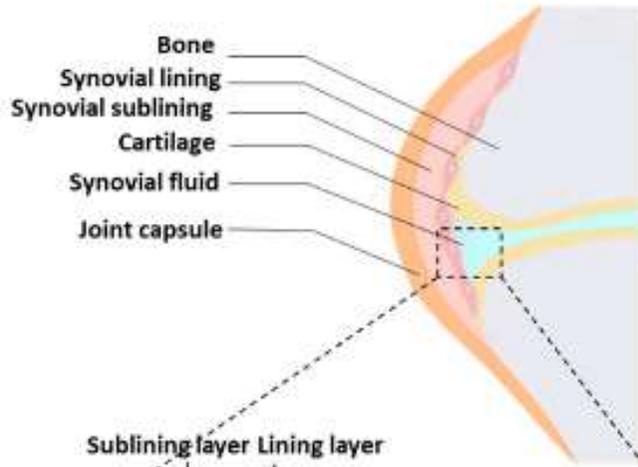
Considérer simultanément
tous ses composants :

- les agents
- les interactions
- l'environnement

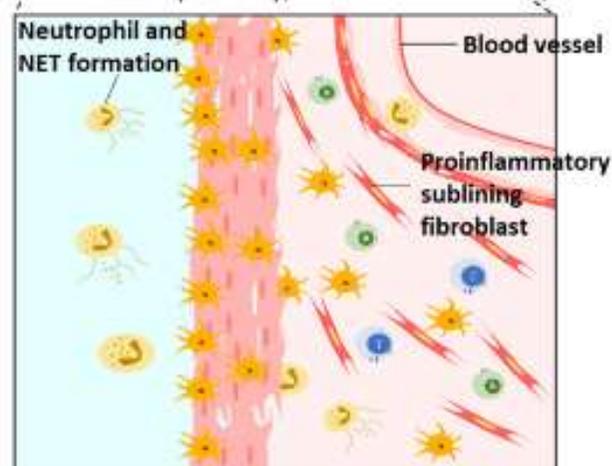
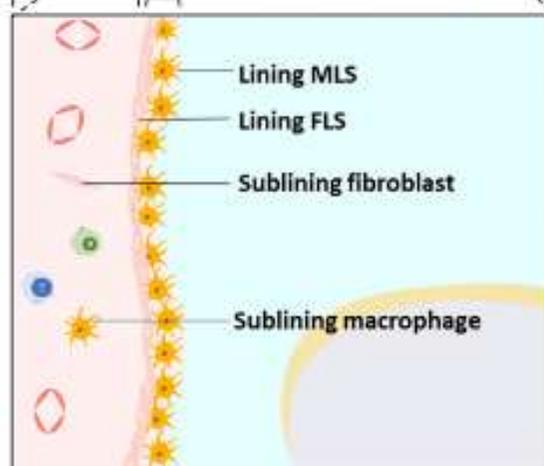
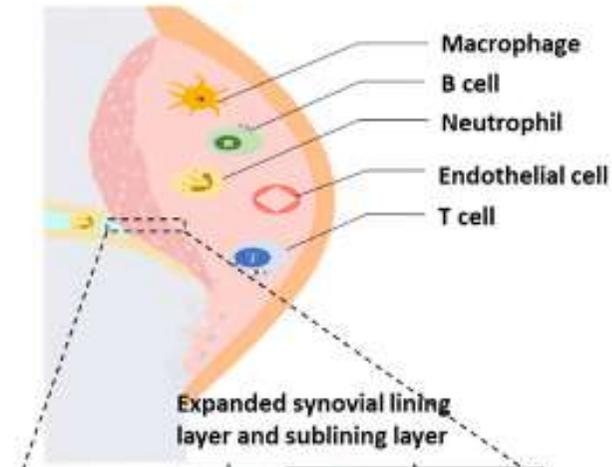




a. Healthy joint



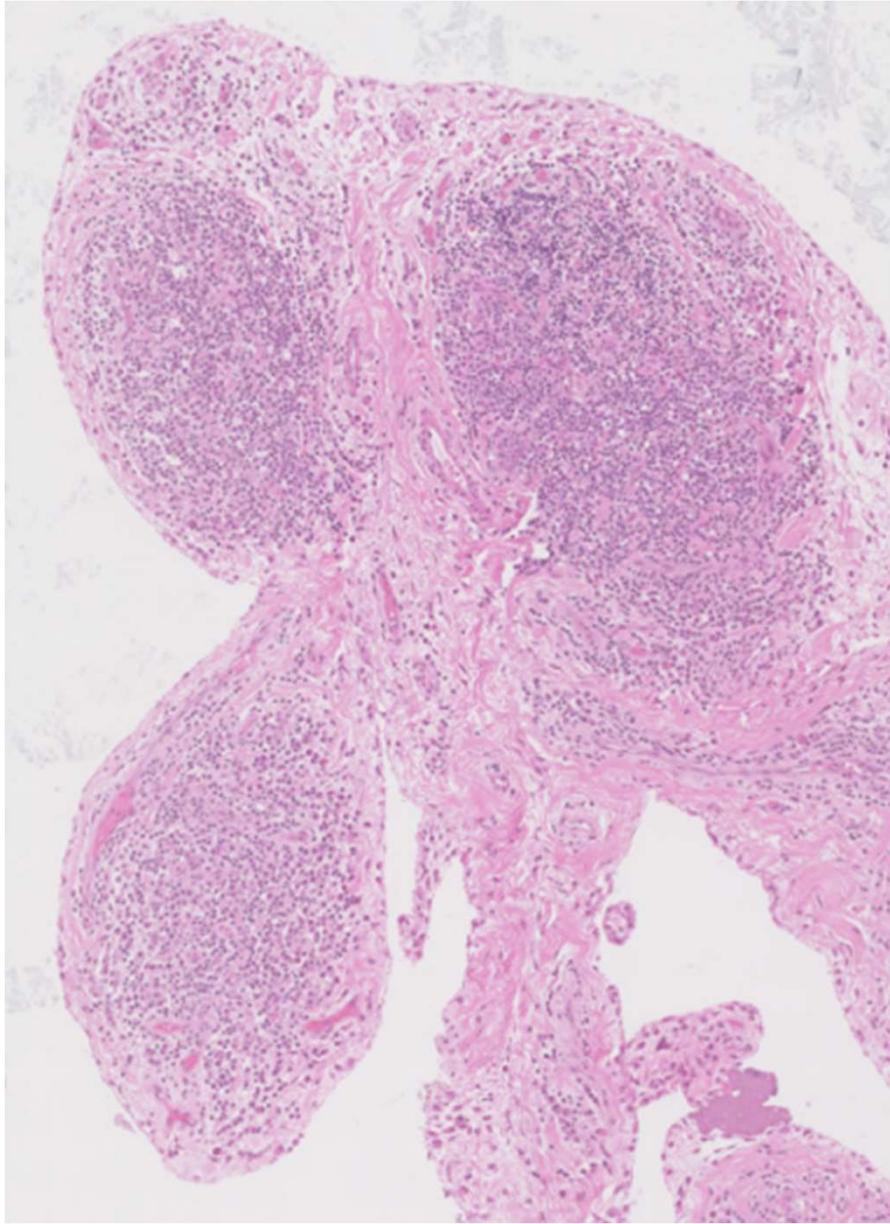
b. Rheumatoid arthritis joint



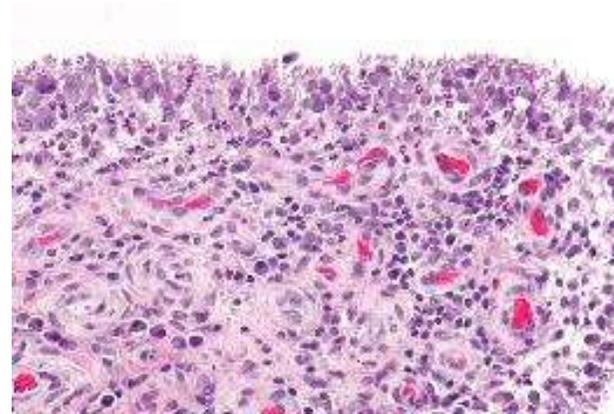
Comment s'en sortir ?

Techniques haut débit + intelligence artificielle

- Single cell analysis
- Imagerie par cytométrie de masse (IMC/Hypérion)
- Spatial transcriptomic
- Analyses de voisinage

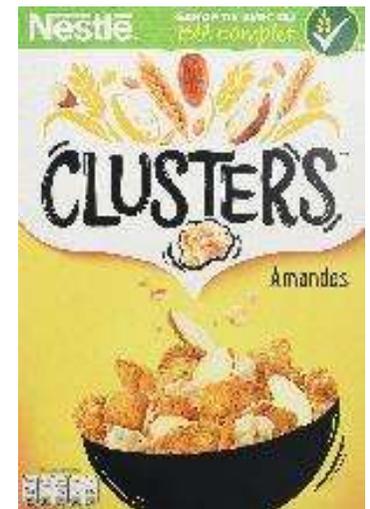
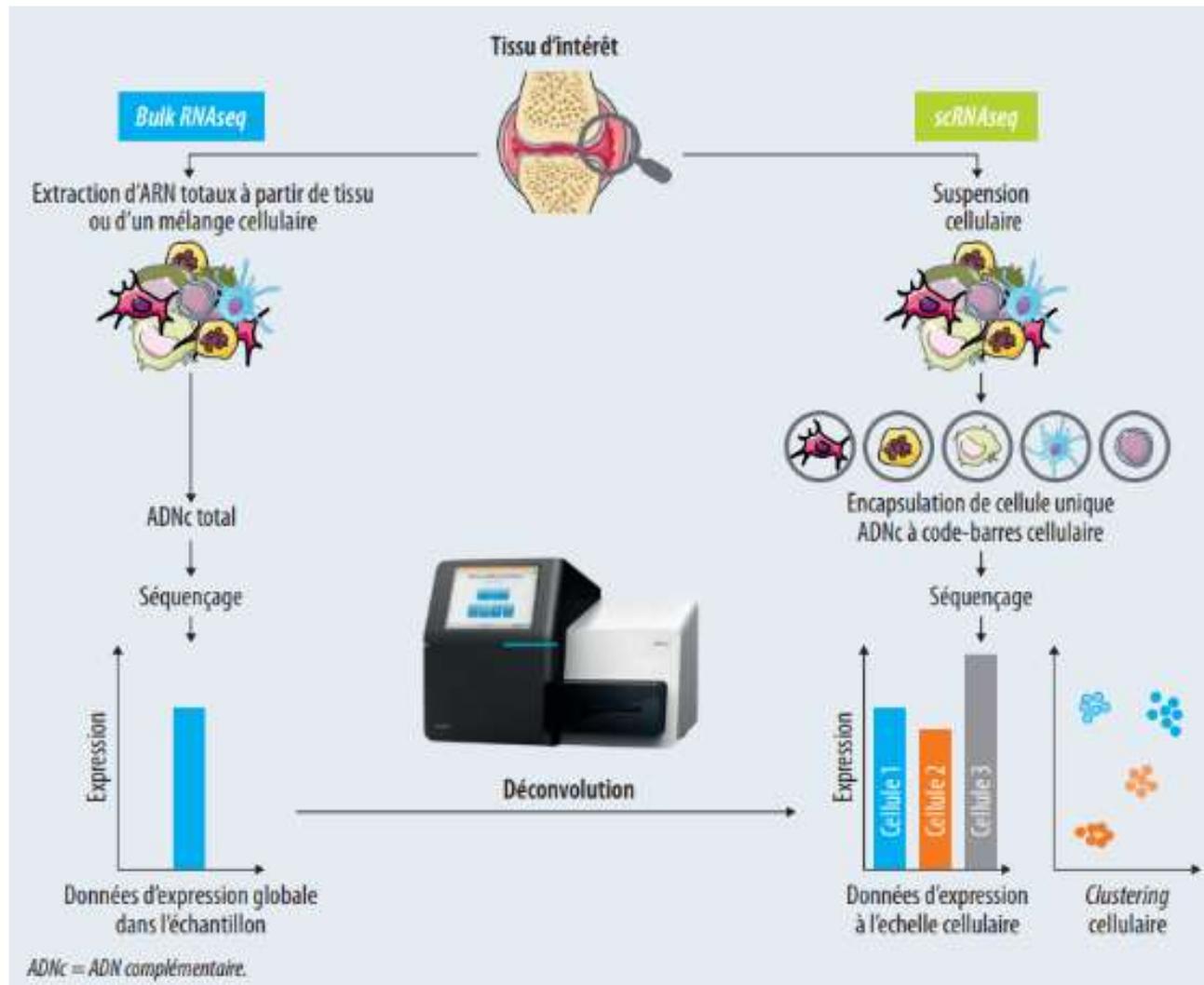


Comment faisait-on avant?

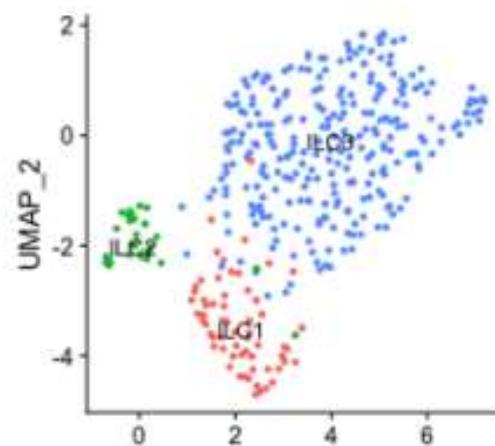
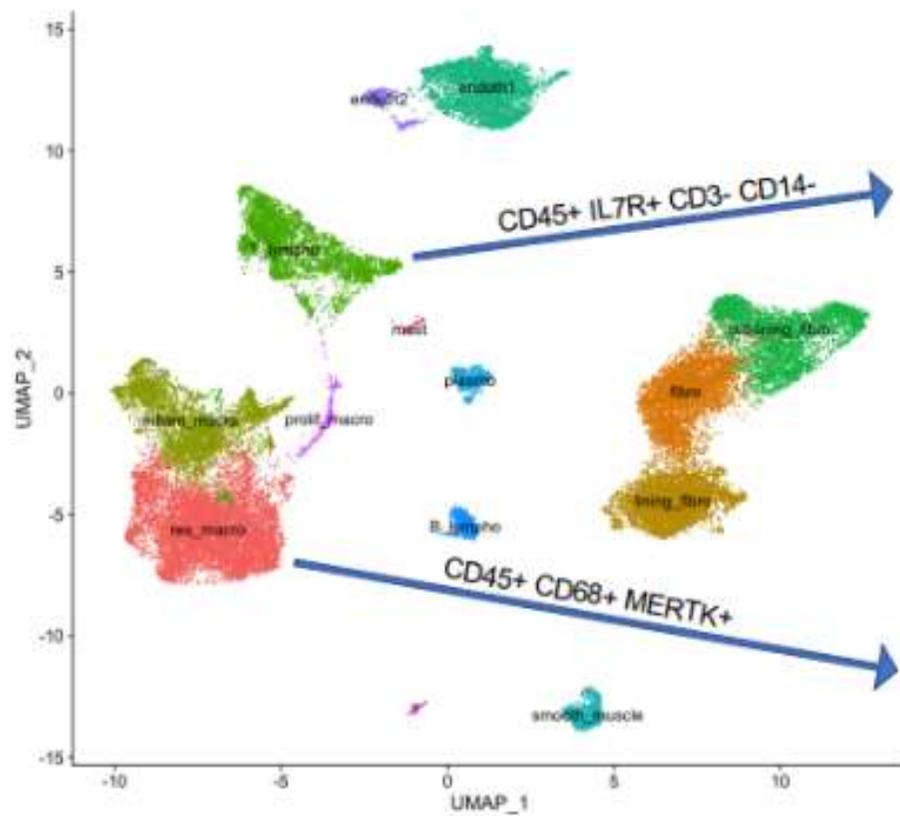


- Histologie H&E
- Immunohistochimie
- Immunofluorescence
- RT-PCR : extraction de l'ARN avec étude l'expression génique

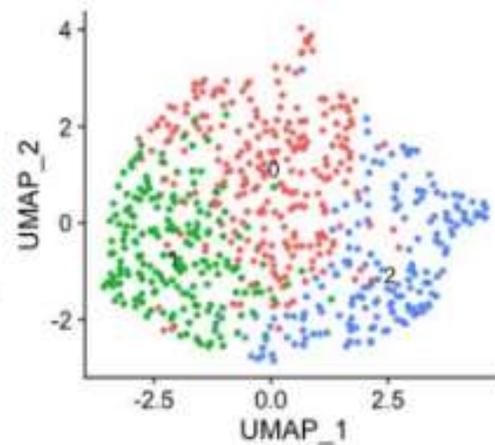
Analyse single cell RNA seq



Cluster « grappes »

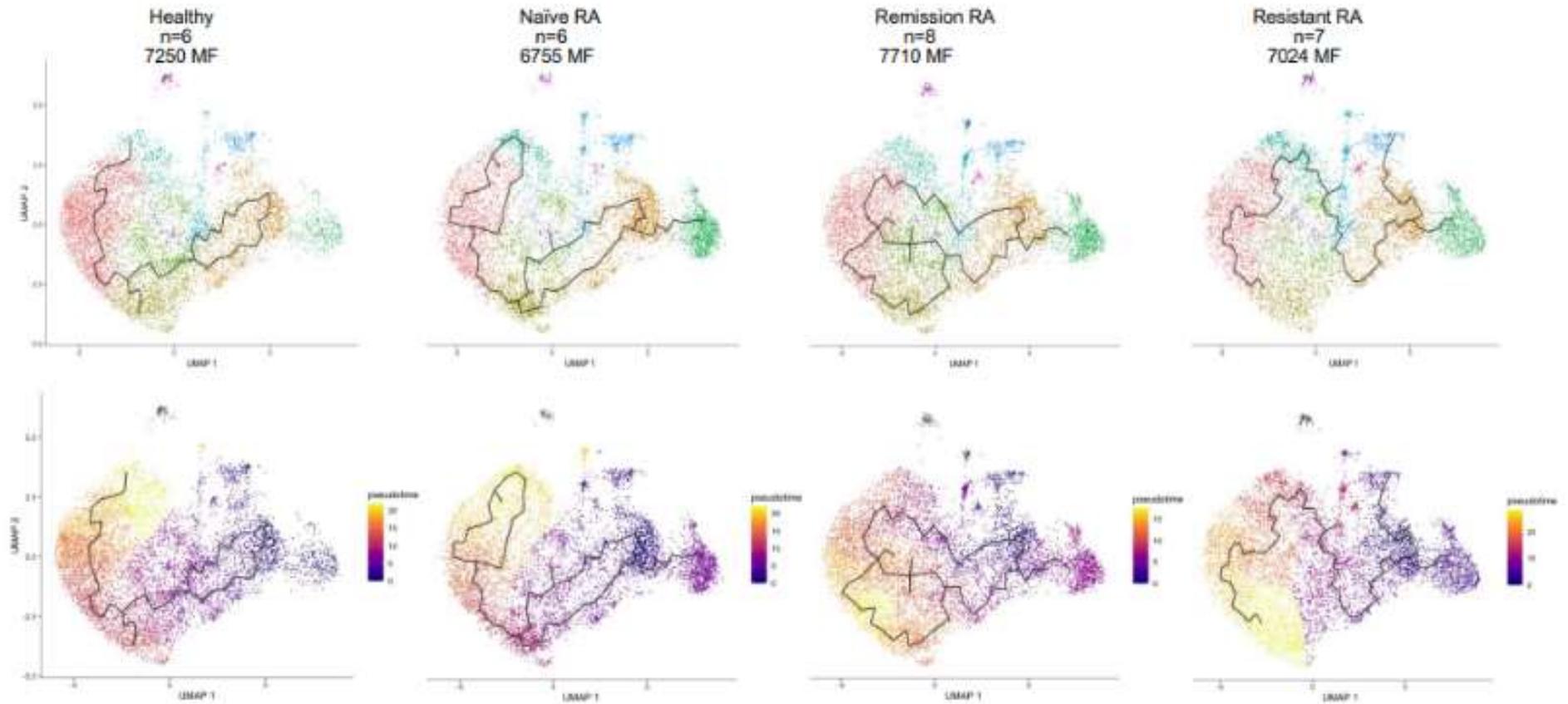


- NK/ILC1: CD161, EOMES, GZMA
- ILC2: CD161, THY1
- ILC3: CD161, CCR6, CCR7

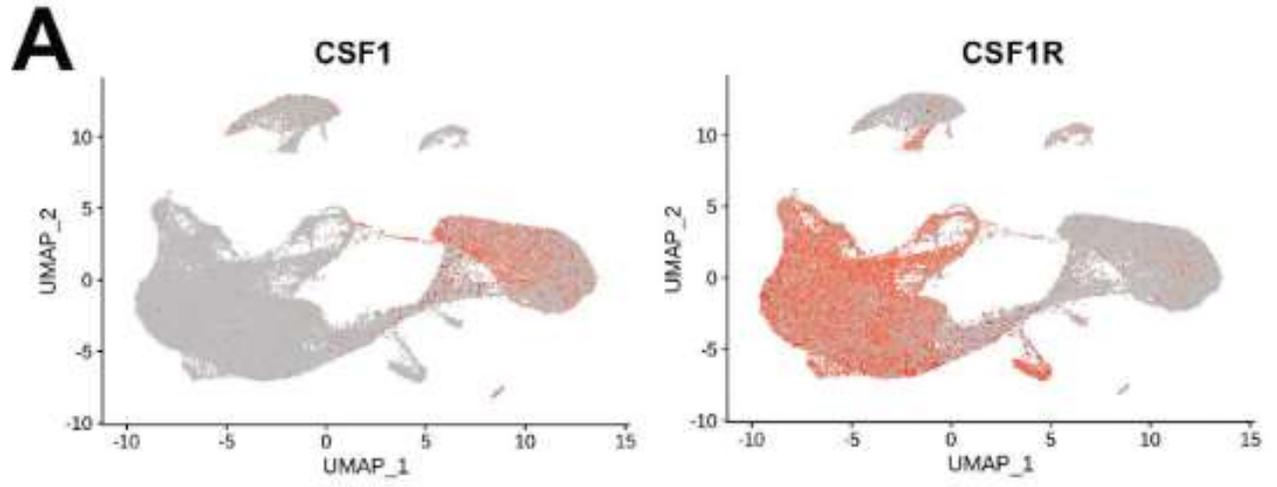
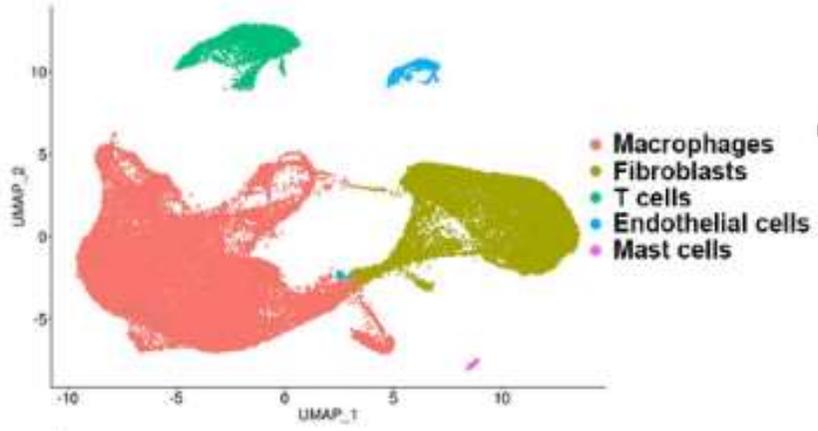
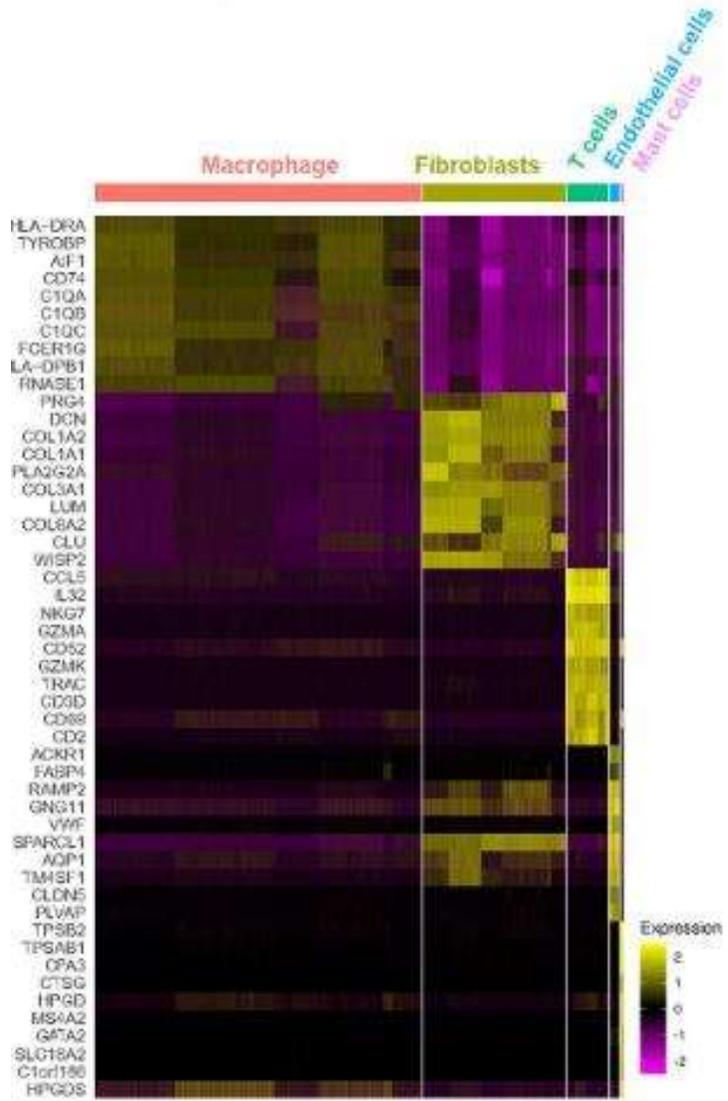
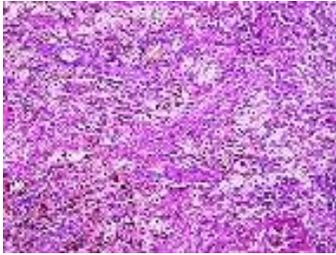


- ResM1: CD163, SPP1
- ResM2: CD163, TIMD4, TREM2
- ResM3: CD163, CSF1R, ICAM1

Modélisation de la plasticité cellulaire



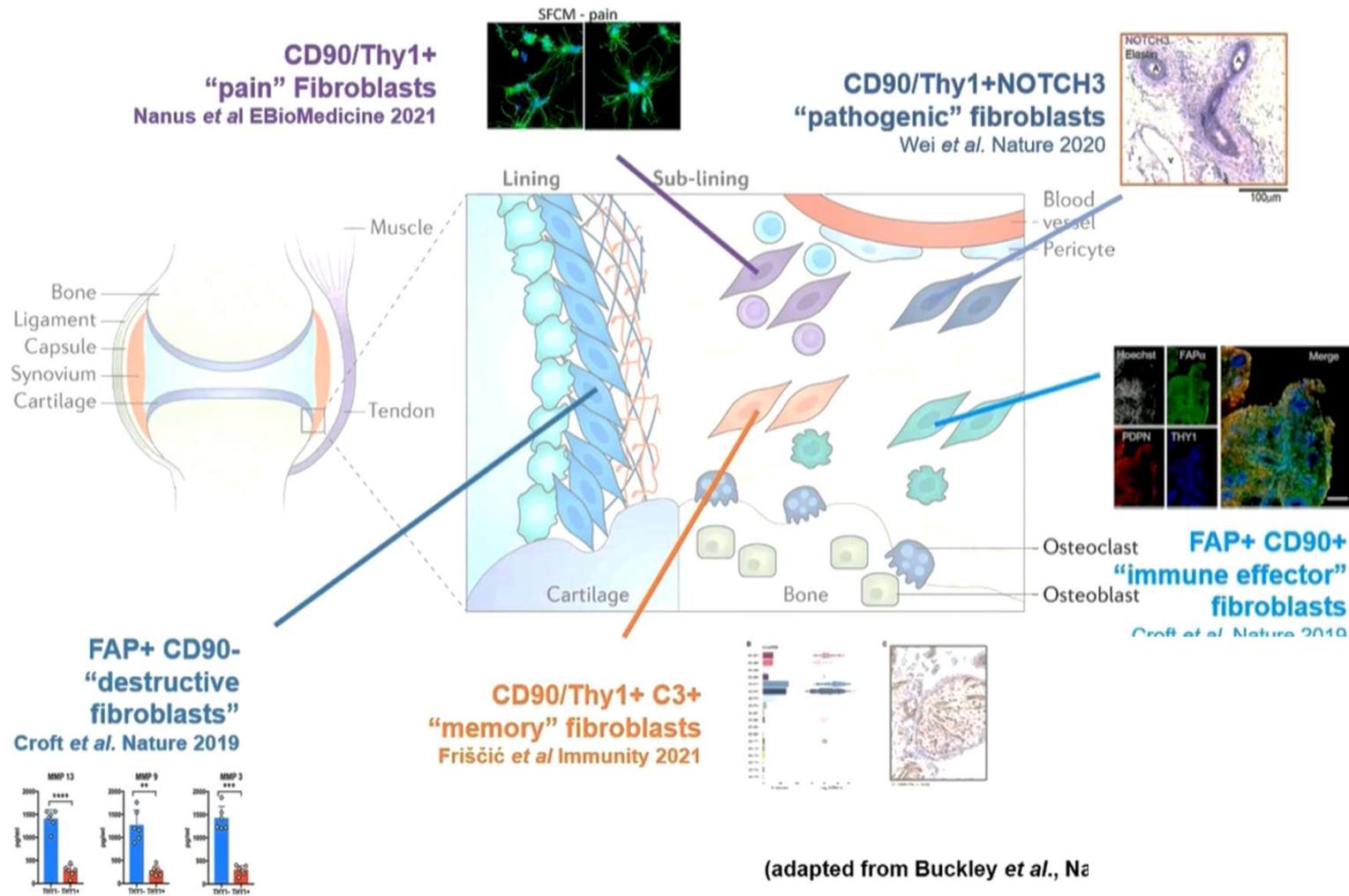
Analyse single cell d'une synovite villonodulaire



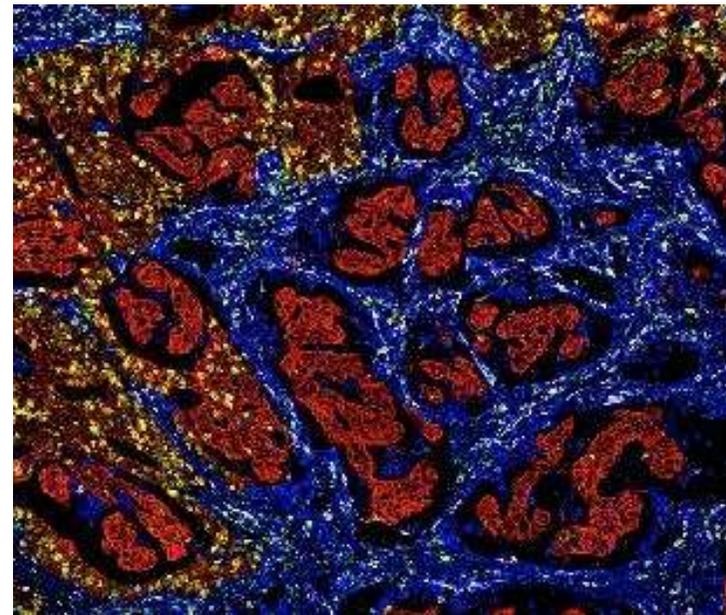
Quel intérêt?

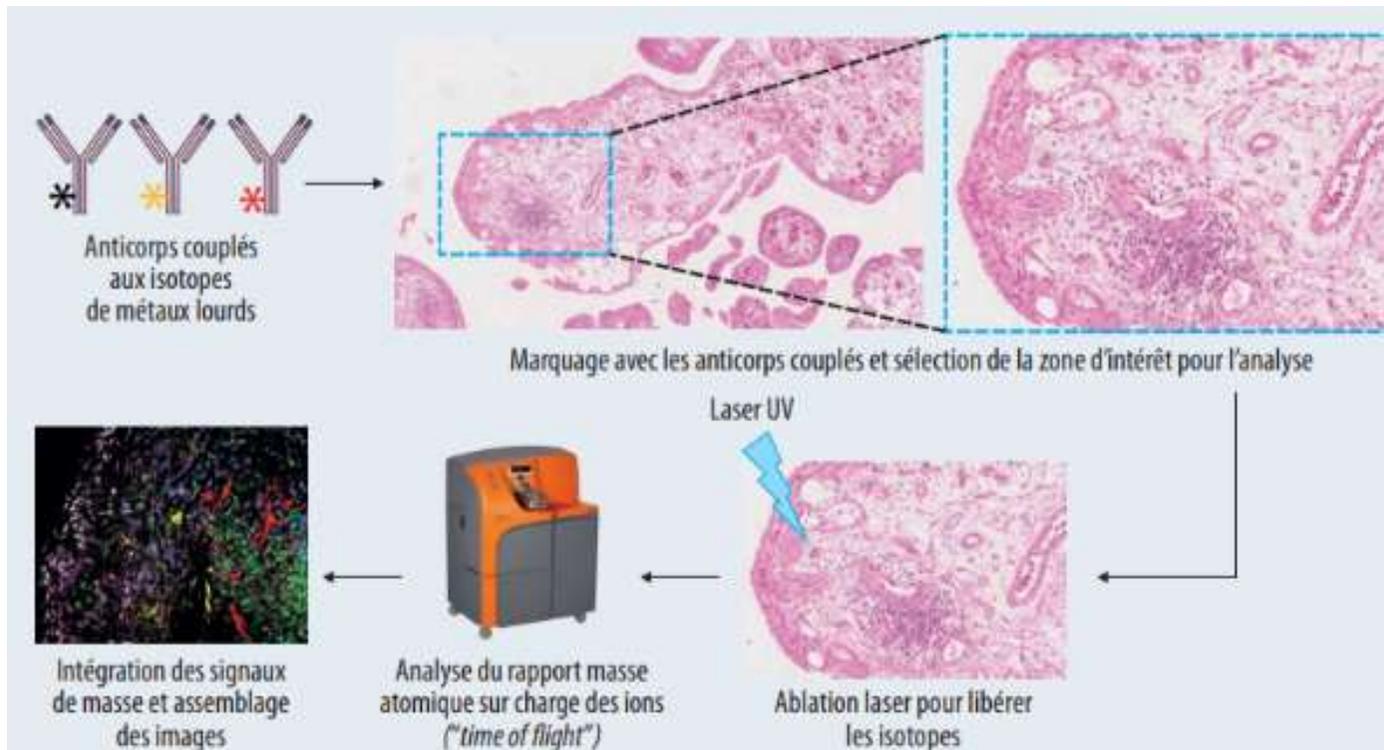
- **Avantage :**
 - Exhaustivité
 - Permet de générer des données originales de manière non supervisées
 - **Inconvénient :**
 - Coût : 2500 euros par patient
 - Pas de détection des expressions faibles
- ➡ « Anciennes techniques » toujours utiles pour la phase exploratoire

Fibroblast composition of the synovium: Function dictated by Location?



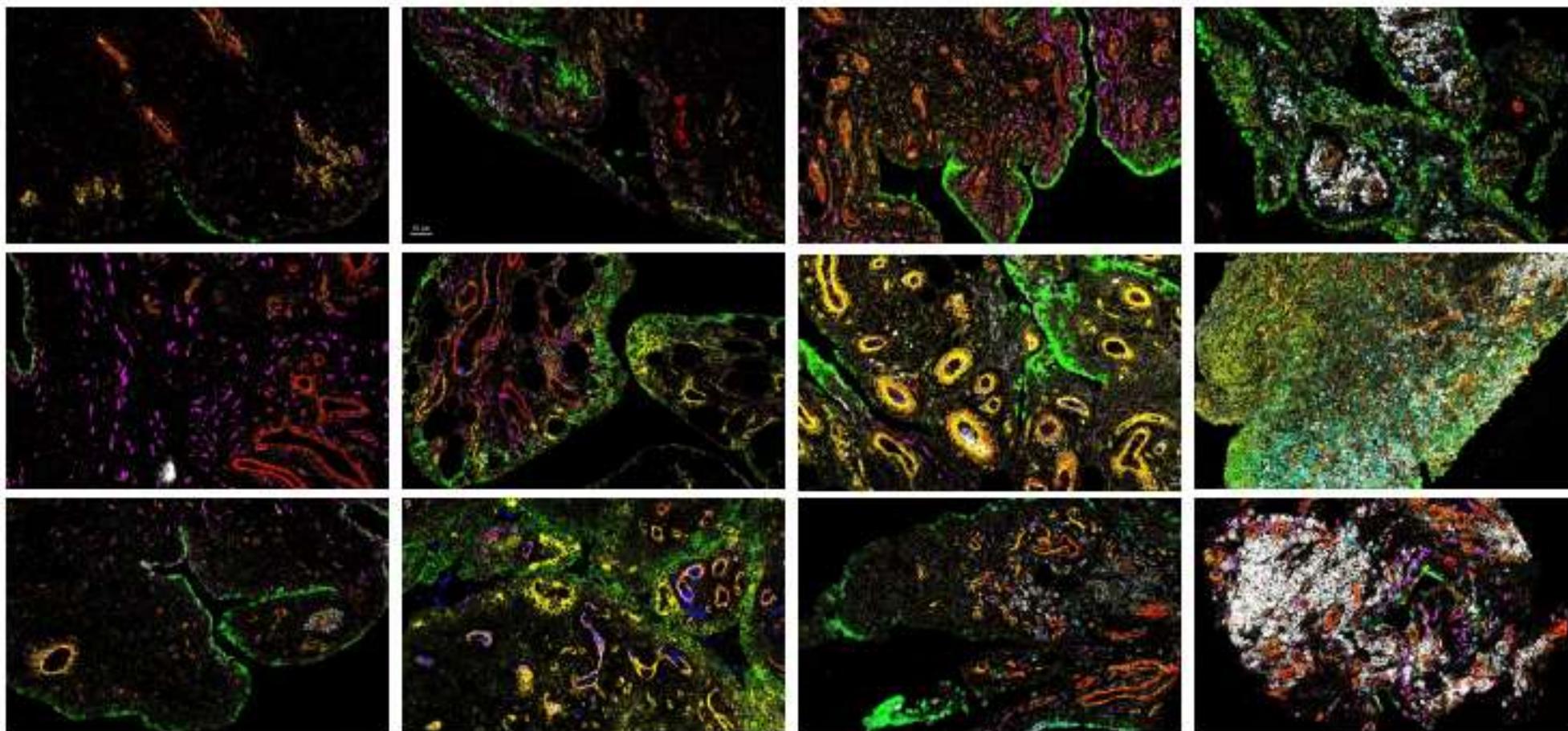
Imagerie par Cytométrie de masse (IMC)



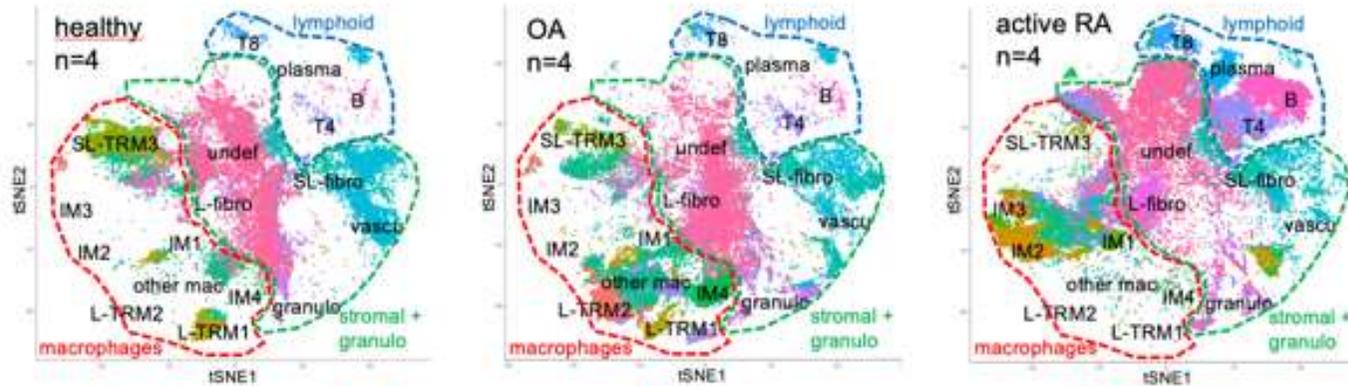


➡ 37 marquages de manière simultanée !!

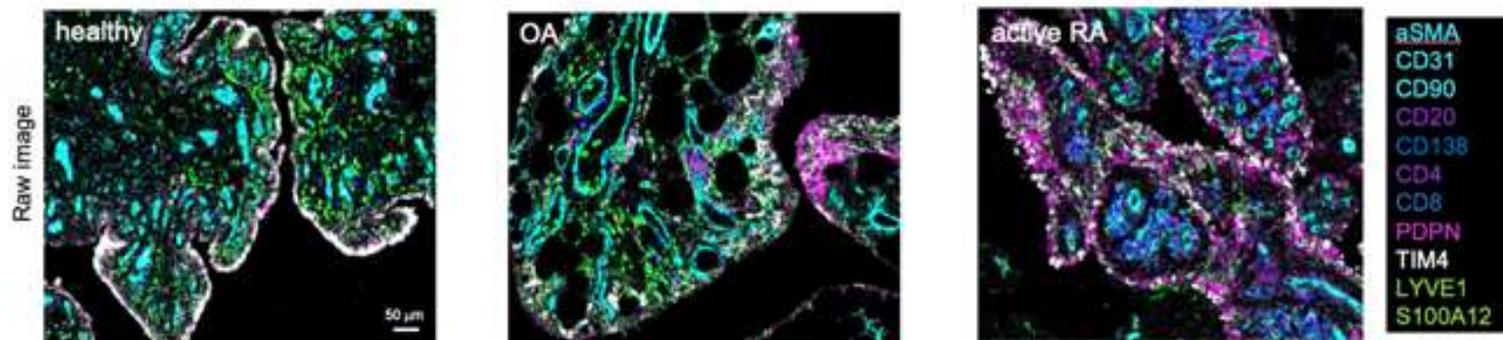
aSMA CD20/CD138/CD3 PDPN/CD90 TIM4 Lyve1 S100A12



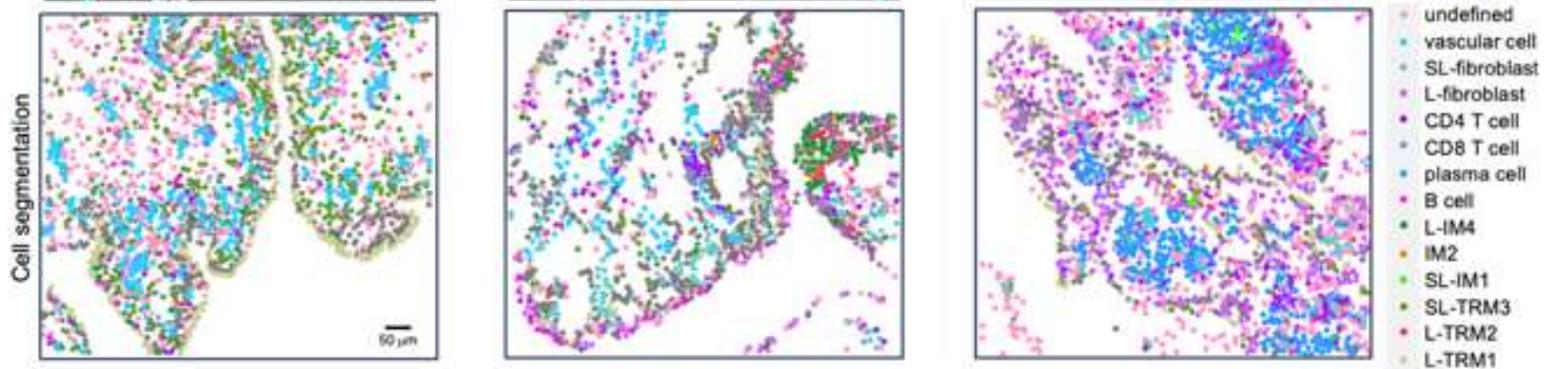
A



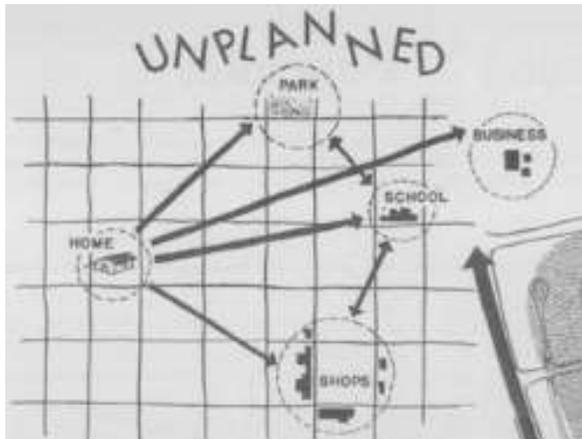
B

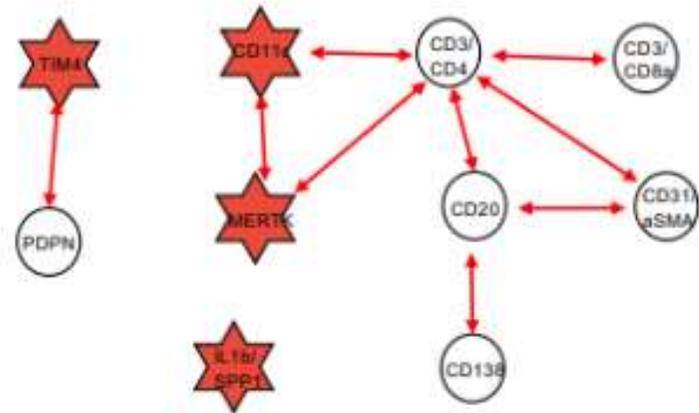
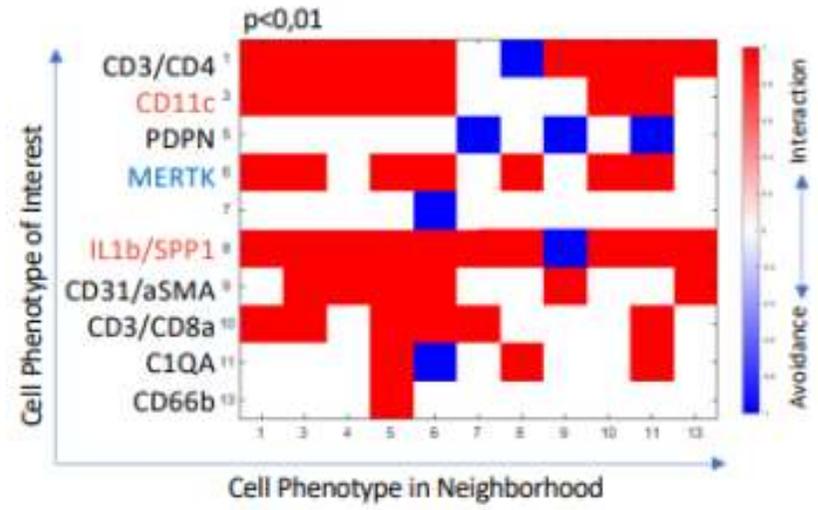
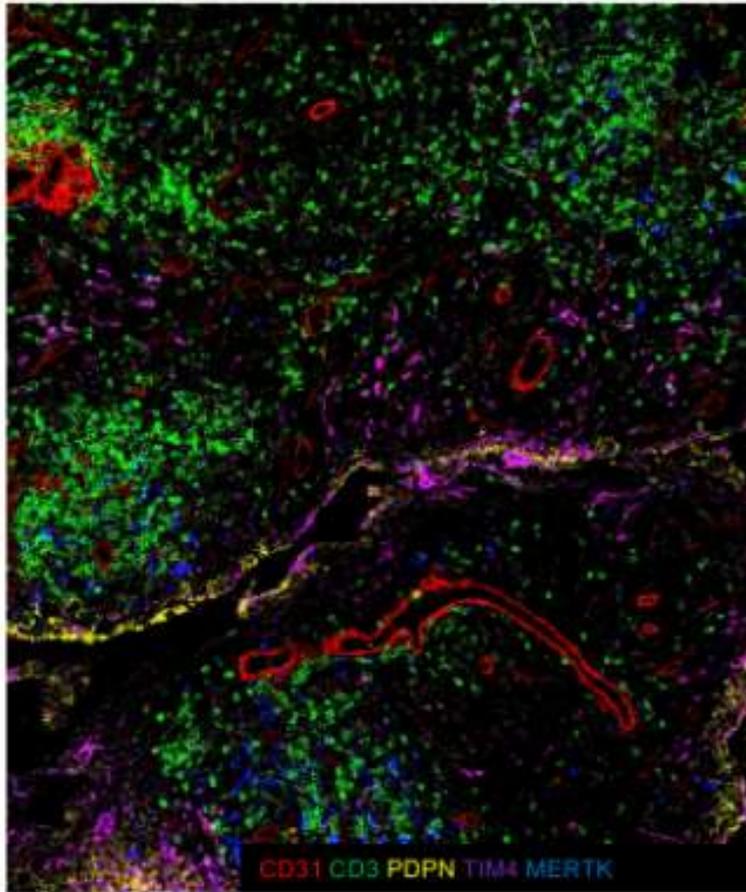


C



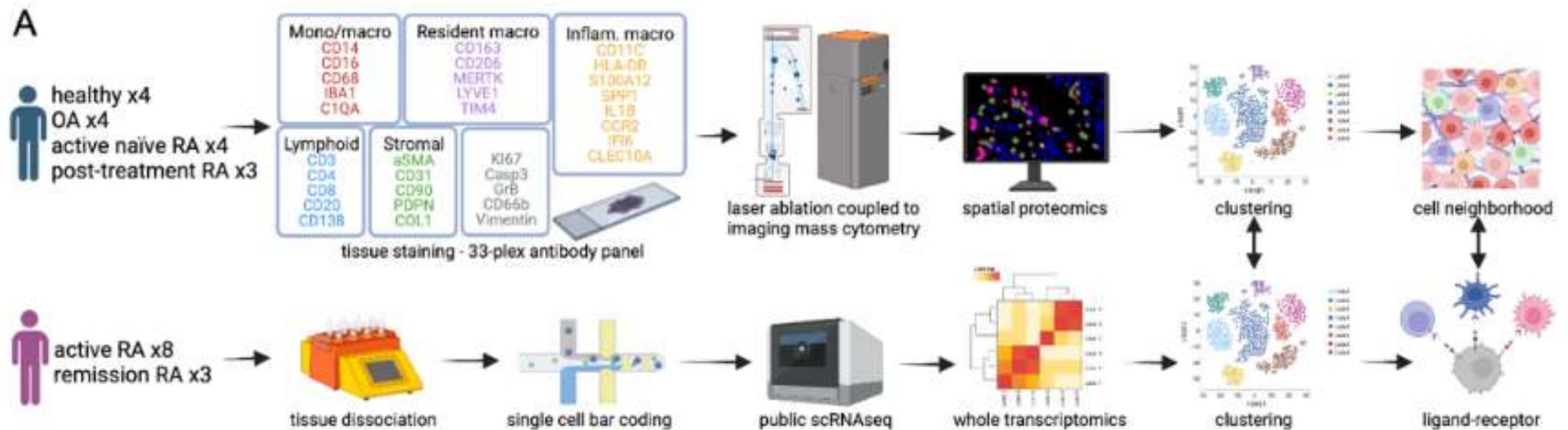
Analyse de voisinage



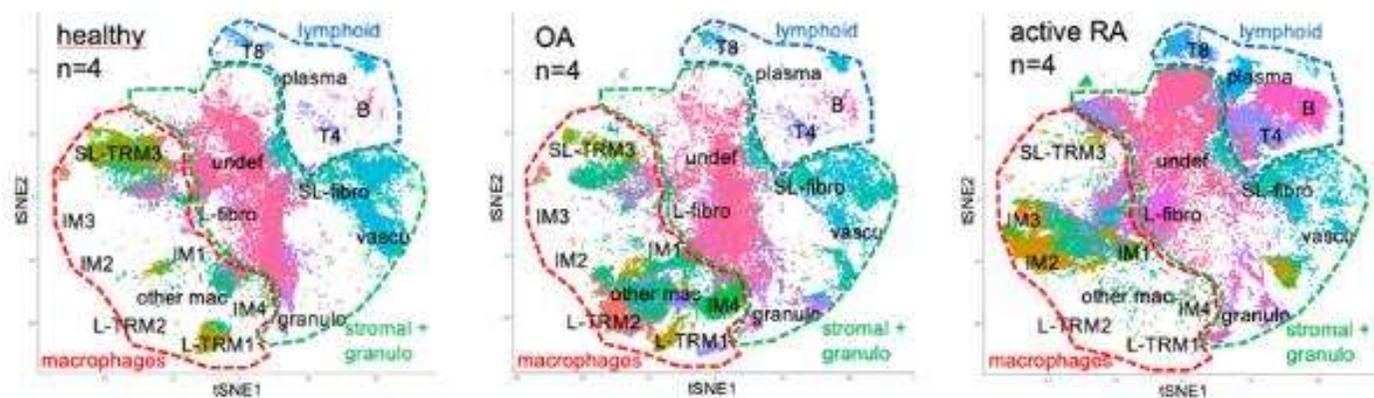


Title: Spatial mapping of rheumatoid arthritis synovial niches reveals specific macrophage networks associated with response to treatment

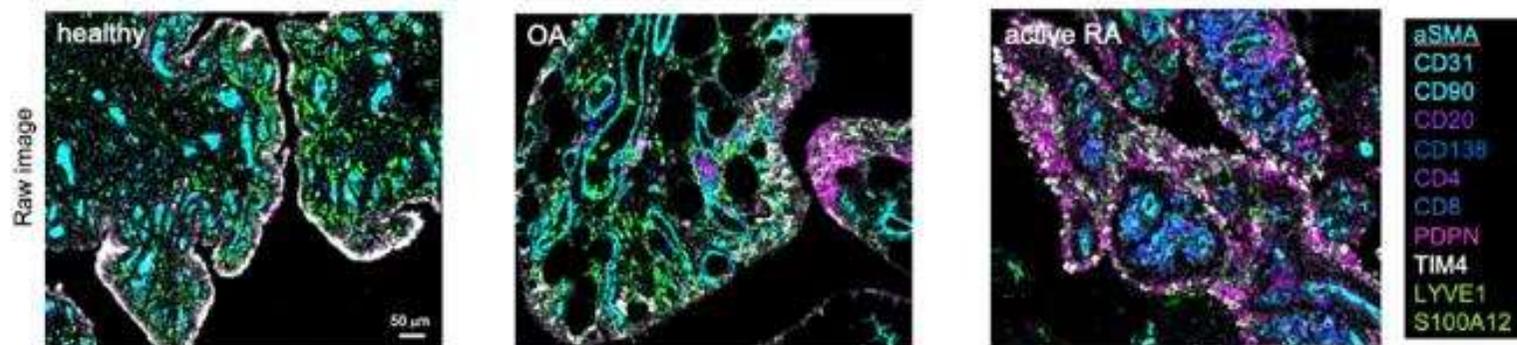
Authors : Julien De Lima¹, Marie-Astrid Boutet^{1,2}, Laure-Agnès Chépeaux³, Yaël Glasson², Anne-Sophie Dumé³, Olivier Bortolotti⁴, Adrien Le Pluart¹, Alessandra Nerviani², Liliane Fossati², Henri-Alexandre Michaud³, Jérôme Guicheux¹, Benoit Le Goff², Costantino Pitzalis^{2,5}, Gabriel Courties¹, Florence Apparailly^{4,6}, Frederic Blanchard^{1*}



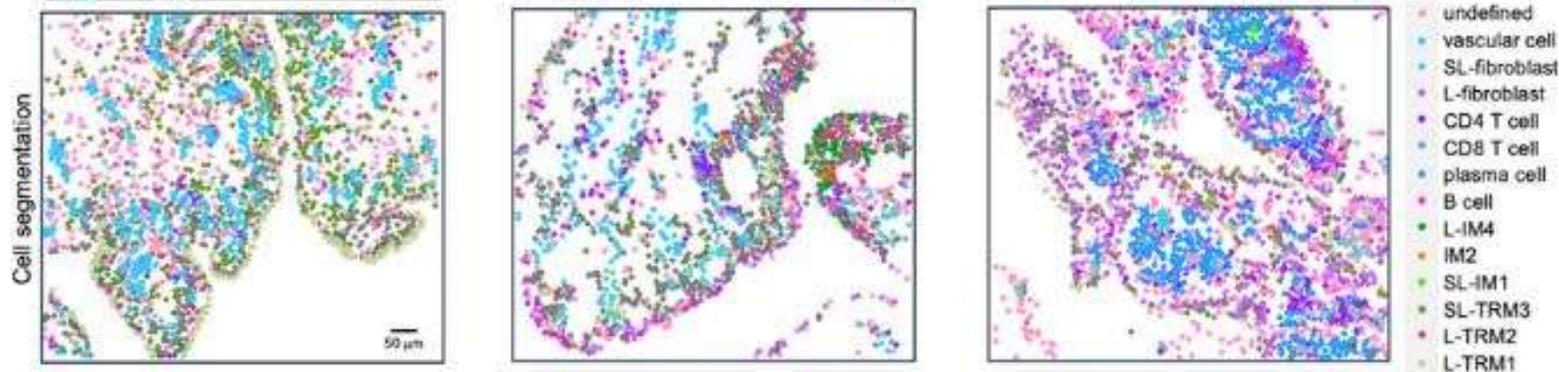
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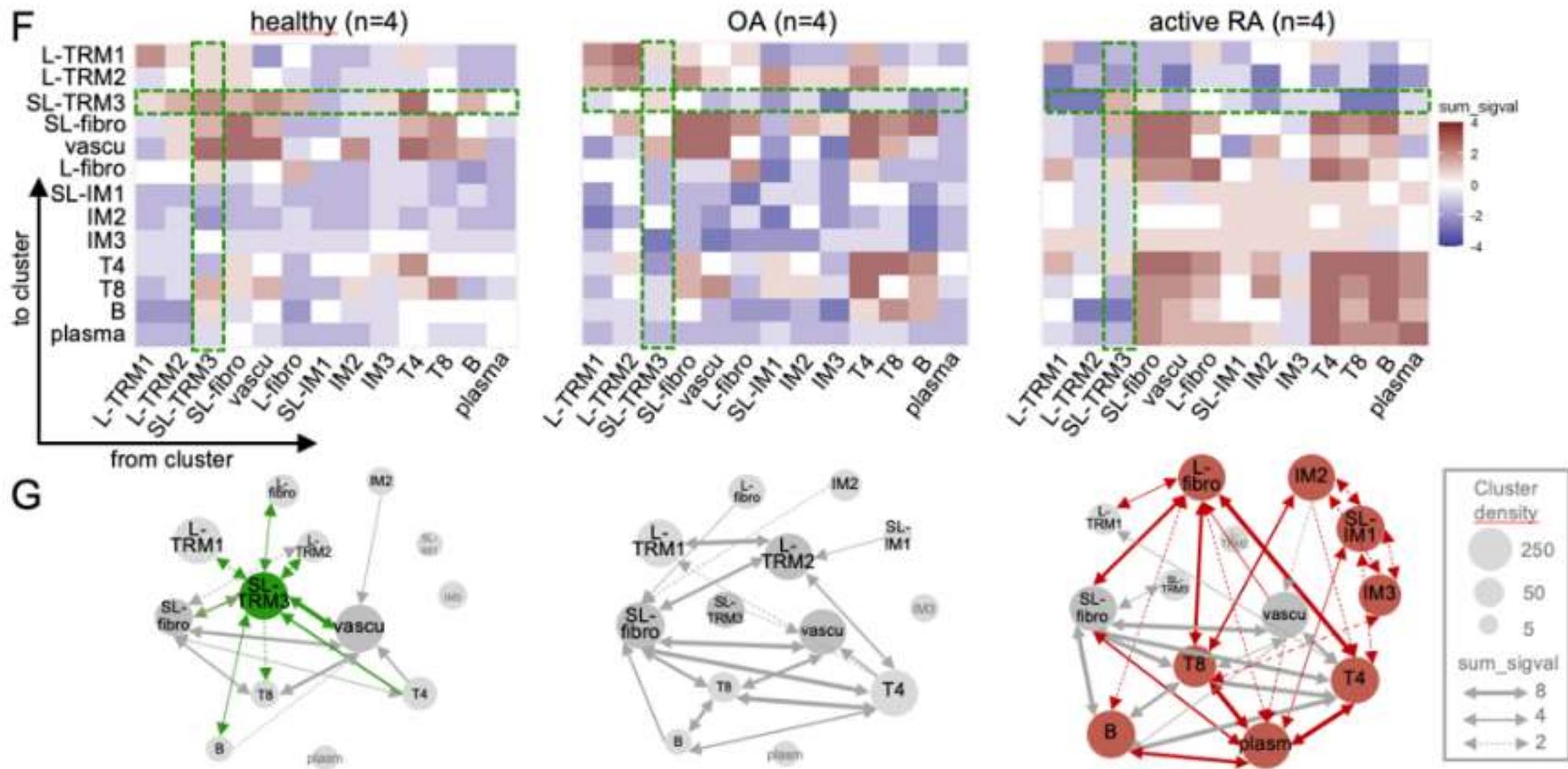


B

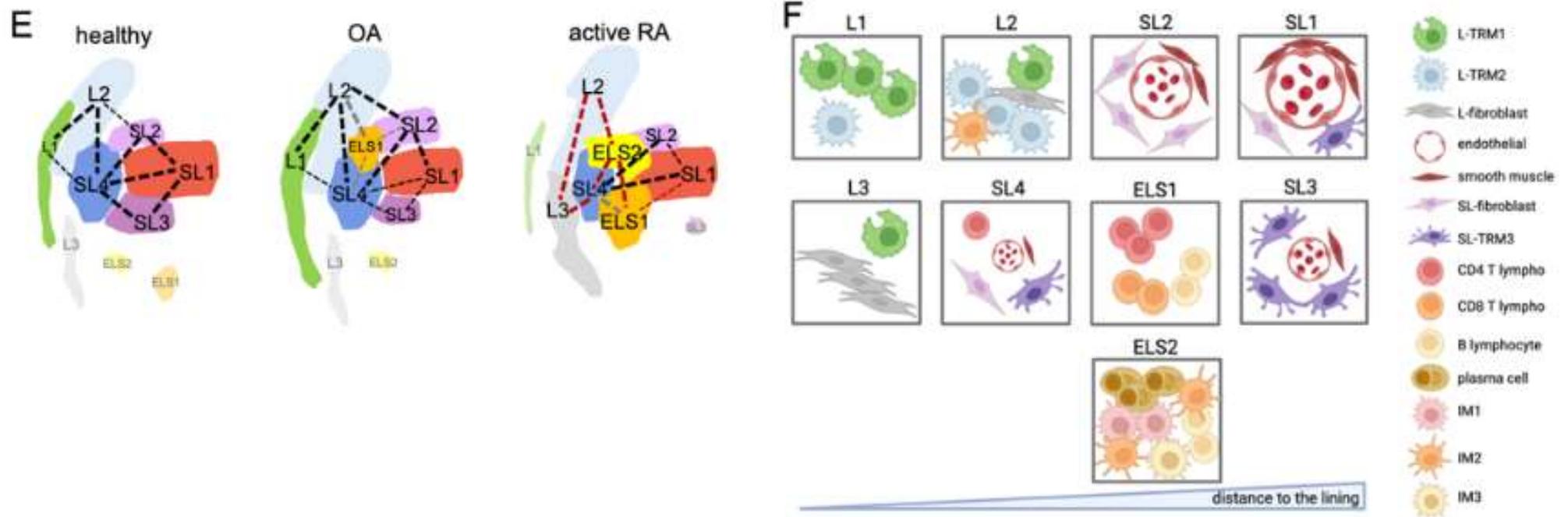


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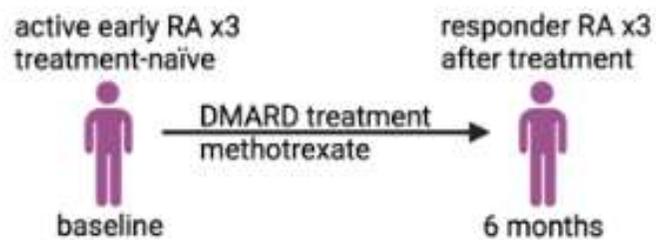




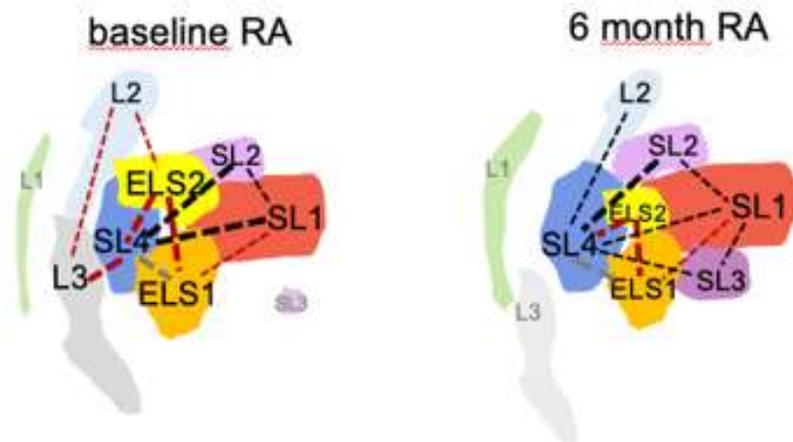
Identification de niches



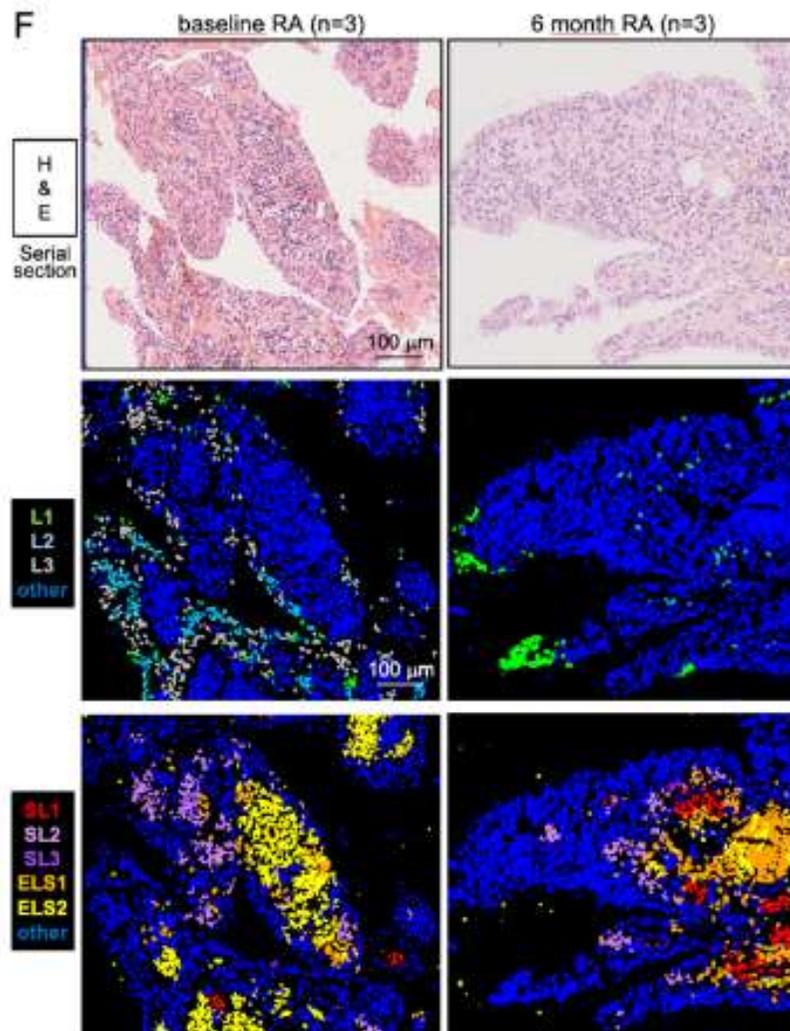
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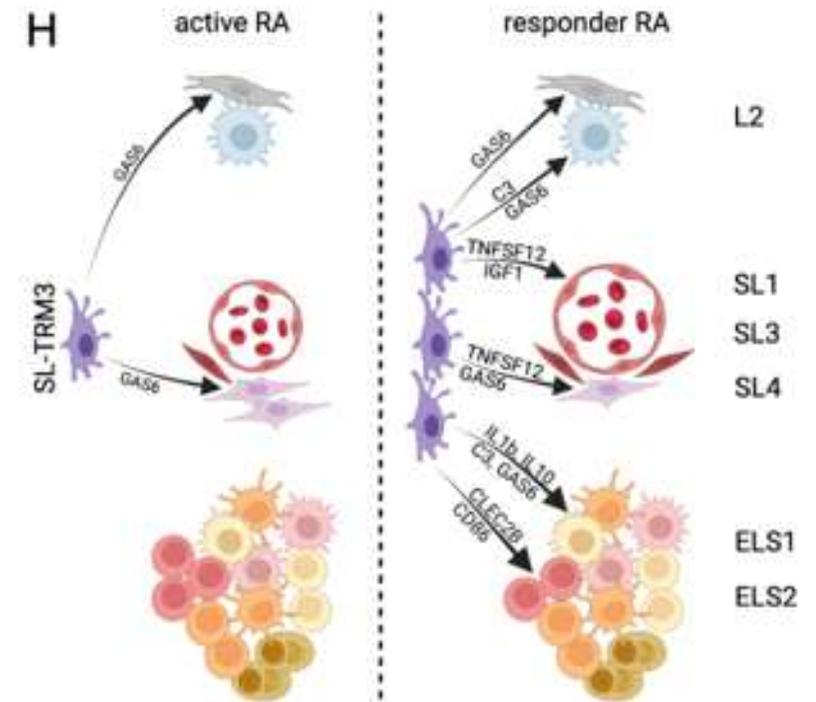
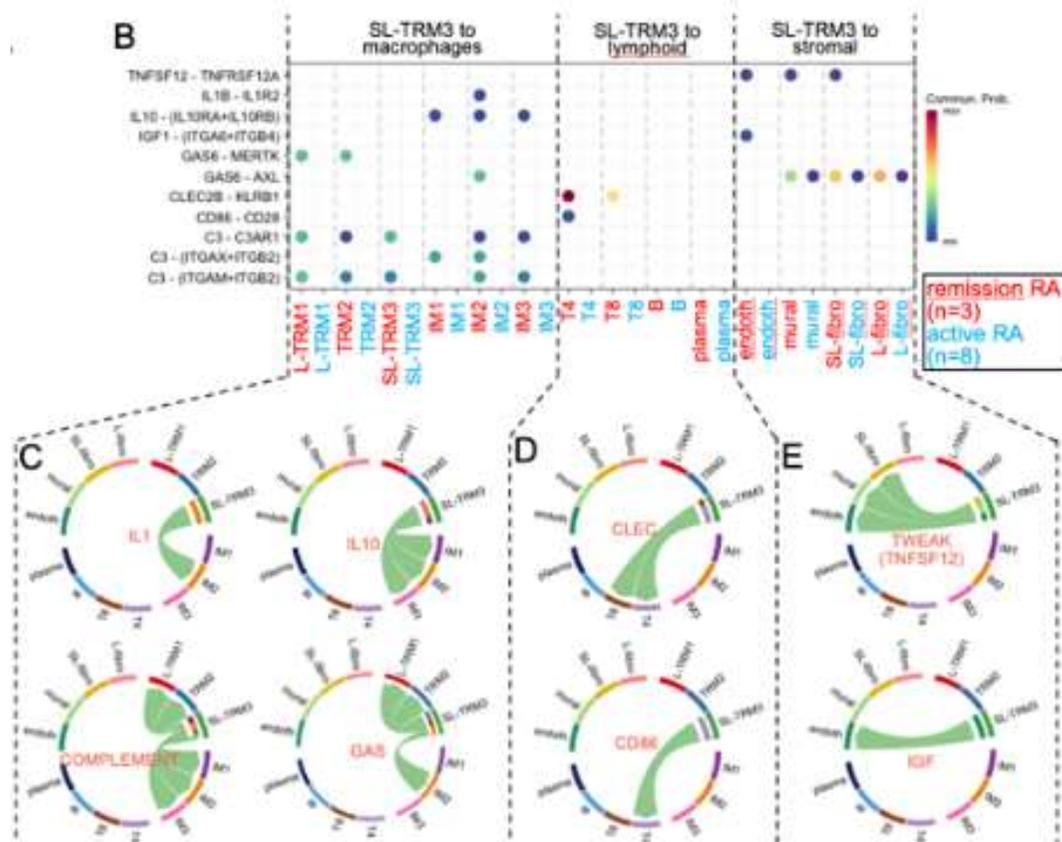
G



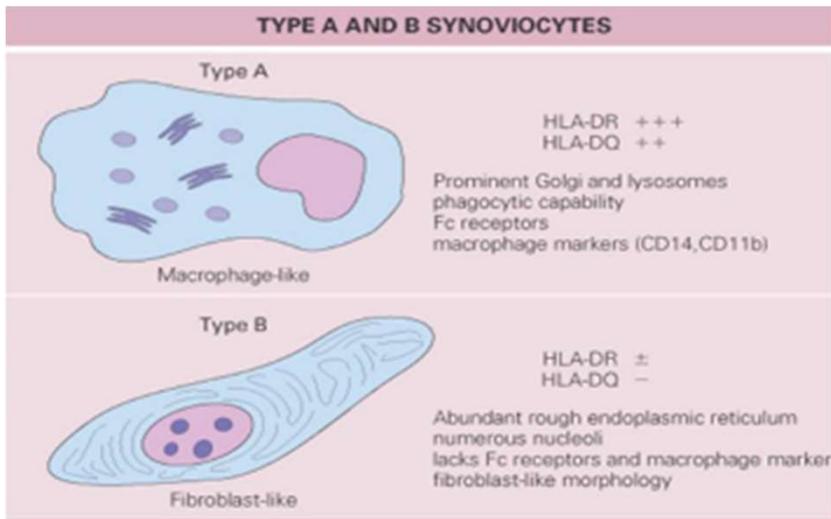
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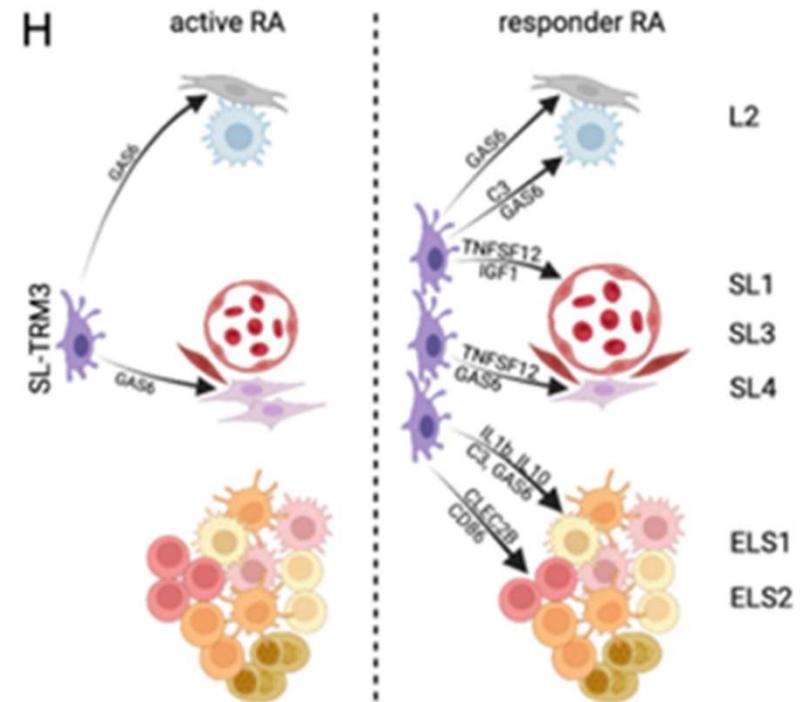
Modélisation des mécanismes d'interaction



Avant



Maintenant



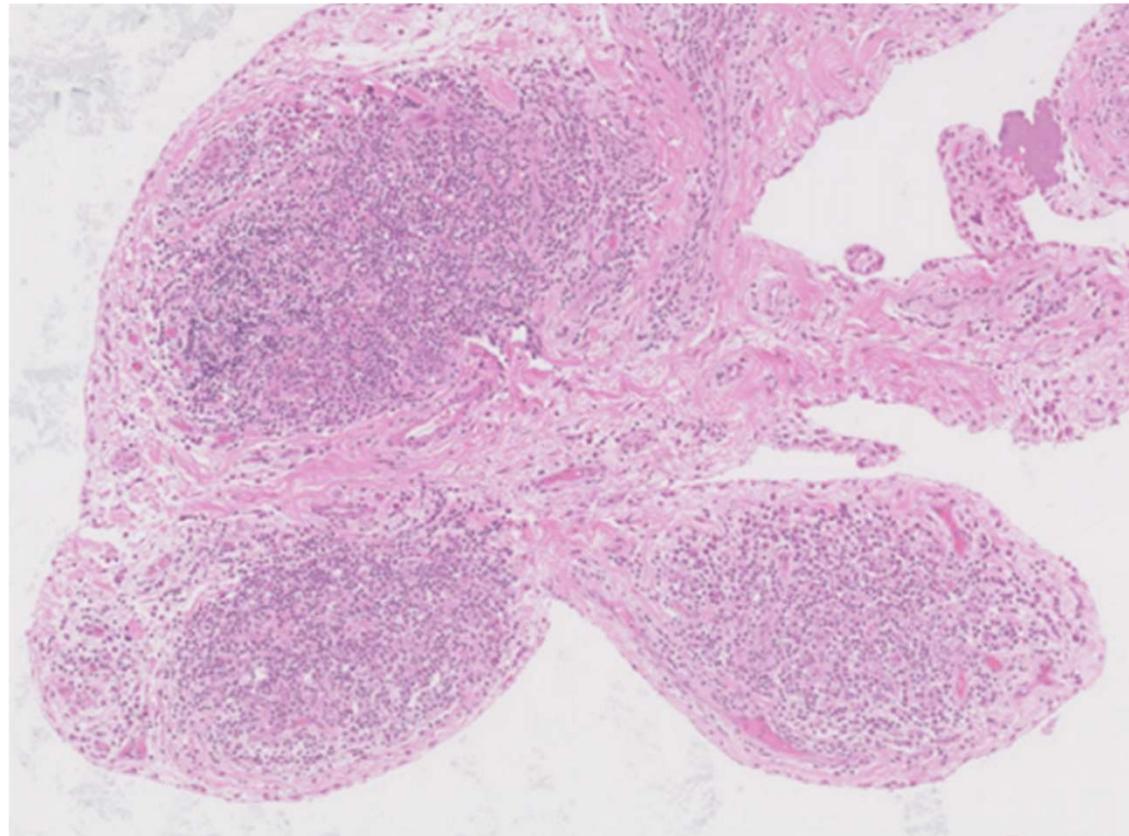
Demain



Analyse transcriptomique spatiale

➡ Combine l'histologie, au séquençage RNA single cell

Est-ce que l'on va finalement arriver à comprendre quelque chose ... ?



Conclusion

- Systèmes biologiques = Systèmes Complexes Adaptatifs
- Toute tentative de synthèse des interactions entre les cellules est forcément réductrice et fausse ... mais reste utile
- Nouvelles technologies à connaître + utilisation de l'IA

