



MASTER 1 UE Biologie Systémique

Unmet needs in IBD

9 décembre 2021

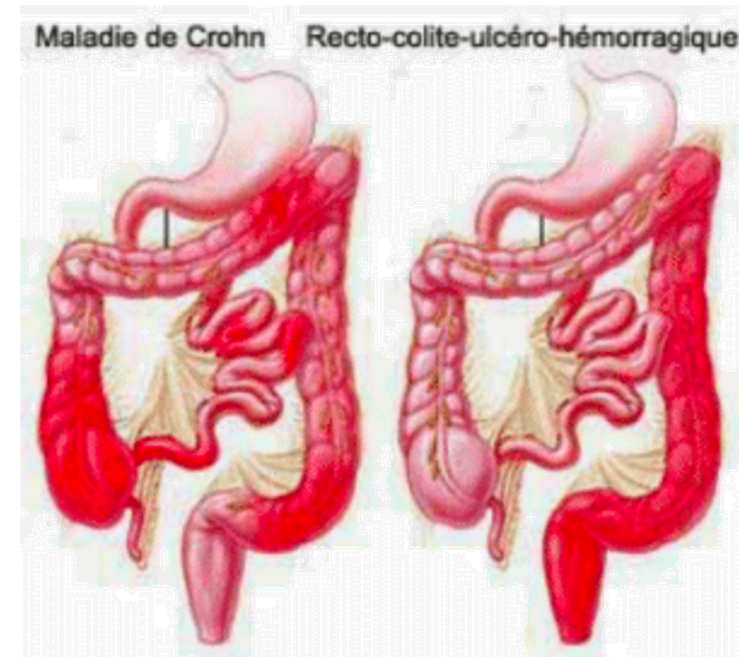
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Inserm UMR1235 – Université de Nantes

Définition des MICI

- Pathologies inflammatoires chroniques du tube digestif
- 3 types :
 - RCH : rectum +/- colon en amont
 - MC : peut atteindre tout le tube digestif avec une prédilection pour la région iléo-cæcale
 - MICI inclassée (jusqu'à 15 %)



Epidémiologie

- Initialement décrites en Europe du Nord et aux États-Unis, désormais présentes dans le monde entier
- Incidence en augmentation depuis une trentaine d'années
- Gradient Nord-Sud et Ouest-Est
- En France, données du SNIIRAM (Système National d'Information Interrégimes d'Assurance Maladie) en 2016 :
 - > 200 000 personnes atteintes d'une MICI
 - 120 000 MC
 - 80 000 RCH

Signes cliniques évocateurs d'une MICI

- Diarrhée chronique +/- glairosanglante
 - Son absence n'exclut pas le diagnostic
- Douleurs abdominales
- AEG
- Aftose buccale
- Lésions proctologiques inhabituelles : fissures multiples et/ou de siège atypique (antérieures, latérales), abcès de la marge anale récidivant, fistules complexes et/ou récidivantes
- Chez l'enfant : retard staturo-pondéral

Signes biologiques évocateurs d'une MICI

- Signes biologiques de malabsorption
 - Carence martiale
 - Carence vitaminique : folates, B12
 - Hypoalbuminémie
- Syndrome inflammatoire biologique

Manifestations extra-intestinales (1)

- Peuvent parfois précéder de plusieurs mois l'apparition des manifestations intestinales :
 - Rhumatologiques +++ (arthropathies périphériques et rhumatisme axial)
 - Cutanéomuqueuses (psoriasis, érythème noueux, pyoderma gangrenosum)
 - Ophtalmologiques (uvéite, sclérite, épisclérite)
 - Hépatobiliaires (cholangite sclérosante primitive, hépatite auto-immune, cholangite biliaire primitive)

Manifestations extra-intestinales (2)

- Evolution :
 - parallèle à la maladie digestive
 - pour leur propre compte de façon non corrélée à l'activité de la MICI (spondylarthropathie axiale, uvéite, pyoderma gangrenosum et CSP)
- Plus d'un tiers des patients atteints de MICI souffrent de MEI, de façon plus fréquente en cas de MC que de RCH à l'exception de la CSP

Diagnostic positif d'une MICI

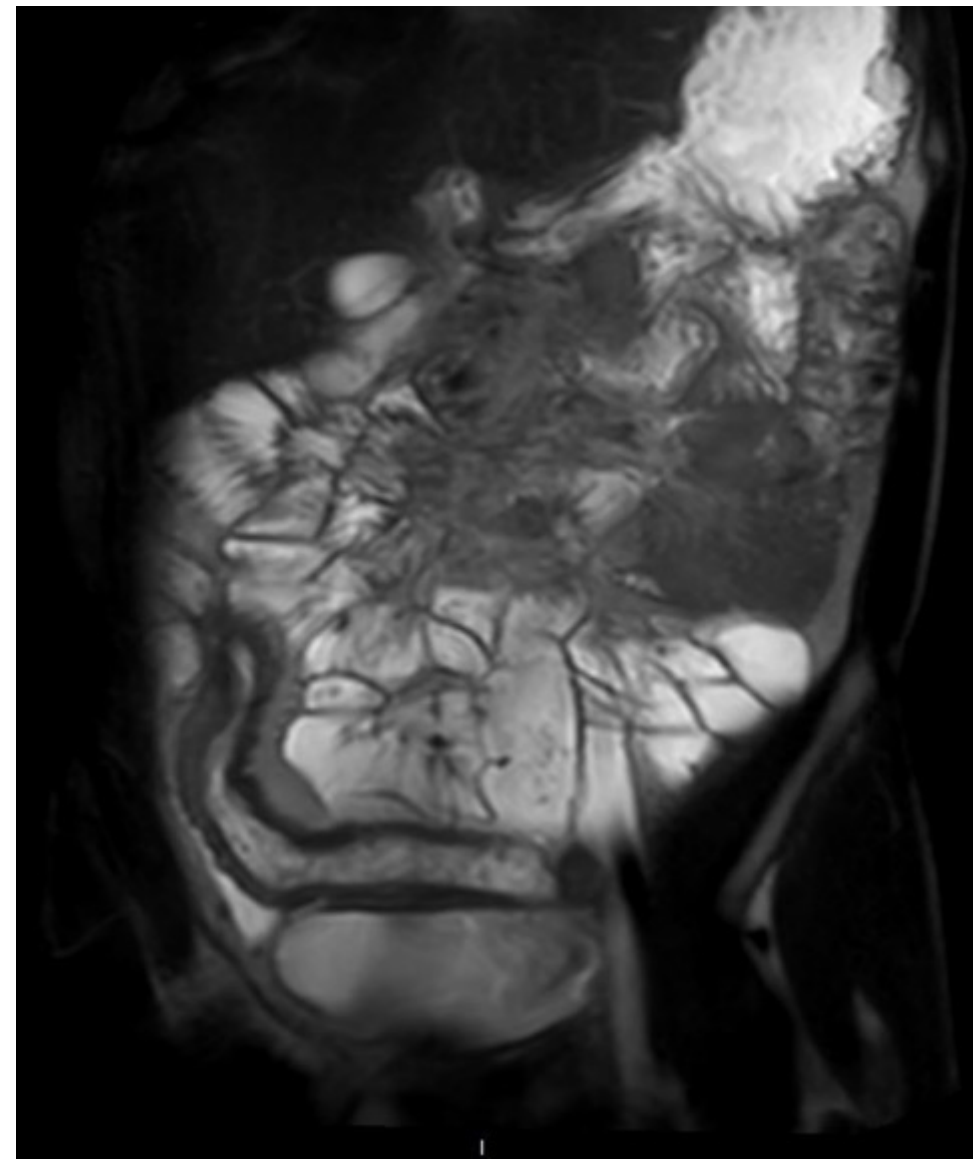
- Aucun « gold standard » n'existe à l'heure actuelle pour affirmer le diagnostic de MICI
- La confirmation diagnostique repose sur un faisceau d'arguments cliniques, biologiques, endoscopiques, histologiques, voire radiologiques

Diagnostic positif d'une MICI

- L'aspect endoscopique diffère selon le type de MICI :
 - RCH :
 - Atteinte continue, commençant dès la jonction ano-rectale, s'étendant plus ou moins loin en amont, avec une muqueuse rouge, granitée, fragile, saignant au contact, plus ou moins associée à des ulcérations voire des décollements muqueux selon la sévérité de l'atteinte
 - L'existence d'un deuxième foyer inflammatoire caecal péri-appendiculaire est classique.
 - MC :
 - Ulcérations (aphtoïdes, en carte de géographie, en rails) non spécifiques, mais l'atteinte est multi-segmentaire et discontinue avec des intervalles de muqueuse saine.

Diagnostic positif d'une MICI

- Exploration de l'intestin grêle par entéro-IRM et/ou vidéo-capsule endoscopique :
 - recommandée pour les patients chez qui il existe une forte suspicion clinique de MC malgré des explorations endoscopiques conventionnelles normales
 - systématique chez tout patient nouvellement diagnostiqué avec une MC



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Histoire naturelle (1)

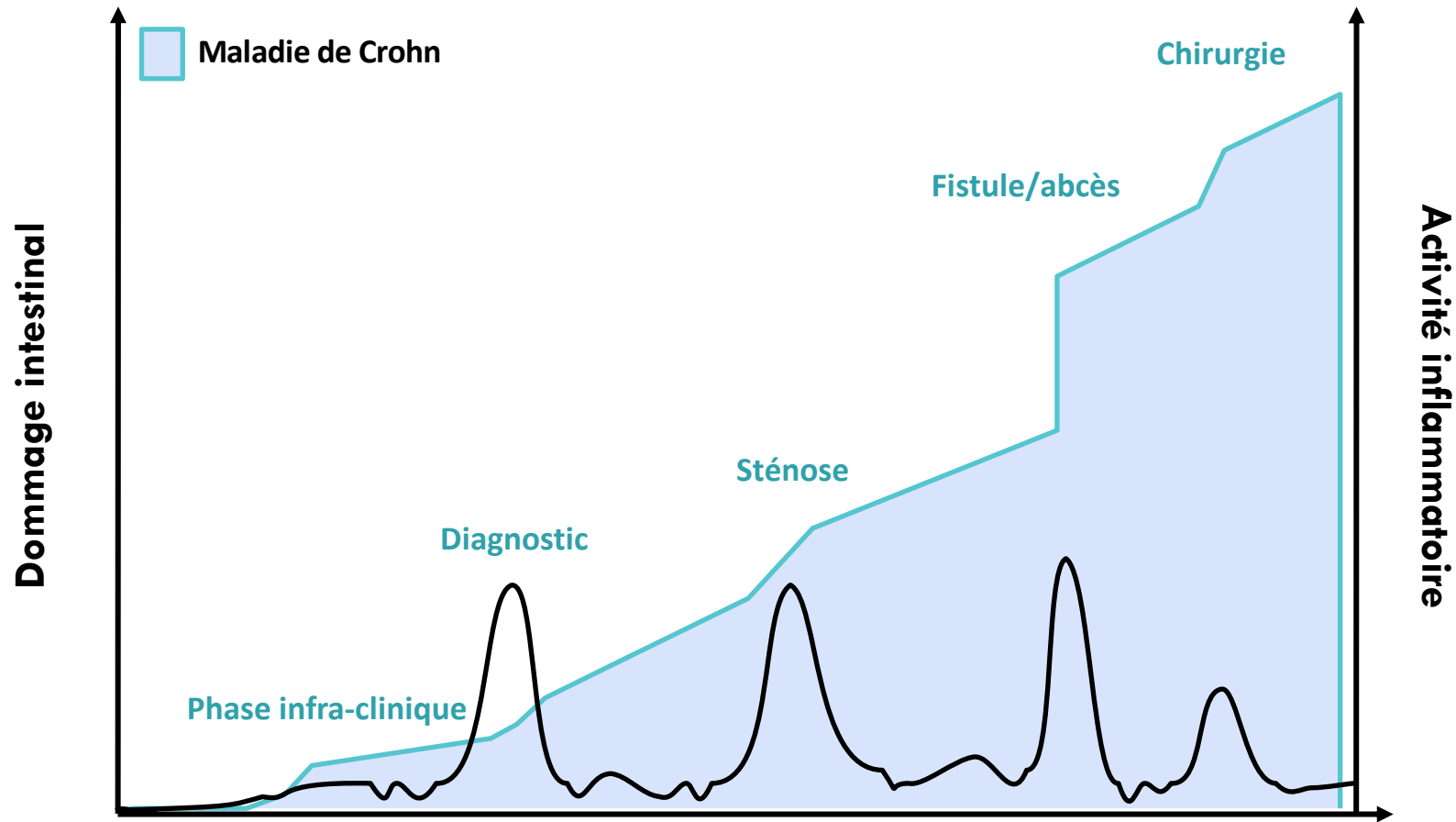
Maladie de Crohn

| | Montréal |
|-------------------|--------------------------|
| Âge au diagnostic | A1 : < 17 ans |
| | A2 : 17-40 ans |
| | A3 : > 40 ans |
| Localisation | L1 : iléon +/- cœcum |
| | L2 : côlon seul |
| | L3 : iléon et côlon |
| | L4 : tube digestif haut* |
| Évolution | B1 : inflammatoire |
| | B2 : sténosante |
| | B3 : fistulisante |
| | P : maladie périnéale |
| Croissance | - |

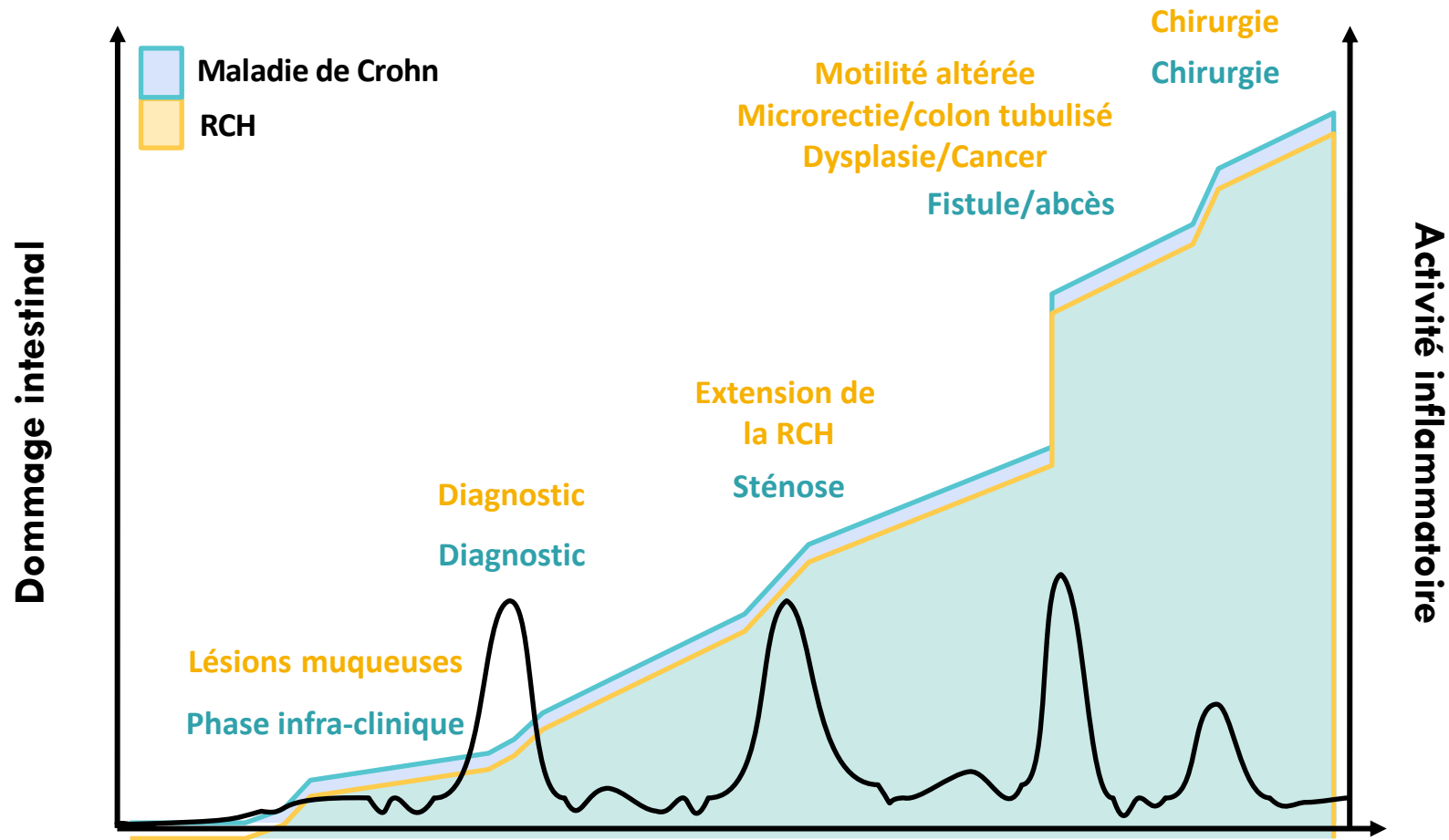
RCH

| | Montréal |
|-----------|--------------------------------------------------------|
| Extension | E1 : proctite |
| | E2 : colite gauche (distale à l'angle splénique) |
| | E3 : colite étendue (proximale à l'angle splénique) |
| Sévérité | S0 : Rémission |
| | S1 : légère |
| | S2 : modérée |
| | S3 : sévère |

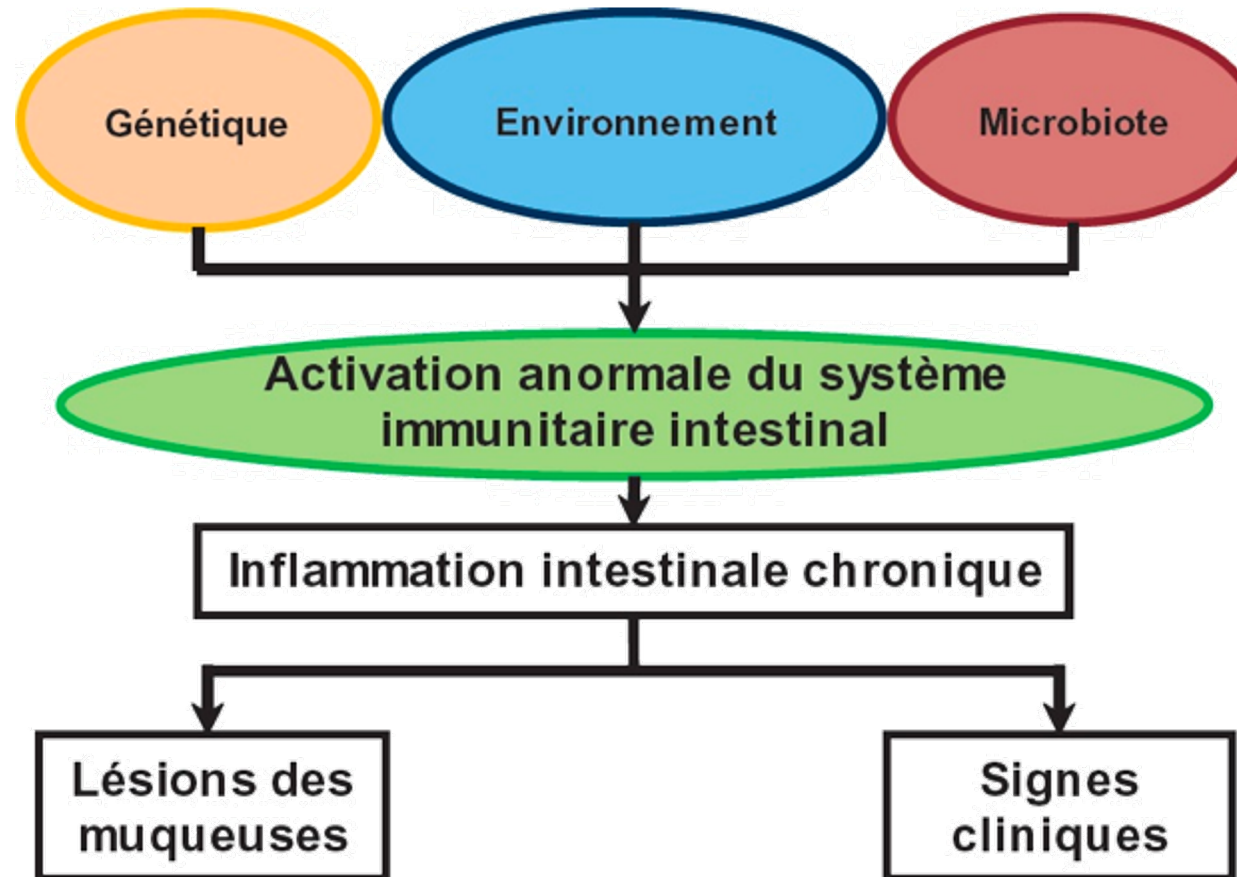
Histoire naturelle (2)



Histoire naturelle (3)



Physiopathologie des MICI



Les objectifs thérapeutiques ont grandement évolué sur la dernière décennie

Approche pas-à-pas basée uniquement sur les symptômes cliniques

Instauration retardée d'un traitement efficace

Dissociation inflammation/symptômes = risque de sous-traiter

Rémission clinique

3 mois

Absence de rectorragies

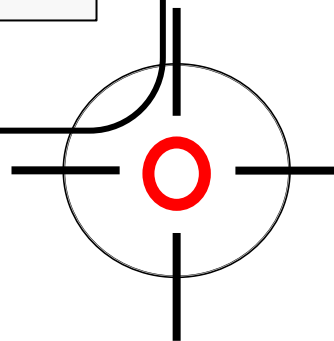
Absence de douleurs abdominales

Normalisation du transit

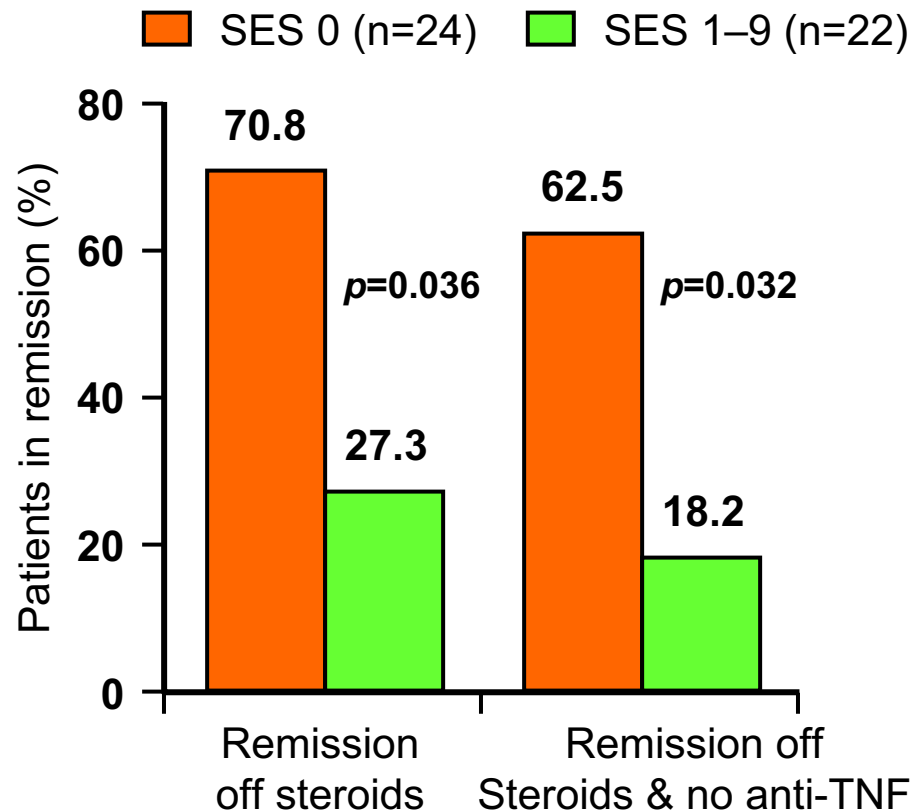
Cibles communes

Cibles pour la RCH

Cibles pour la MC

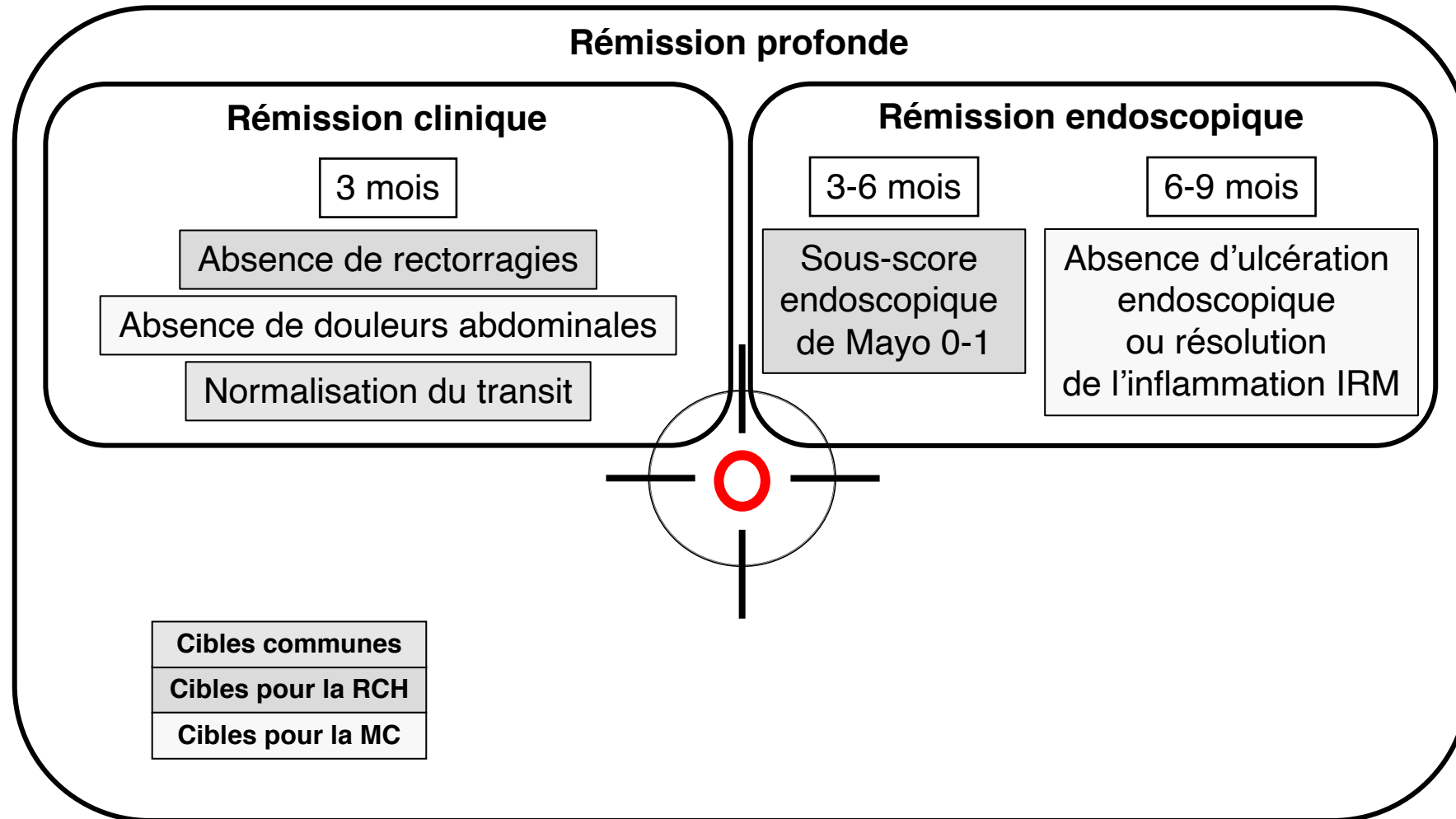


Au-delà de la rémission clinique

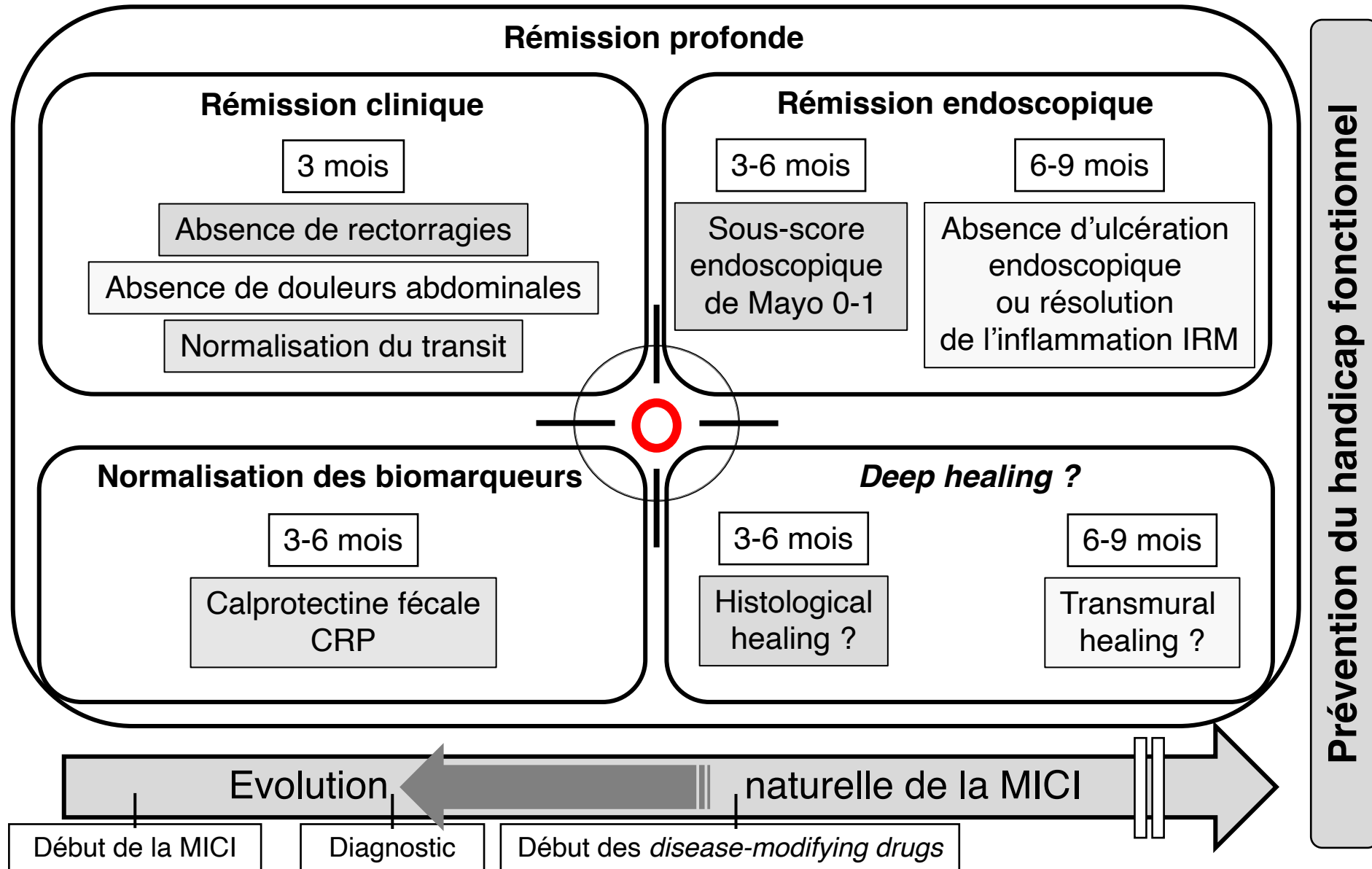


Une cicatrisation endoscopique à 2 ans est associée à une rémission clinique maintenue à 4 ans

Les cibles thérapeutiques en 2015 : le consensus STRIDE



Les cibles thérapeutiques en 2021 : le consensus STRIDE-II



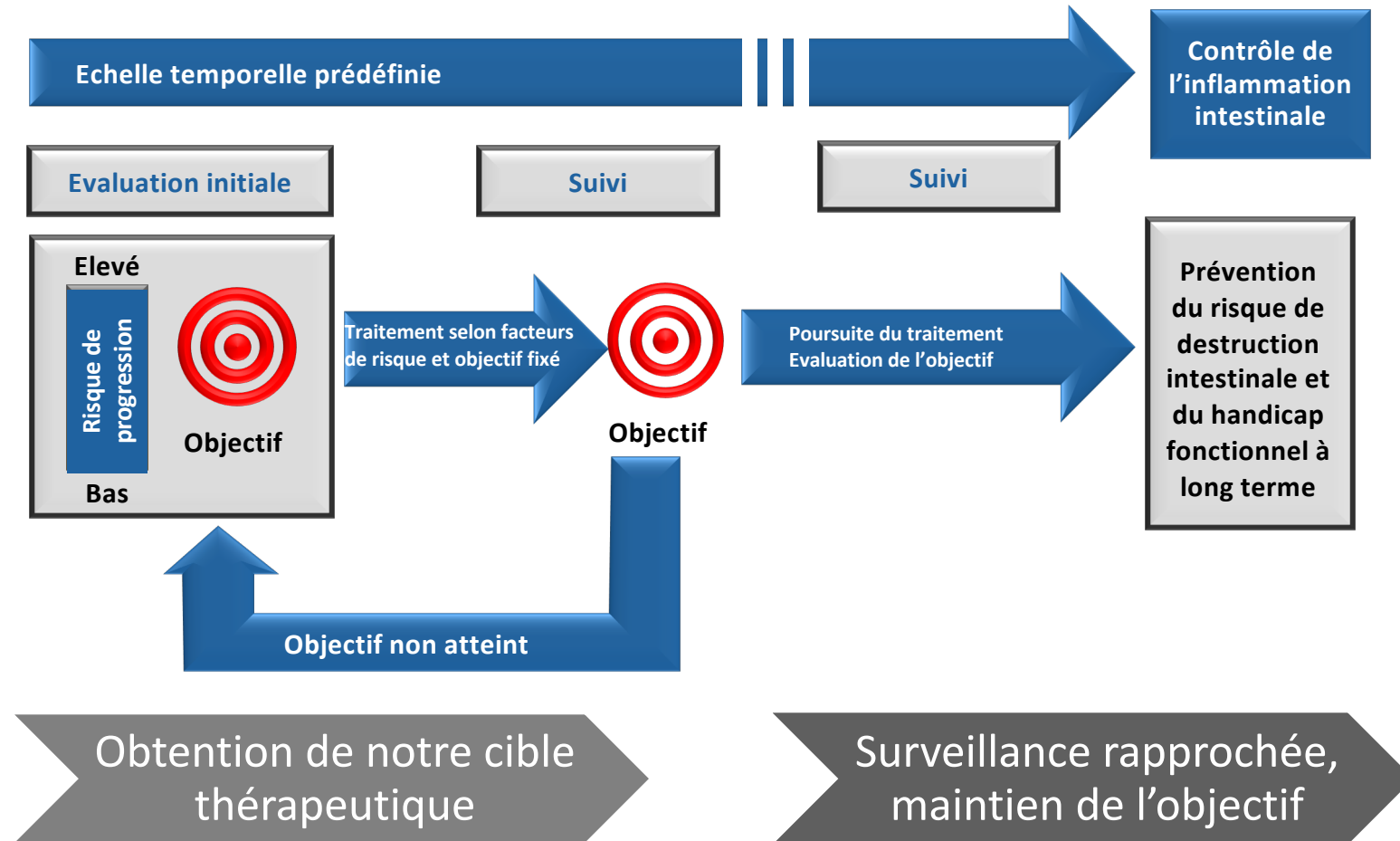
Comment atteindre ces objectifs ?

- “Treat-to-target” (au-delà des symptômes)
- Intervention thérapeutique précoce
- Monitoring (“tight control”)
- Prédire le cours évolutif de la maladie
- Personnaliser le traitement (médecine de précision)

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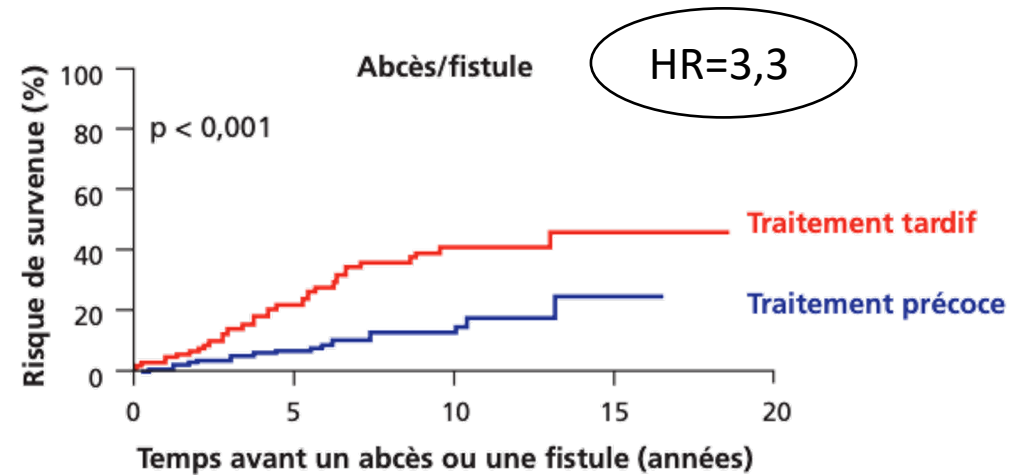
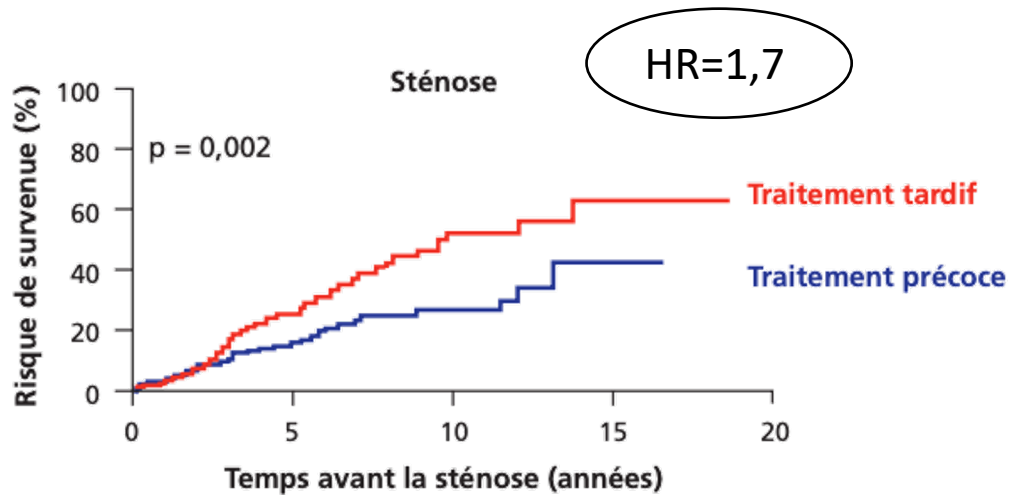
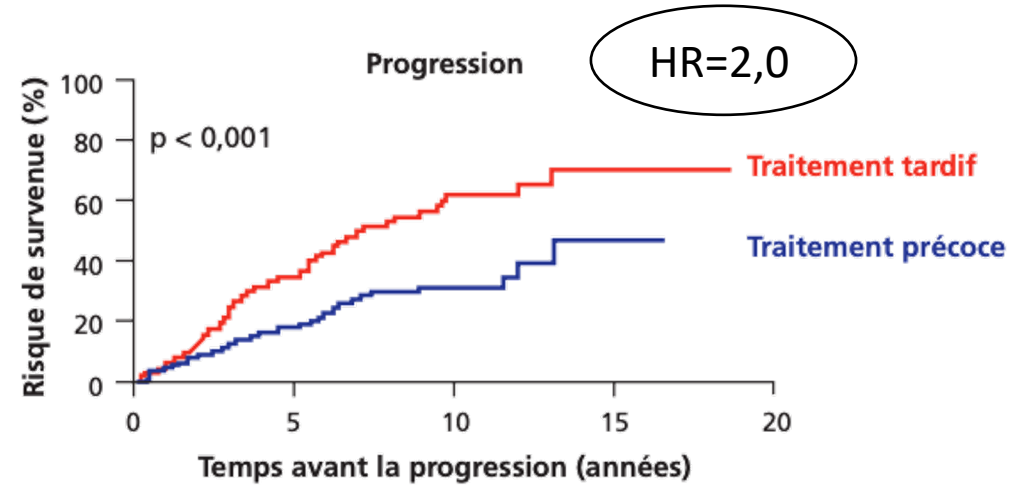
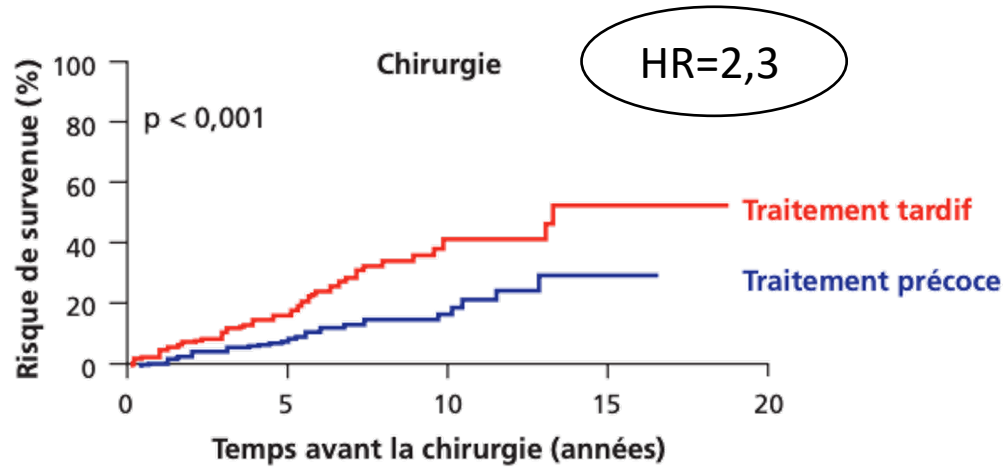
« Treat-to-target »



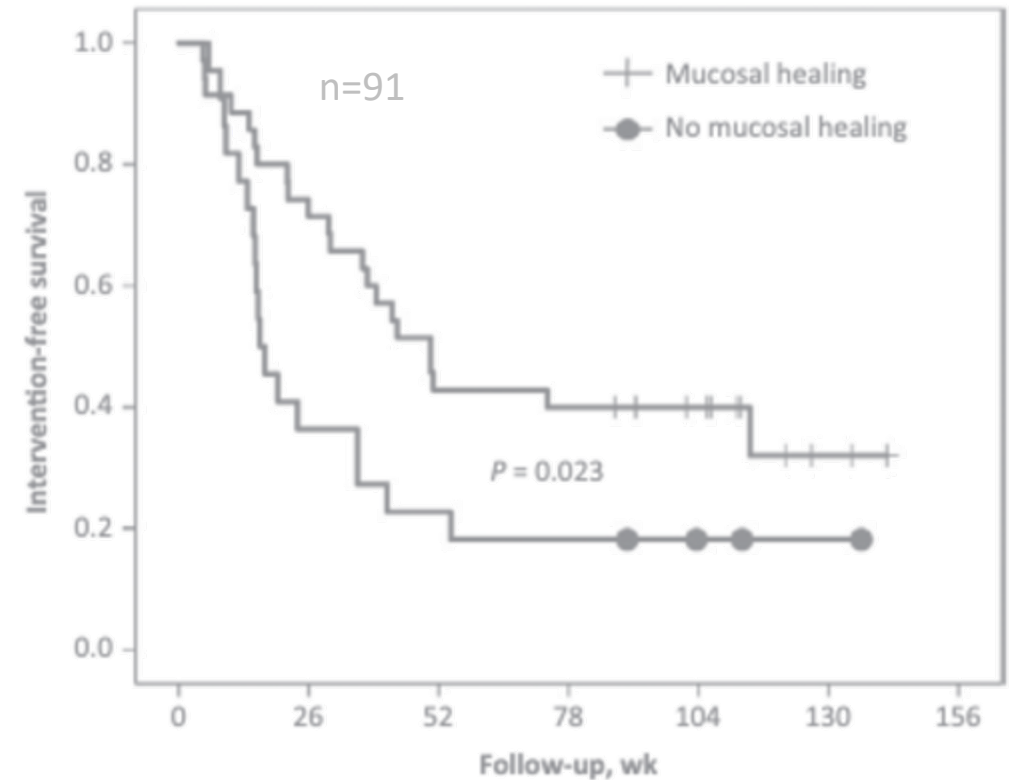
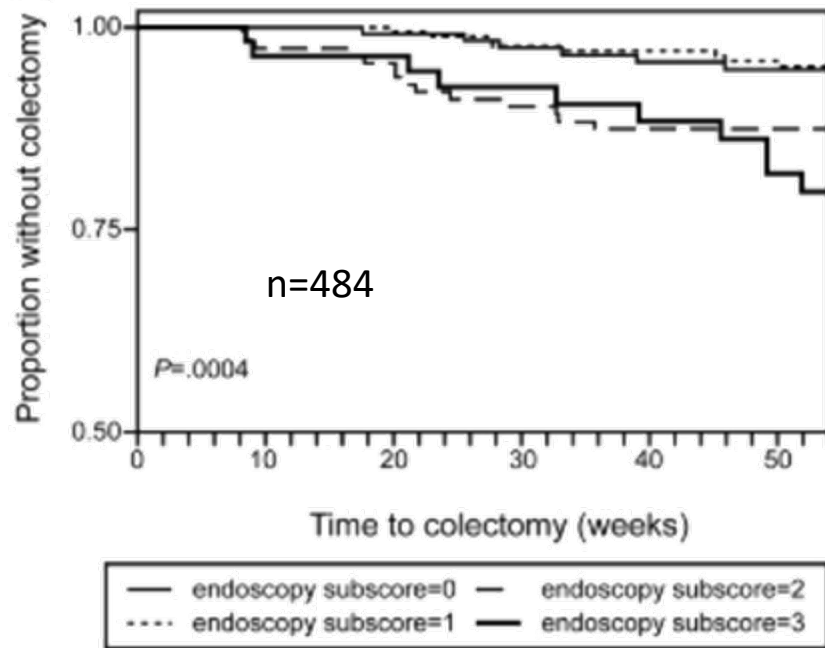
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Une prise en charge précoce est associée à une meilleure évolution de la MC



Une cicatrisation muqueuse précoce est associée à une meilleure évolution de la RCH

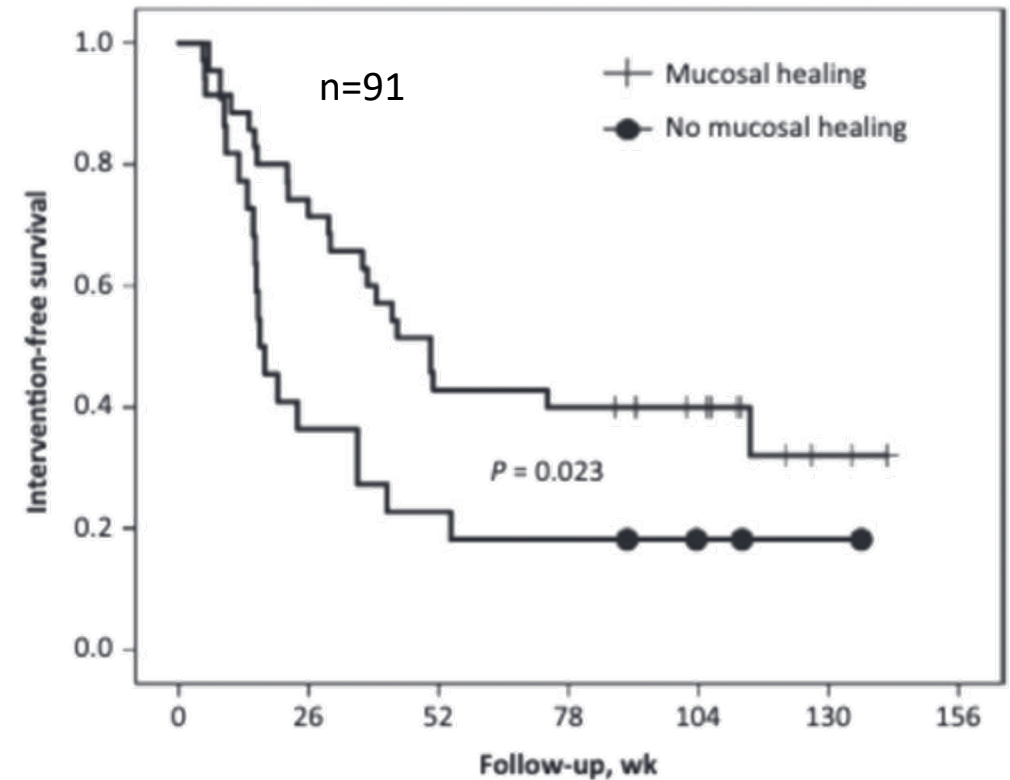
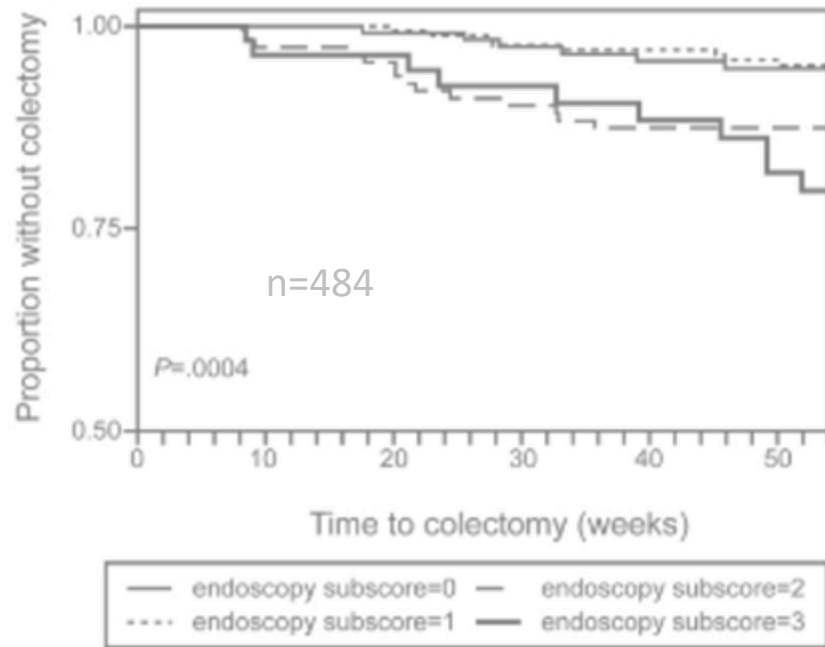


Week 30

| Week 8 Mayo endoscopy subscore ^a | Median corticosteroid dose ^b | Corticosteroid-free, n/n (%) | P value ^c | Corticosteroid-free symptomatic remission, n/n (%) | P value ^c |
|---------------------------------------------|-----------------------------------------|------------------------------|----------------------|----------------------------------------------------|----------------------|
| Infliximab | | | | | |
| 0 | 0 | 40/65 (62) | <.0001 | 30/65 (46) | <.0001 |
| 1 | 4.5 | 47/102 (46) | | 35/102 (34) | |
| 2 | 10 | 14/71 (20) | | 8/71 (11) | |
| 3 | 10 | 3/31 (9.7) | | 2/31 (6.5) | |

| No. at risk | 35 | 25 | 15 | 14 | 10 | 2 | 0 |
|-------------|----|----|----|----|----|---|---|
| | 22 | 8 | 5 | 4 | 3 | 1 | 0 |

Une cicatrisation muqueuse précoce est associée à une meilleure évolution de la RCH



Week 30

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Le concept de « early disease »

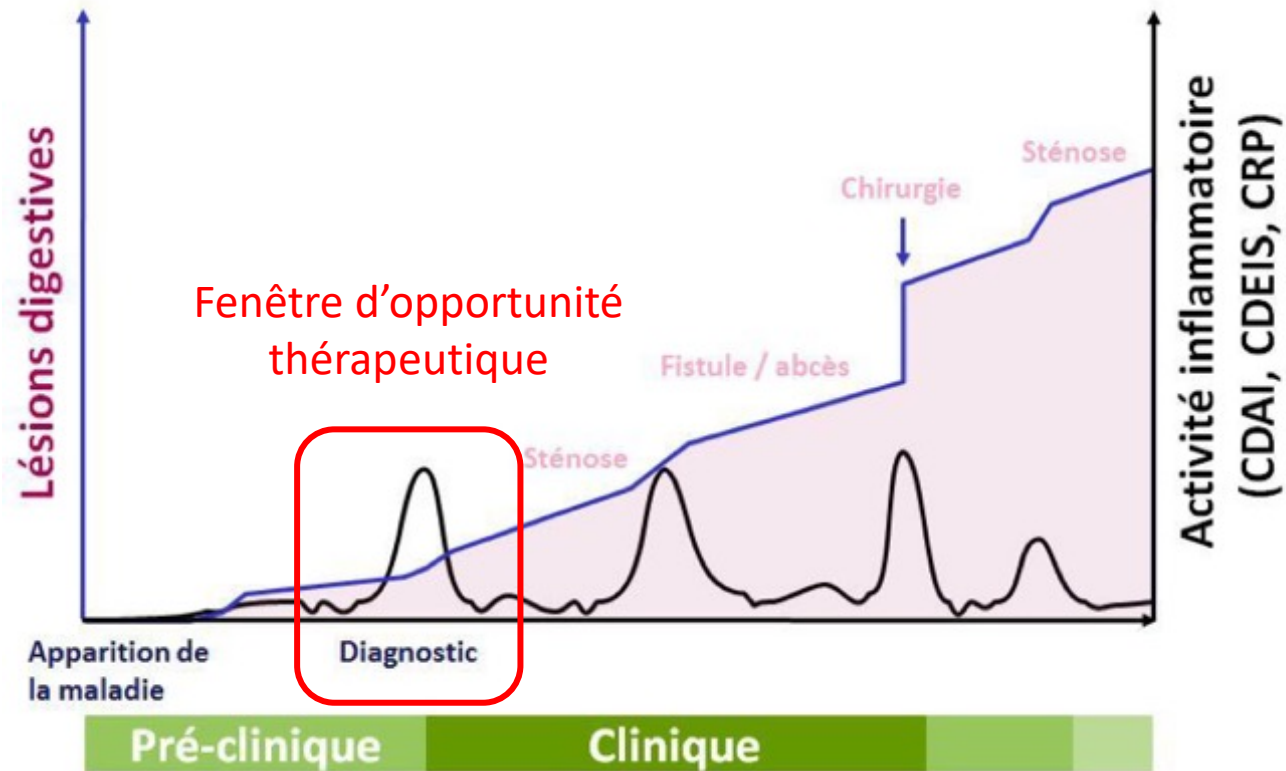


Table 3. Paris criteria defining early Crohn's disease for use in disease-modification trials (evidence level D)

| Component ^a | Definition |
|------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|
| Disease duration | ≤18 months after diagnosis |
| Treatment | No previous or current use of immunomodulators and/or biologics Previous or current use of 5-aminosalicylate and/or corticosteroids permitted |

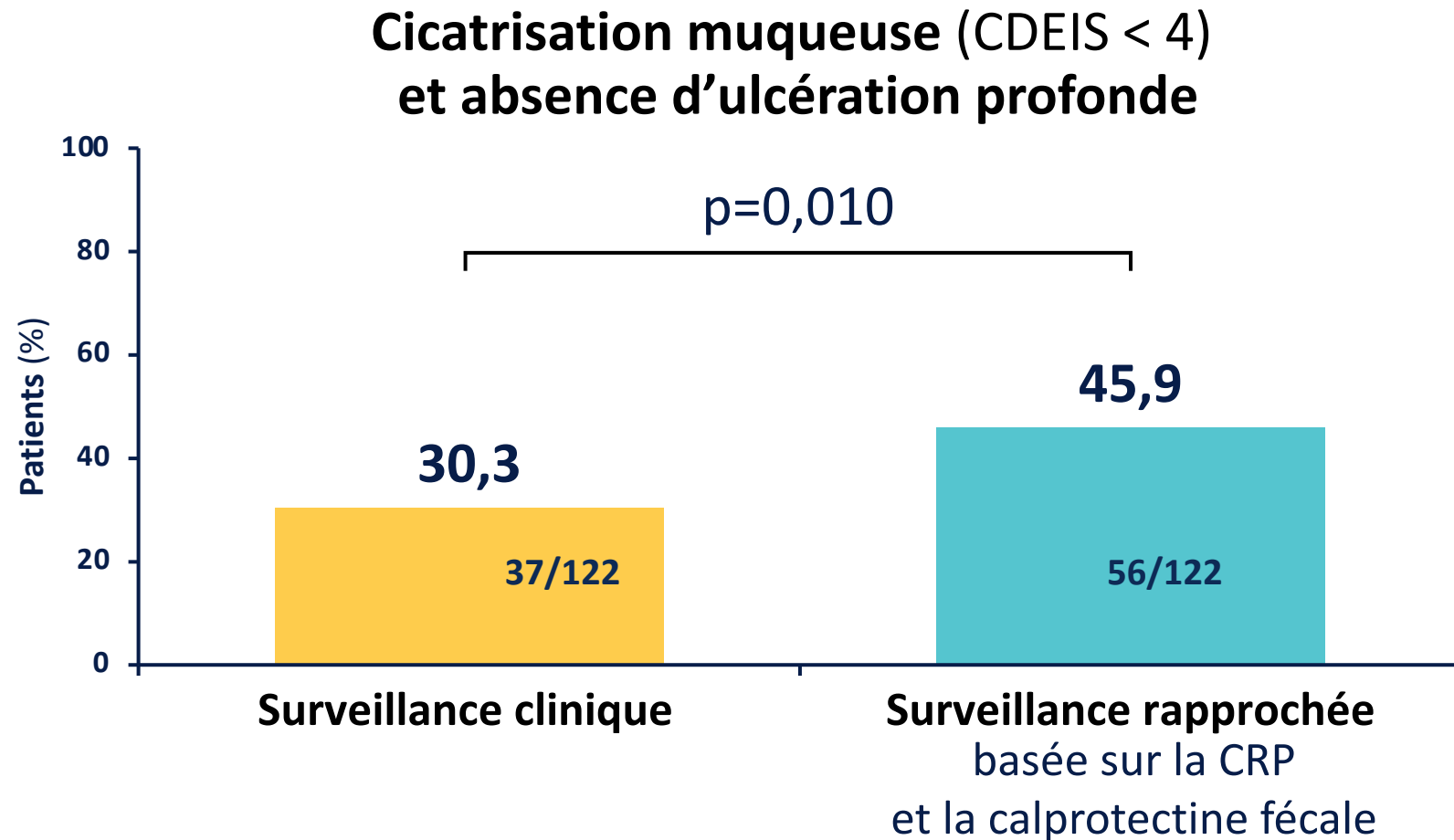
^aAs a prerequisite, the previous diagnosis of Crohn's disease has to be confirmed according to the criteria adopted by Lennard-Jones (26).

Comment atteindre ces objectifs ?

- “Treat-to-target” (au-delà des symptômes)
- Intervention thérapeutique précoce
- **Monitoring (“tight control”)**
- Prédire le cours évolutif de la maladie
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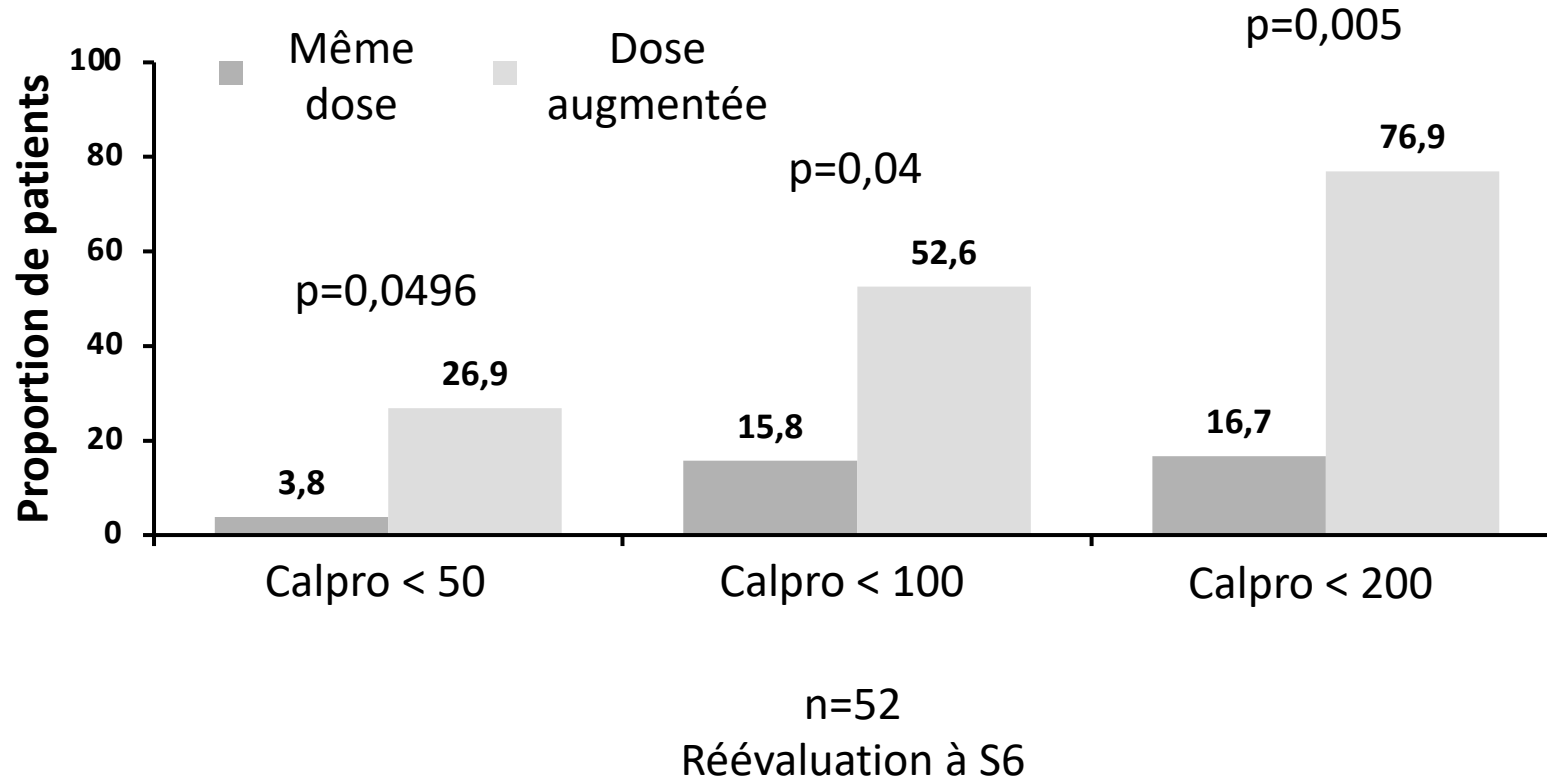
Un contrôle serré est associé à une meilleure évolution de la MC

- N=244
- Durée d'évolution de la maladie (moyenne) :
 - 0,9 an (groupe suivi clinique)
 - 1,0 an (groupe T2T)
- Pas de différence en terme d'effets indésirables entre les 2 groupes

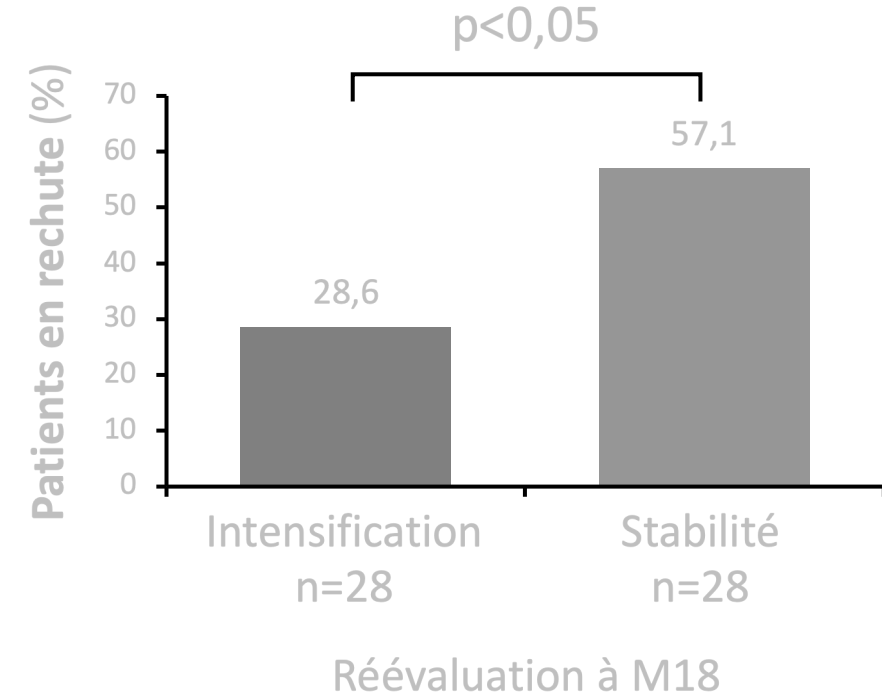


Peut-on transposer CALM aux patients atteints de RCH ?

RCH quiescente + calprotectine >50 µg/g + 5-ASA < 3 g/jour
Randomisation (1:1) : même dose vs intensification

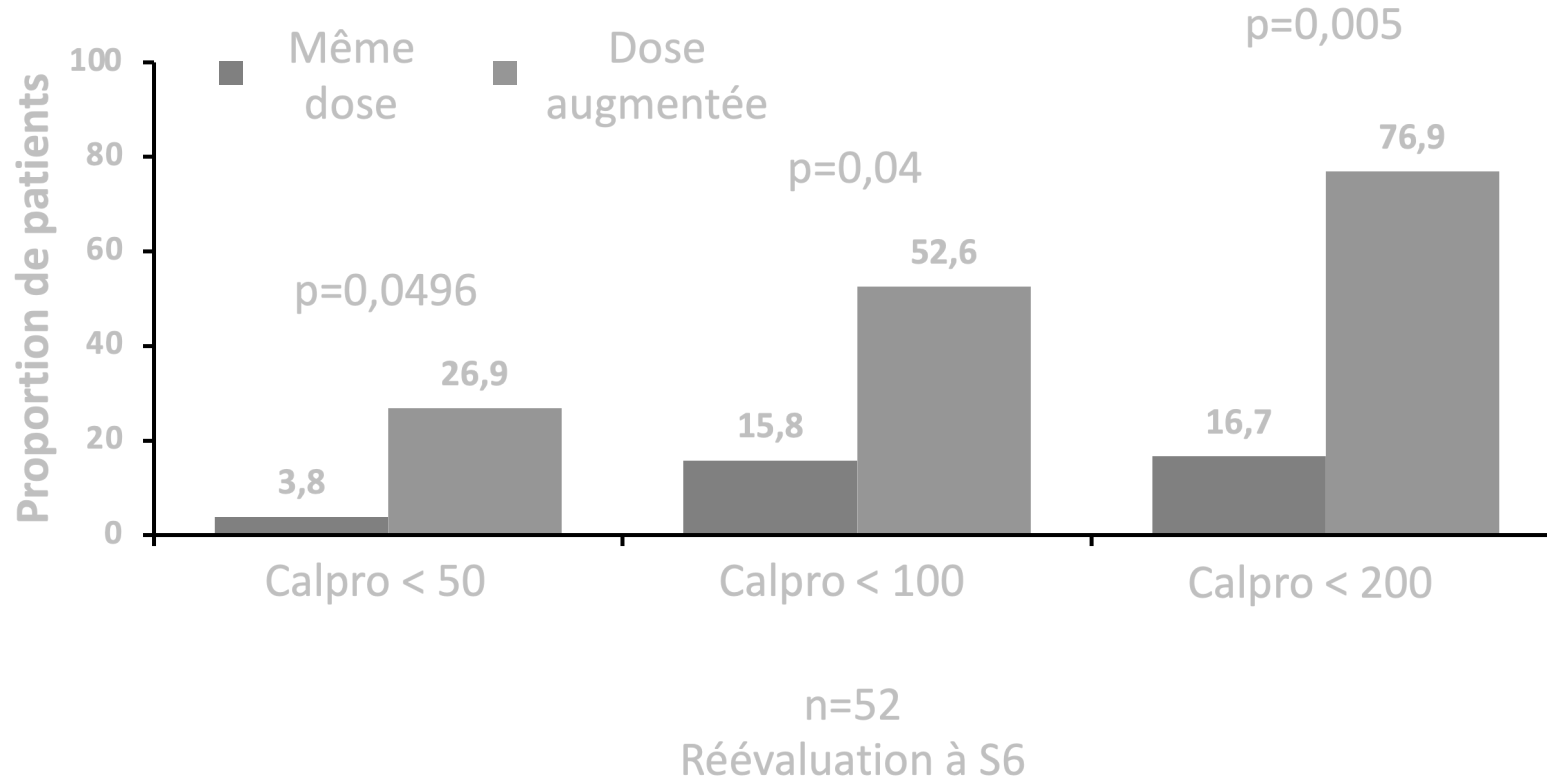


Calprotectine > 300 µg/g
Intensification vs stabilité de dose

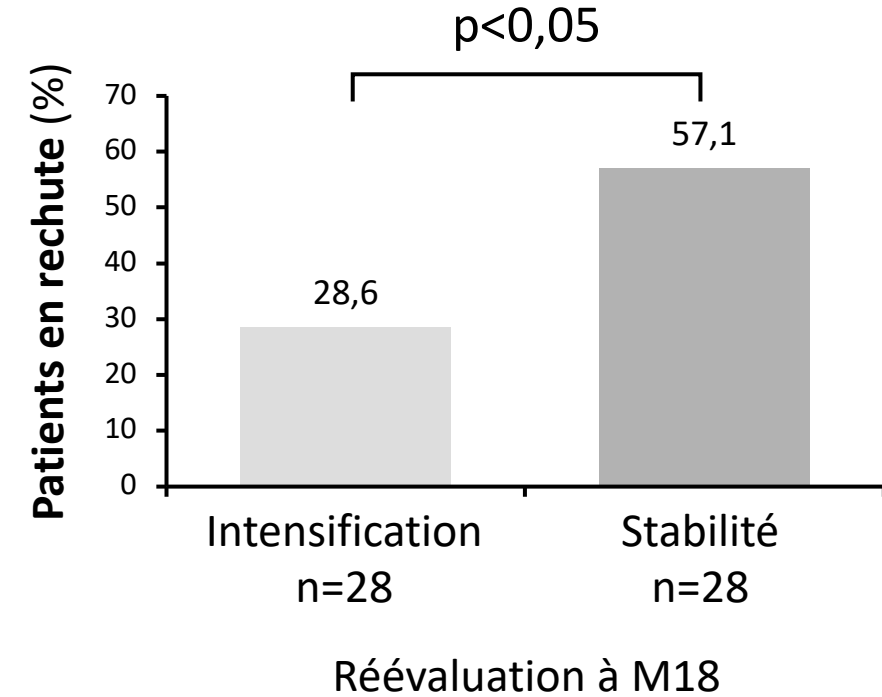


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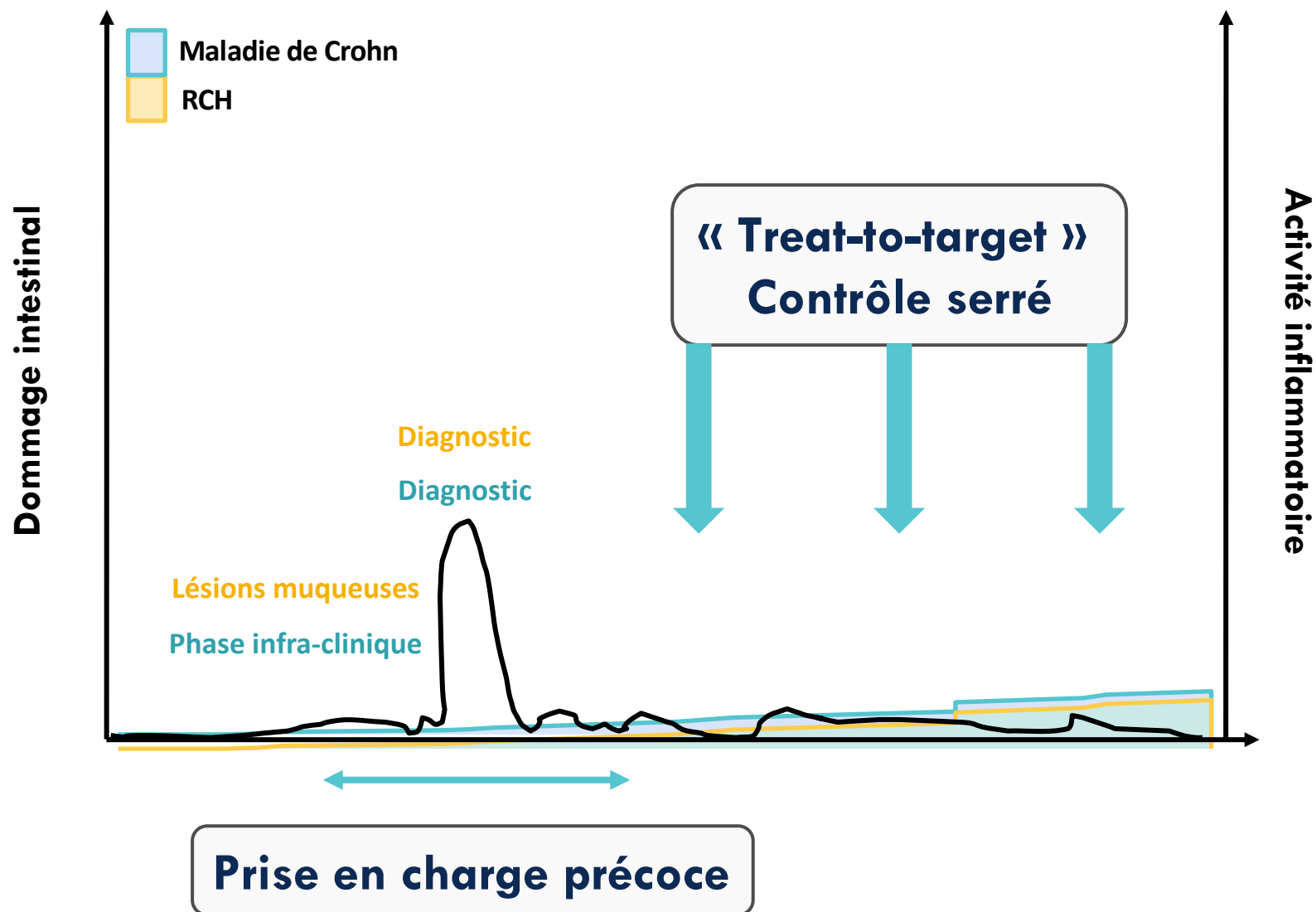
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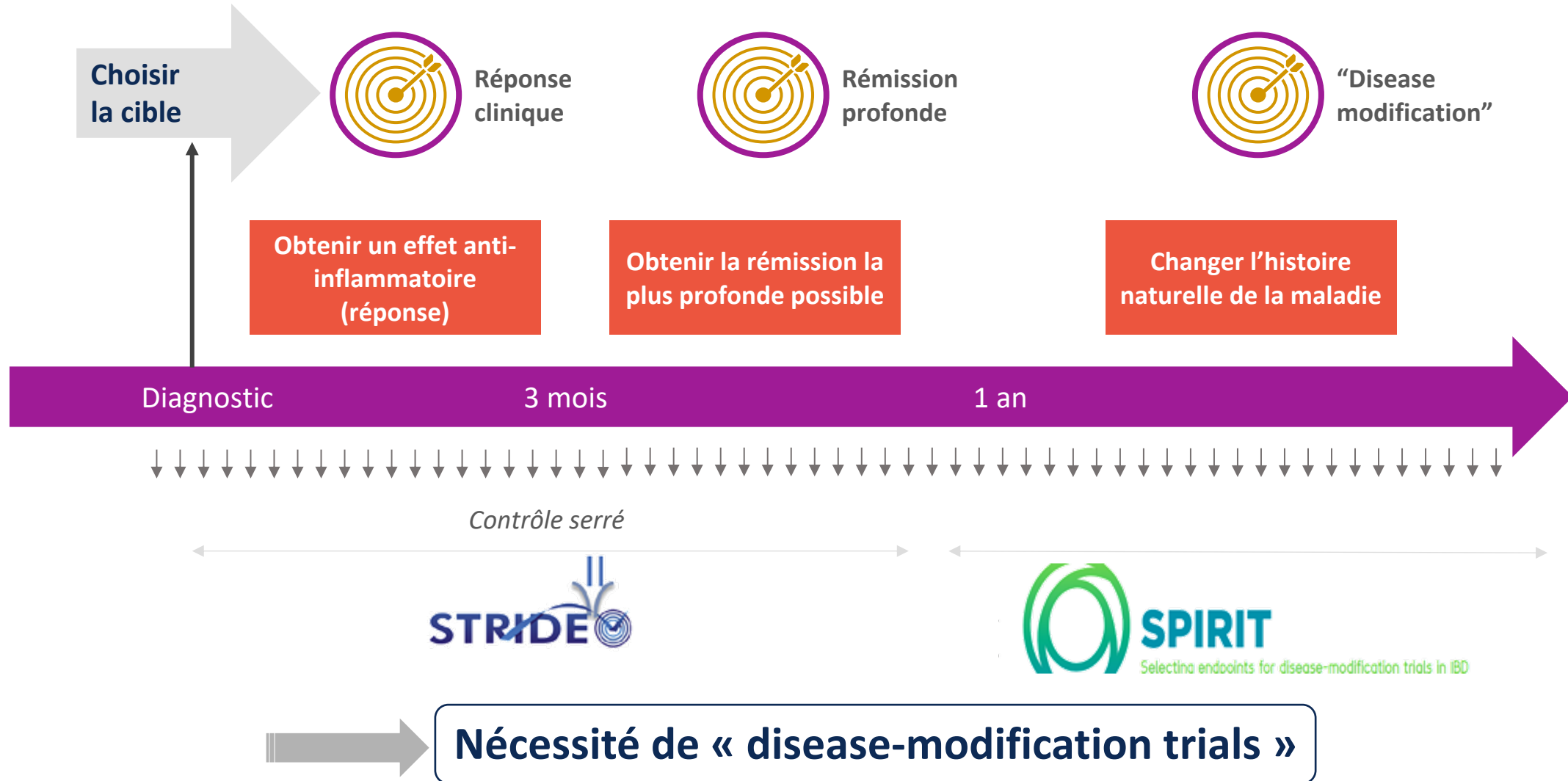
Calprotectine > 300 µg/g
Intensification vs stabilité de dose



Le but ultime de cette stratégie est de ralentir l'évolution naturelle de la maladie



Cette stratégie permet-elle vraiment de modifier l'histoire naturelle de la maladie ?



Comment atteindre ces objectifs ?

- “Treat-to-target” (au-delà des symptômes)
- Intervention thérapeutique précoce
- Monitoring (“tight control”)
- **Prédire le cours évolutif de la maladie**
- Personnaliser le traitement (médecine de précision)

Prédire le cours évolutif



Indolent



Aggressive

Step-up

Eviter une thérapie agressive
menant à une immunosuppression
et des effets secondaires

Top-down

Assurer une intervention
thérapeutique précoce pour éviter
les complications de la maladie

Overall disease severity index

- Disease severity \neq Disease activity
 - Activité de la maladie = cliché instantané
 - Sévérité de la maladie = qualité de vie, handicap fonctionnel, complications à +/- long terme même en l'absence d'activité
- Consensus Delphi par l'IOIBD.
- Echelle de 0 à 100 points pour la maladie de Crohn et la RCH.

Overall disease severity index

Table 2 Disease attribute contributions to overall disease severity

| Attribute of Crohn's disease | Proportion (%) | Attribute of UC | Proportion (%) |
|------------------------------|----------------|----------------------------|----------------|
| Mucosal lesions | 15.8 | Mucosal lesions | 18.1 |
| Fistula | 10.9 | Impact on daily activities | 14.0 |
| Perianal abscess | 9.7 | C reactive protein | 11.2 |
| Prior bowel resection | 7.4 | Prior biologic use | 10.1 |
| Stoma | 7.1 | Recent hospitalisation | 7.7 |
| Disease extent | 5.8 | Recent steroid use | 7.6 |
| Frequency of loose stools | 5.6 | Anaemia | 5.1 |
| Stricture | 5.4 | Frequency of loose stools | 4.8 |
| C reactive protein | 5.3 | Albumin | 4.8 |
| Prior biologic use | 5.3 | Disease extent | 4.8 |
| Impact on daily activities | 4.8 | Nocturnal bowel movements | 4.3 |
| Albumin | 4.2 | Anorectal symptoms | 4.0 |
| Anorectal symptoms | 3.9 | Rectal bleeding | 3.5 |
| Anaemia | 3.6 | | |
| Abdominal pain | 3.1 | | |
| Recent steroid use | 2.3 | | |

Index non validé
pour le moment

Comment atteindre ces objectifs ?

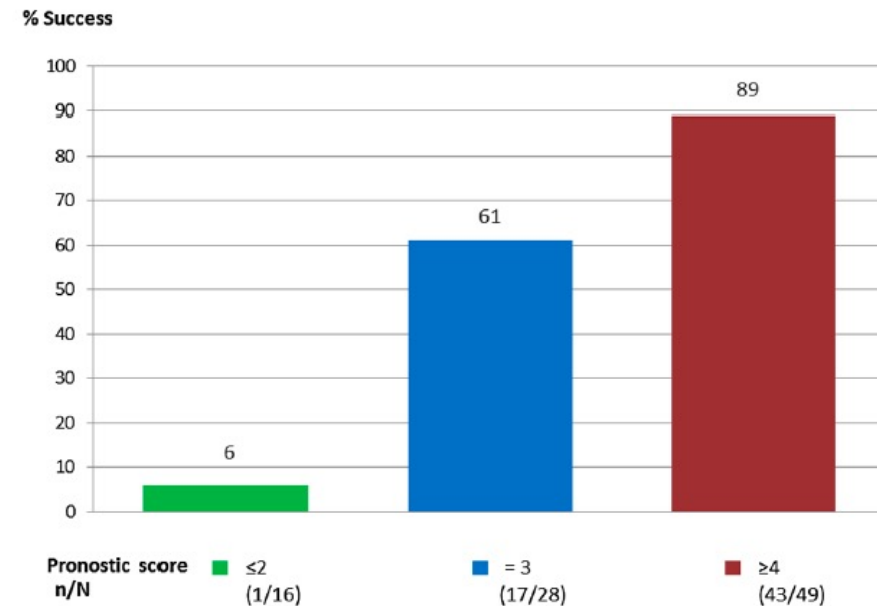
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Personnaliser le traitement

Un exemple : l'étude CREOLE

- Prédiction du succès d'un anti-TNF en cas de maladie de Crohn avec sténose symptomatique de l'intestin grêle.

| | | |
|---------------------------------------------------------------------|-------|---|
| Immunosuppressive treatment | Yes 1 | _ |
| | No 0 | |
| Crohn's disease obstructive score >4 | Yes 1 | _ |
| | No 0 | |
| Duration obstructive symptoms < 5 weeks | Yes 1 | _ |
| | No 0 | |
| Length of stricture < 12 cm | Yes 1 | _ |
| | No 0 | |
| Maximal small bowel diameter proximal to stricture between 18-29 mm | Yes 1 | _ |
| | No 0 | |
| Marked enhancement on delayed T1-weighted sequence | Yes 1 | _ |
| | No 0 | |
| No fistula | Yes 1 | _ |
| | No 0 | |
| Total Score | | _ |



Les traitements disponibles dans les MICI sont de plus en plus nombreux

5-ASA

Oral
2-4 g/jour
= PENTASA,
ROWASA,
FIVASA

Topique
3 g/semaine

Immunosuppresseurs

Thiopurines (PO)

Azathioprine
= IMUREL

6-mercaptopurine
= PURINETHOL

Thioguanine
= LANVIS

Methotrexate
= METOJECT (SC)
Ou IMETH (PO)

Anti-TNF

Infliximab (IV)
= REMICADE,
INFLECTRA,
REMSIMA

Adalimumab (SC)
= HUMIRA, HULIO,
AMGEVITA, IMRALDI...

Golimumab (SC)
= SIMPONI

Certolizumab (SC)
= CIMZIA

Biothérapies

Anti-intégrine

Vedolizumab (IV)
= ENTYVIO

Anti-IL12/IL23

Ustekinumab
(IV puis SC)
= STELARA

Petites molécules

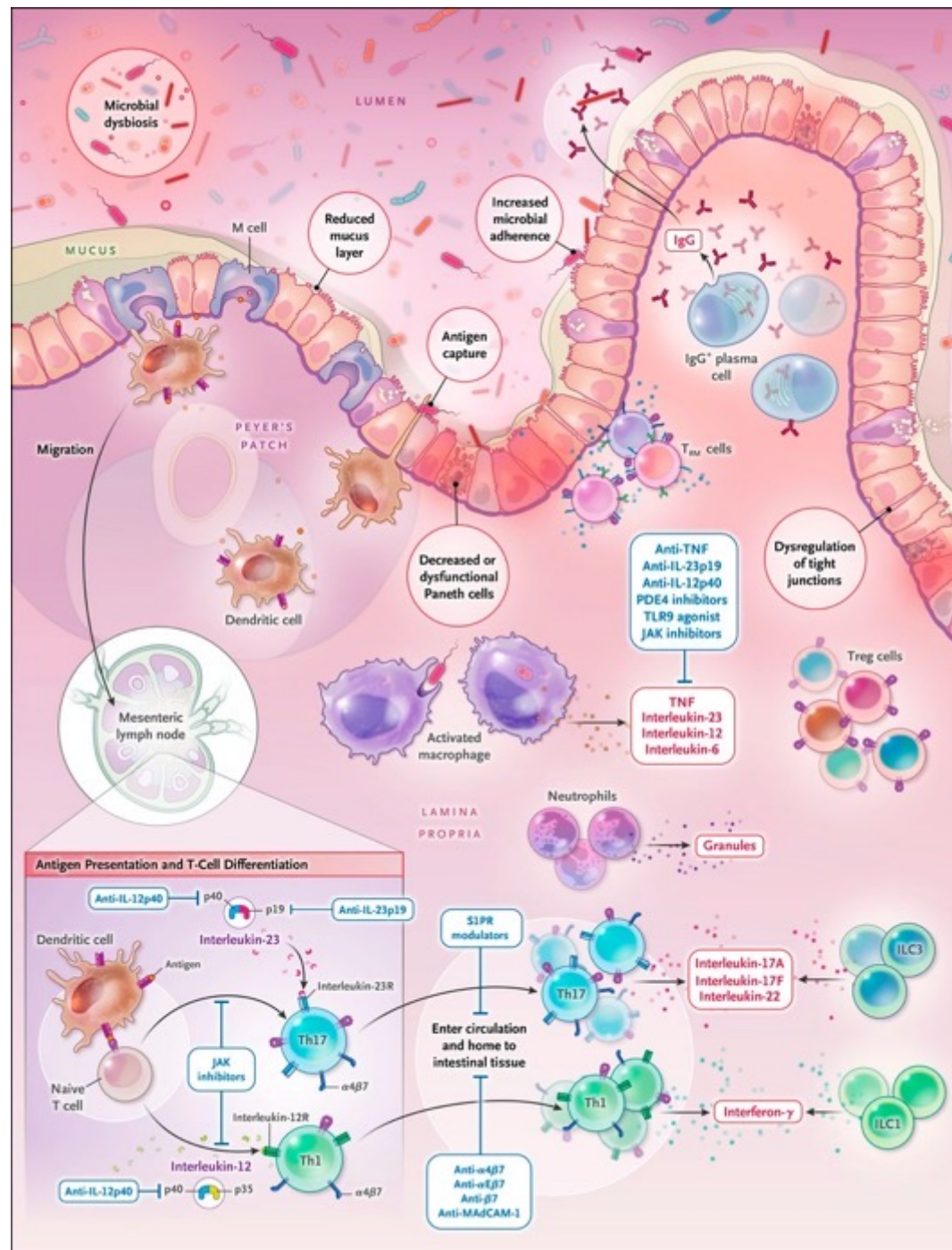
Anti-Jak

Tofacitinib
= XELJANZ

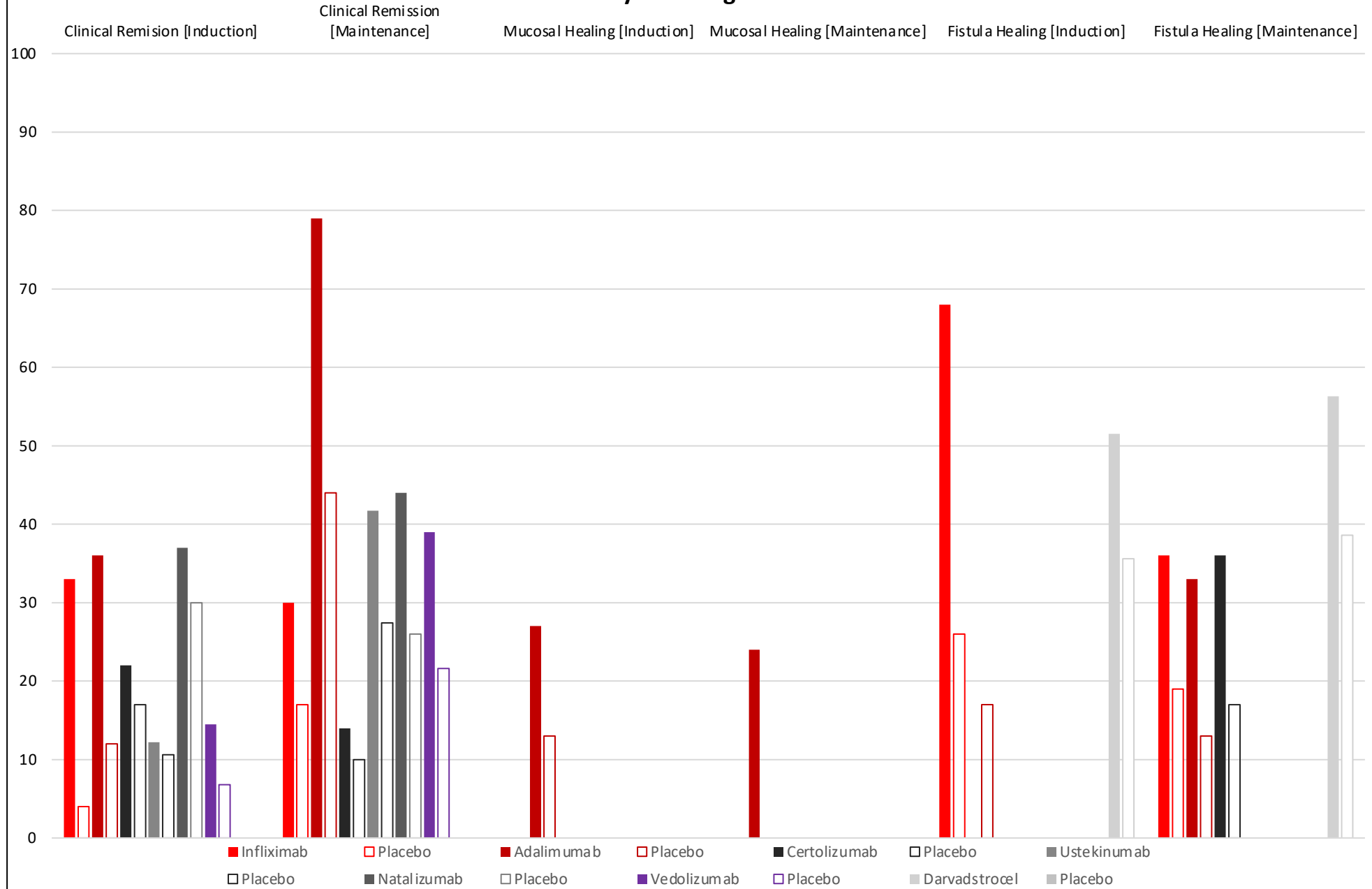
Traitements communs

Traitements pour la RCH

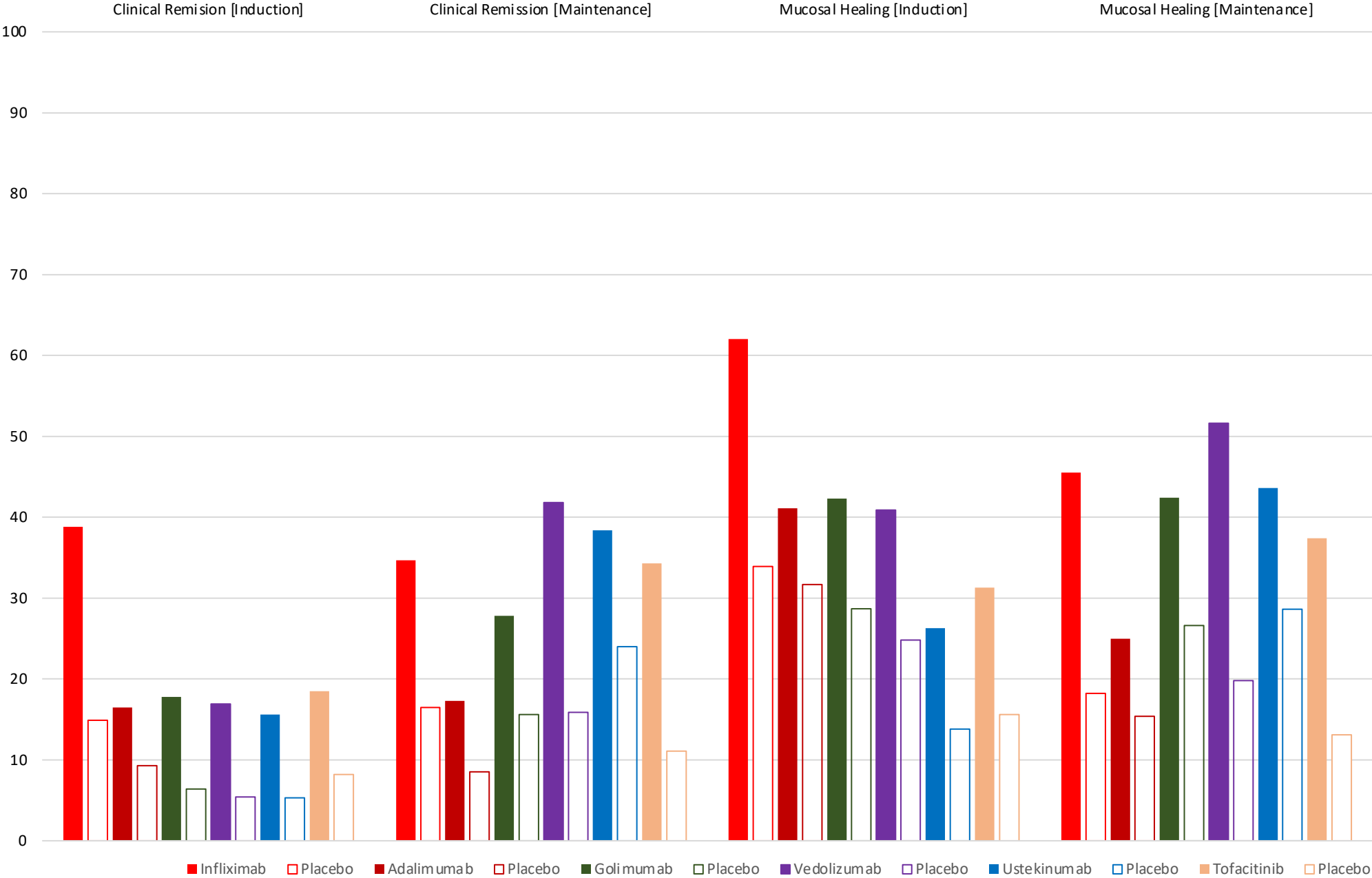
Traitements pour la MC



Pivotal Trial Efficacy of Biologics in Crohn's Disease

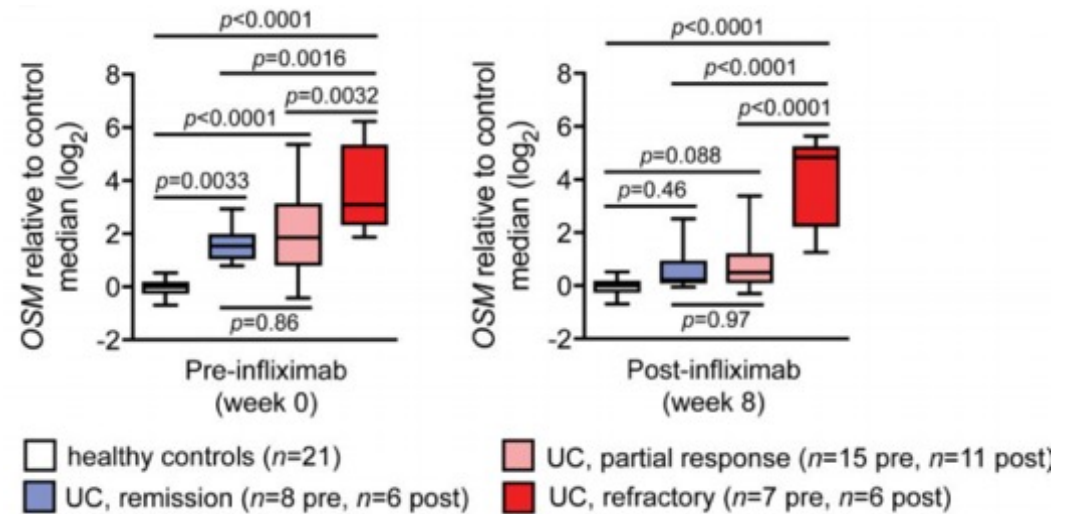
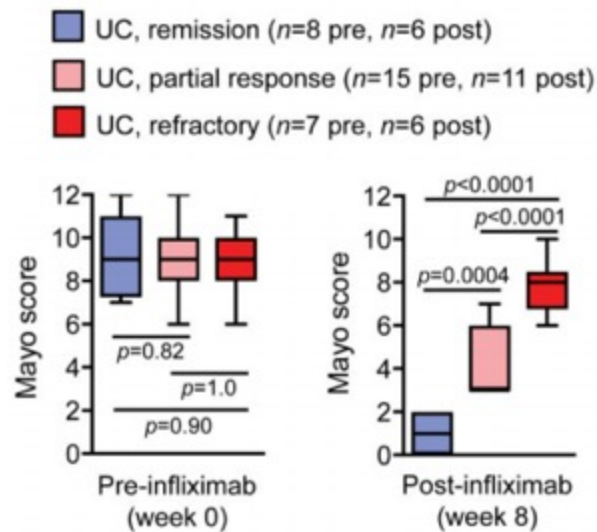


Pivotal Trial Efficacy of Biologics in Ulcerative Colitis

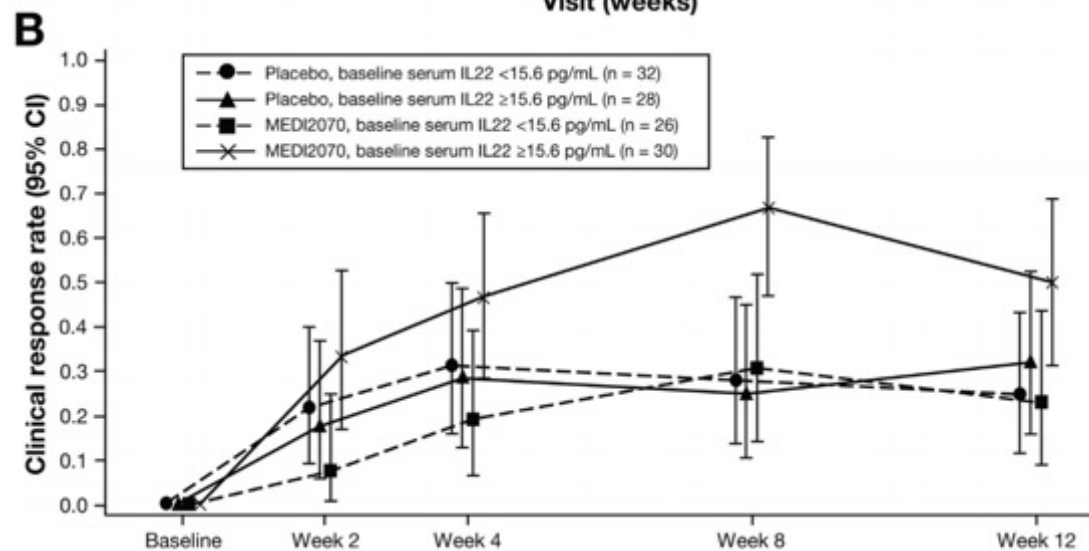
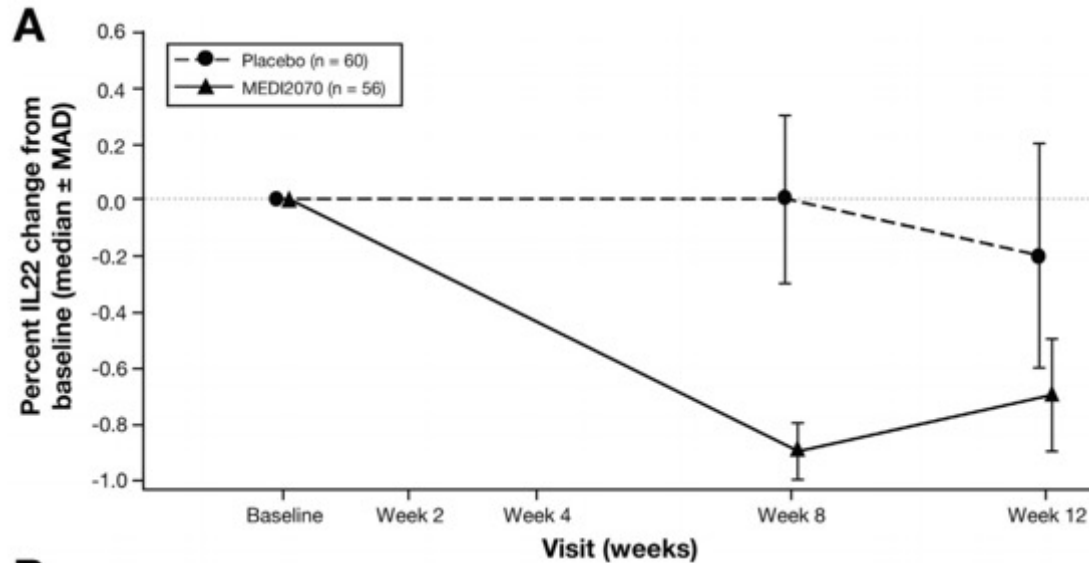


Personnaliser à l'échelle moléculaire

Surexpression colique de l'oncostatine M associée à un échec des anti-TNF



Personnaliser à l'échelle moléculaire



Concentration sérique élevée d'IL-22 associée à une meilleure réponse à un anti-IL-23

Conclusion

- Des objectifs thérapeutiques de plus en plus stricts.

- Trois concepts déjà bien établis :

- « Treat-to-target »
- Intervention thérapeutique précoce
- « Tight control » (biomarqueurs)

⇒ Nécessité de « disease-modification trials ».

- Deux autres concepts à approfondir :

- Médecine prédictive = évaluer la sévérité de la maladie pour en prédire son cours évolutif.
- Médecine personnalisée = administrer le bon traitement au bon patient.

MASTER 1 UE Biologie Systémique

Applying high dimensional single cell approaches to the
characterization of immunopathogenic responses in IBD

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Centre de recherche en Transplantation et Immunologie
INSERM UMR1064 – Université de Nantes

- How good is our understanding of immunopathogenic responses in IBD inflamed tissues ?
- What are the exact mechanisms by which current targeted therapies actually work?
- Why does it work in subsets of patients only?
- How can we identify these patients before treatment?
- What targets should be prioritized in those patients who do not respond to current targeted therapies ?

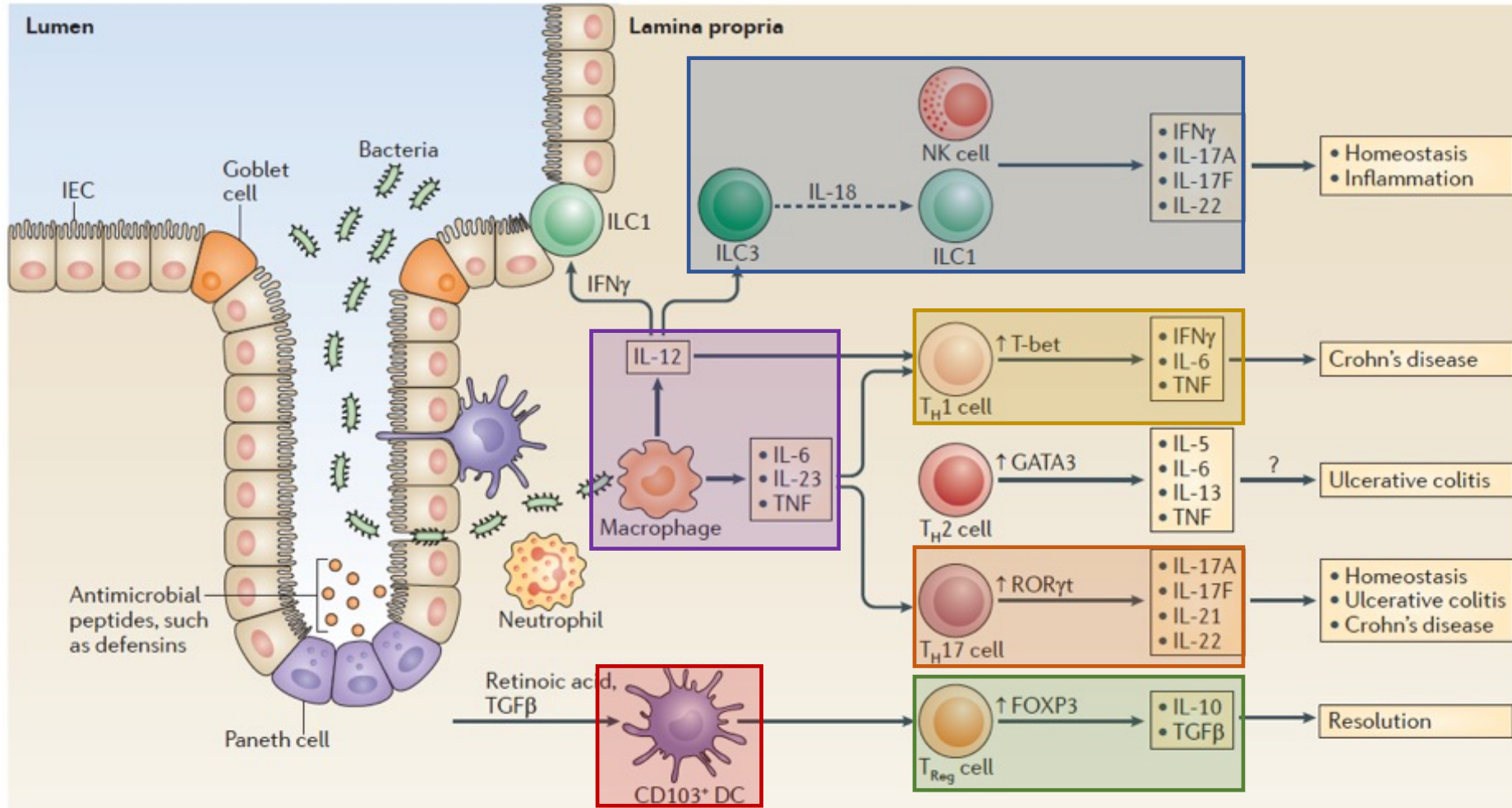
Diseases are caused by complex and dysregulated responses involving multiple cell types, interactions and effector mechanisms in tissues

Urgent need to achieve a deep characterization of pathogenic cellular responses involved in IBD patient tissues at the system level

Is the current pathophysiological model reflecting what really happens in tissues ?

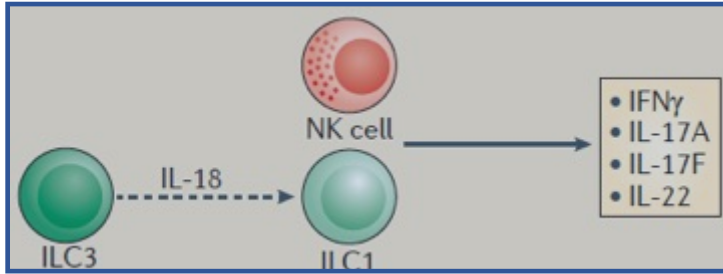
Working model

IBD



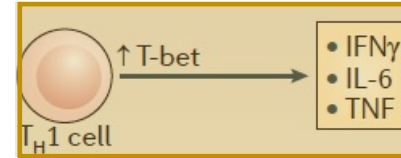
The immunological jigsaw puzzle of Crohn's disease inflammation

"Reality"



Fontolizumab
Secukinumab

Bernink JH, Nat Immunol, 2013
Geremia A, J Exp Med, 2013
Glatzer T, Immunity, 2013
Takayama T, Gastroenterology, 2010



Sakaruba A, Gastroenterology, 2009
Fuss IJ, J Immunol, 1996
Breese E, Immunology, 1993
Fais S, Gut, 1991

Fontolizumab
Tocilizumab
Infliximab
Adalimumab
Certolizumab
Golimumab

Natalizumab
Vedolimumab

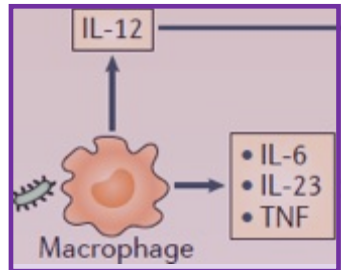
Human studies

How should the pieces be put together?
Should the pieces be put together?



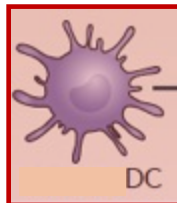
Secukinumab

Pariente B, Gastroenterology, 2011
Kleinschek MA, J Exp Med, 2009
Kobayashi T, Gut, 2009
Caprioli F, J Immunol, 2008

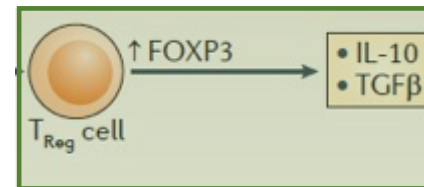


Tocilizumab
Ustekinumab
MEDI2070
Risankizumab
Infliximab
Adalimumab
Certolizumab
Golimumab

Thiesen S, J Leuk Biol, 2014
Koch S, Clin Exp Immunol, 2010
Kamada N, J Clin Invest, 2008
Schenk M, J Clin Invest, 2007
Mahida MR, Gut, 1989
Benardo D, Mucosal Immunol, 2018
Chapuy L, Mucosal Immunol, 2019



Magnusson MK, Mucosal Immunol, 2016
Middel P, Gut, 2006
Hart AL, Gastroenterology, 2005

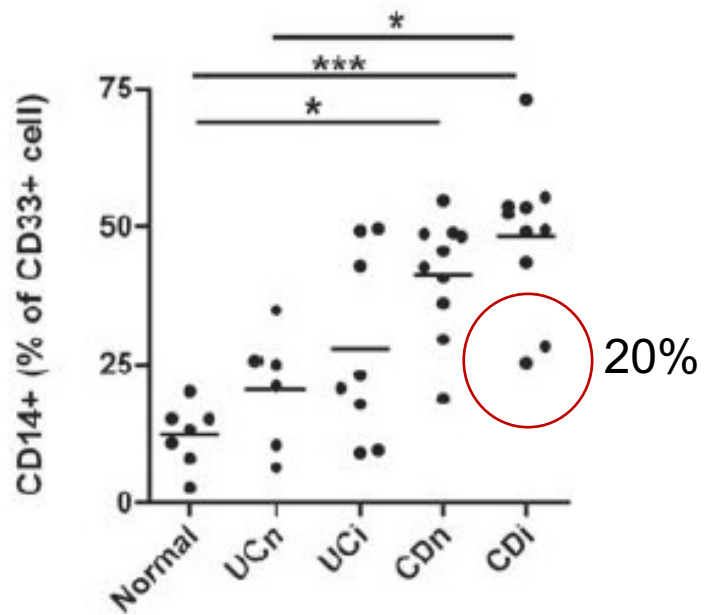


Maul J, Gastroenterology, 2005

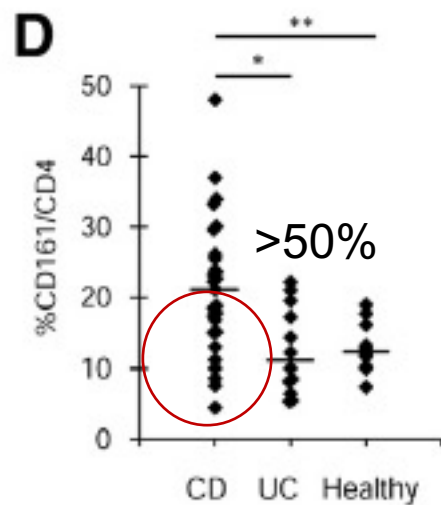
rIL10
Mongersen

Limitations:

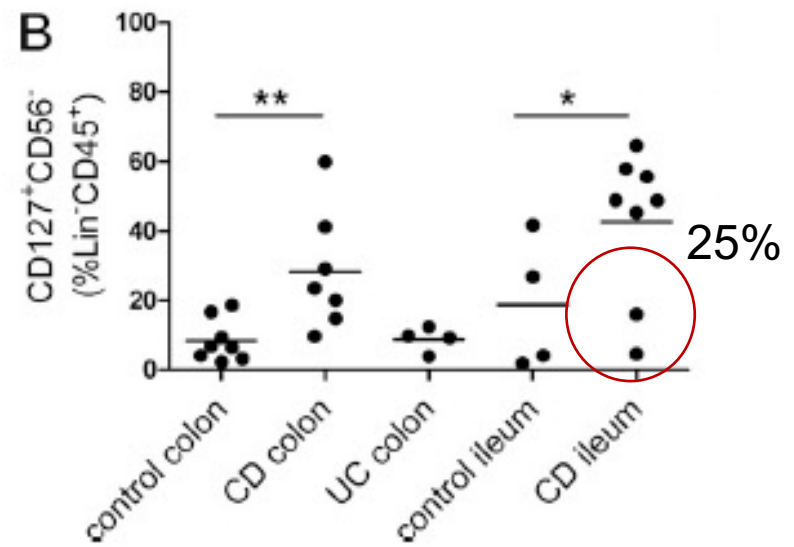
- Different cohorts
- Different methods
- Different cellular definitions
- Different paradigms...



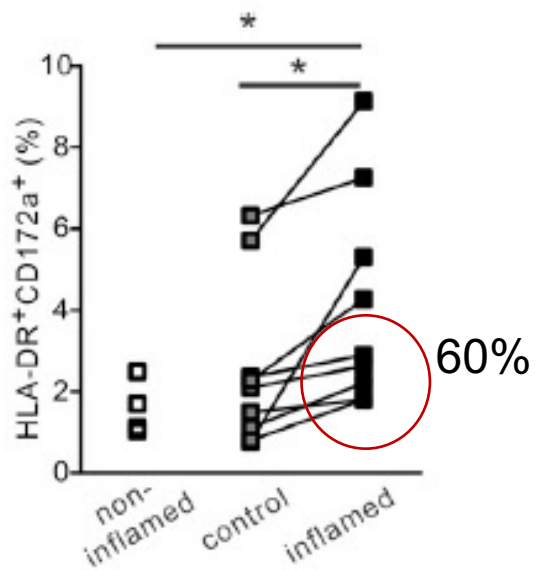
Kamada N, J Clin Invest, 2009



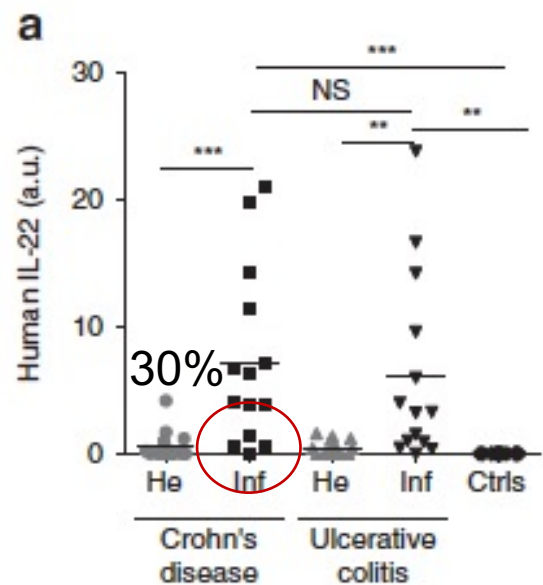
Pariente B, Gastroenterology, 2011



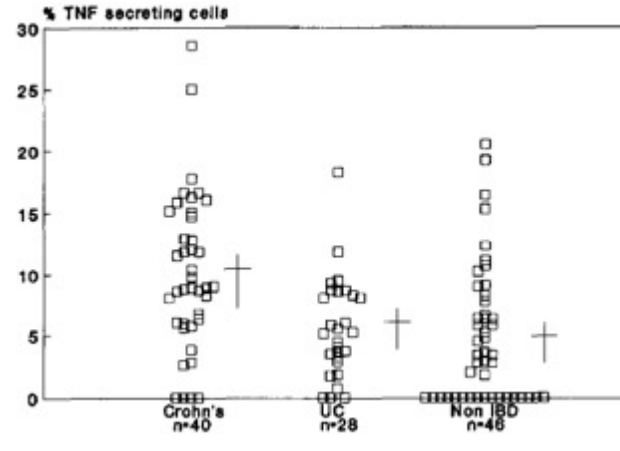
Geremia A, J Exp Med, 2013



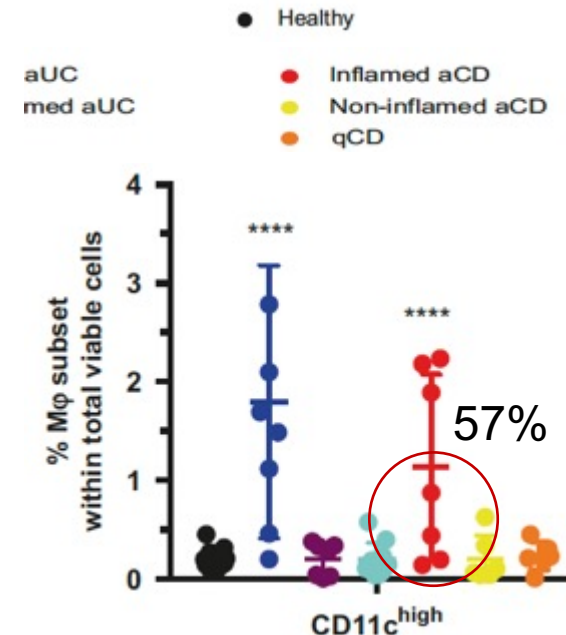
Baba N, J Exp Med, 2013



Martin JC, Mucosal Immunol, 2016



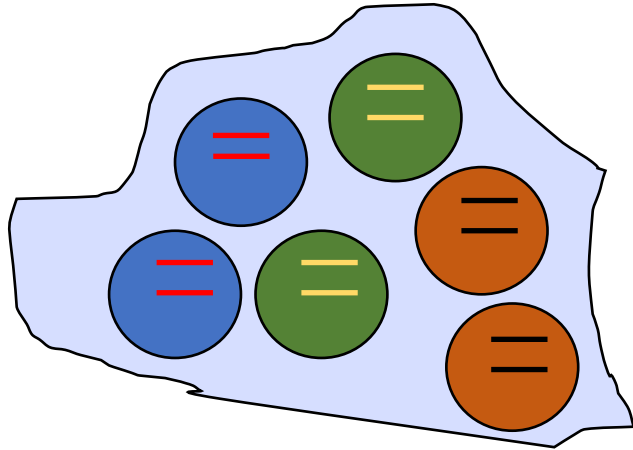
Breese EJ, Gastroenterology, 1994



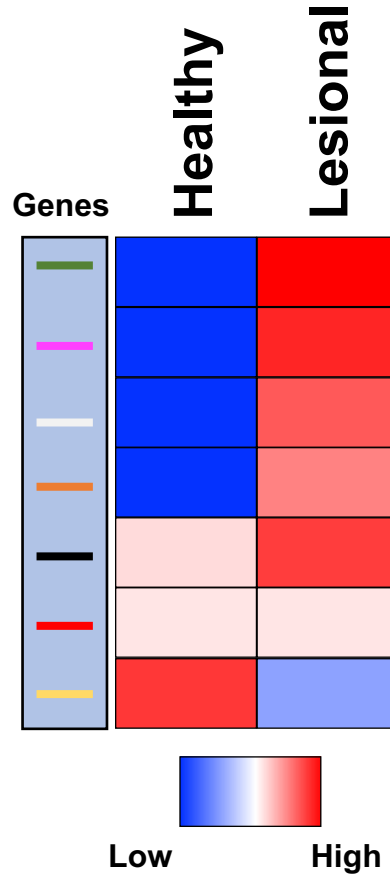
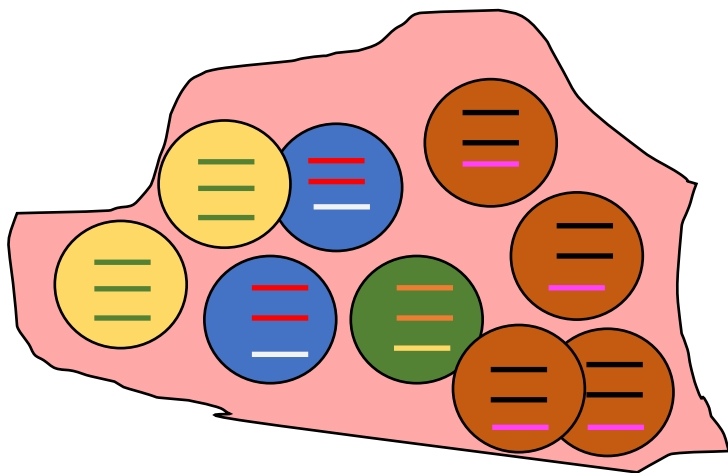
Bernardo D, Mucosal Immunol, 2018

Tissue

Healthy



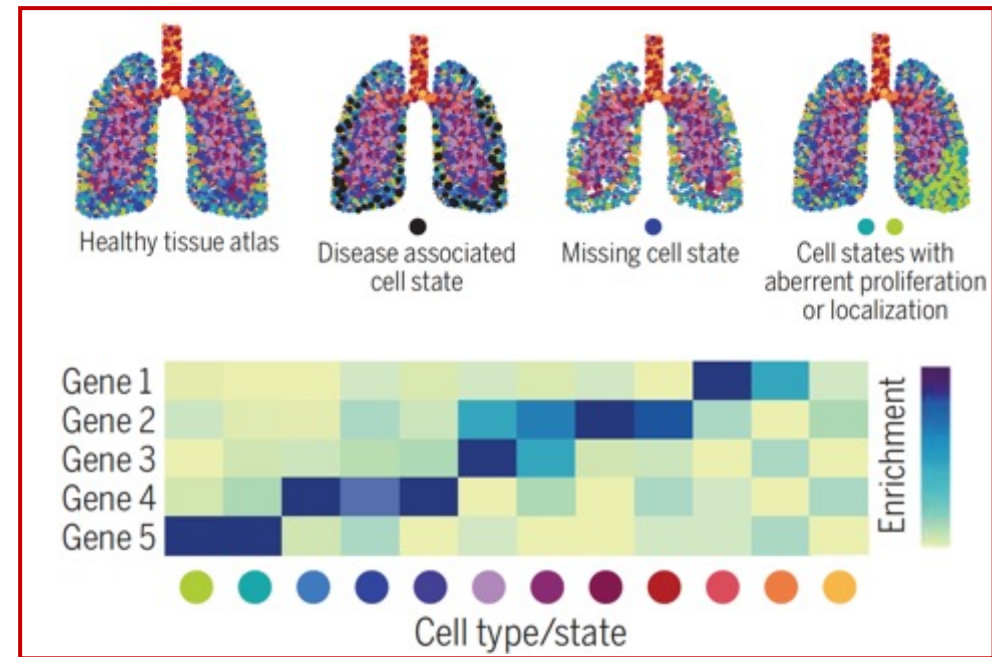
Lesional



Tissue profiling by RNA-seq

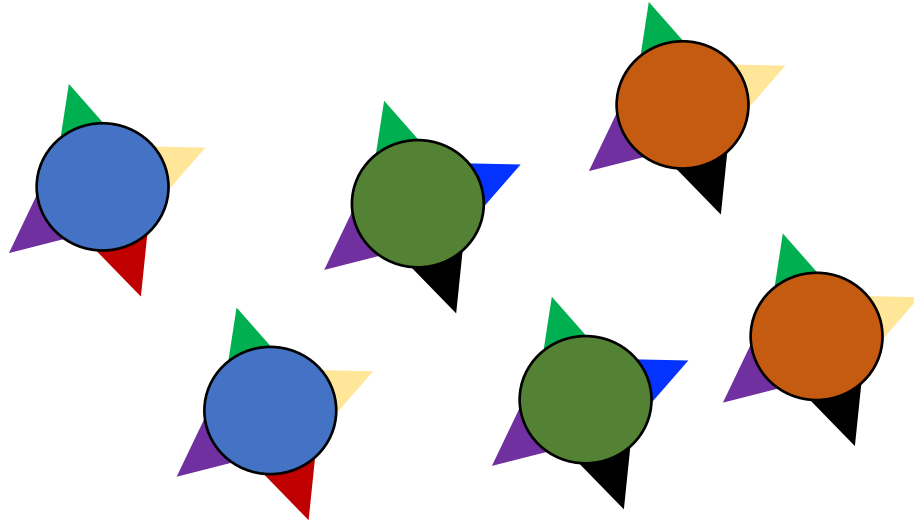
Transcriptomic characterization of healthy and lesional tissues in bulk





How do we connect transcriptomic variations to changes of cellular composition, activation etc...?



Single cell characterization by flow cytometry

Heterogenous suspension of cells to study



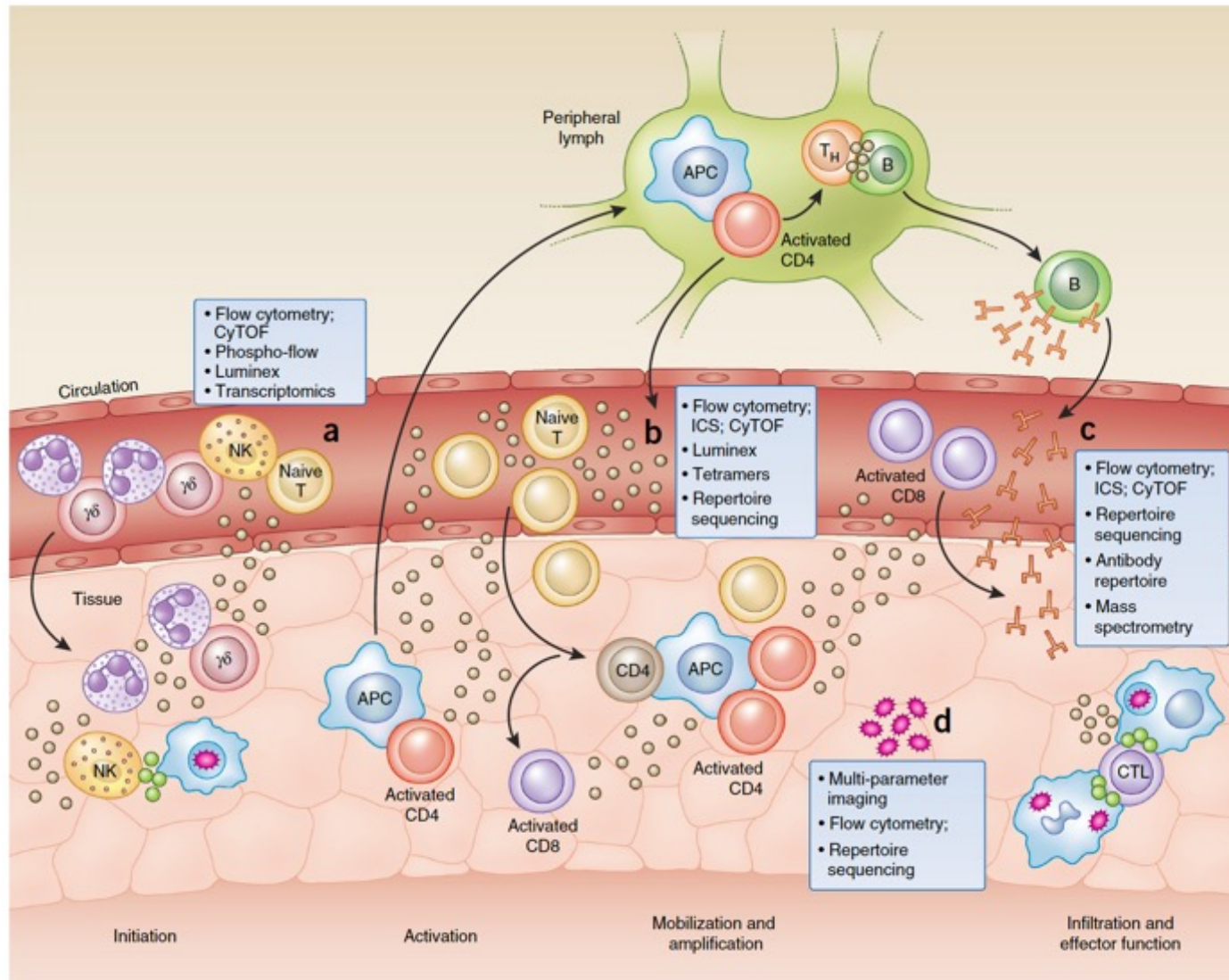
- All cells share the expression of  
-  distinguishes **green** and **orange** from **blue** cells but not **green** from **orange**
-  distinguishes **blue** and **orange** from **green** cells but not **blue** from **orange**
- etc..

Cell sorting to study protein secretion, transcriptome, co-culture with other cells etc...

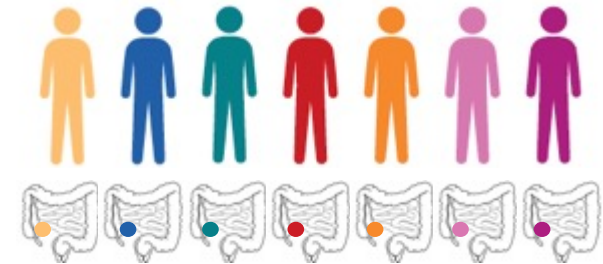
If we only know about the existence of    (design of the Ab panel, availability of Ab, characterization of the protein etc...) **blue** and **orange** cells will not be resolved and will be sorted together

Incorrect conclusions will be brought with regard to **blue/orange** cell biology

New single-cell technologies allow the study of immunopathogenic responses in human tissues at the system level

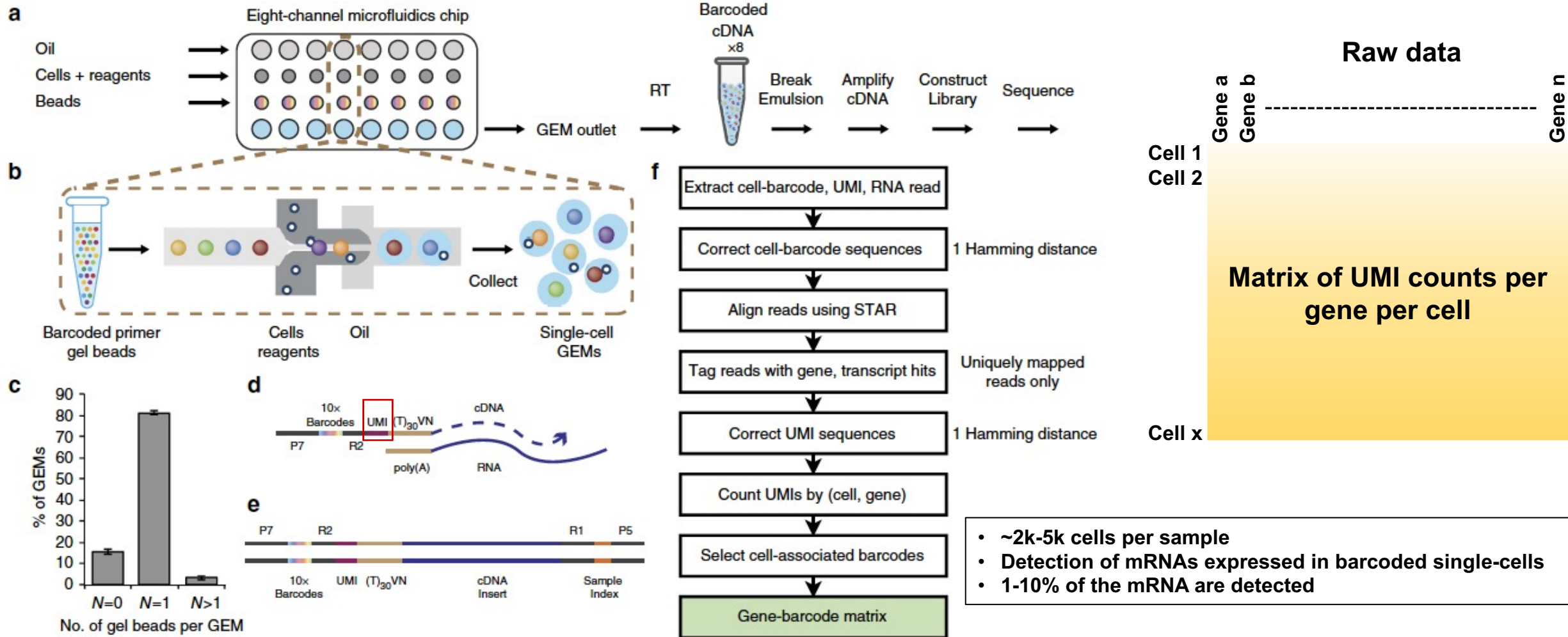


Limited success of immunotherapies to subgroup of patients could relate to heterogenous immunopathogenic responses between subgroups of patients

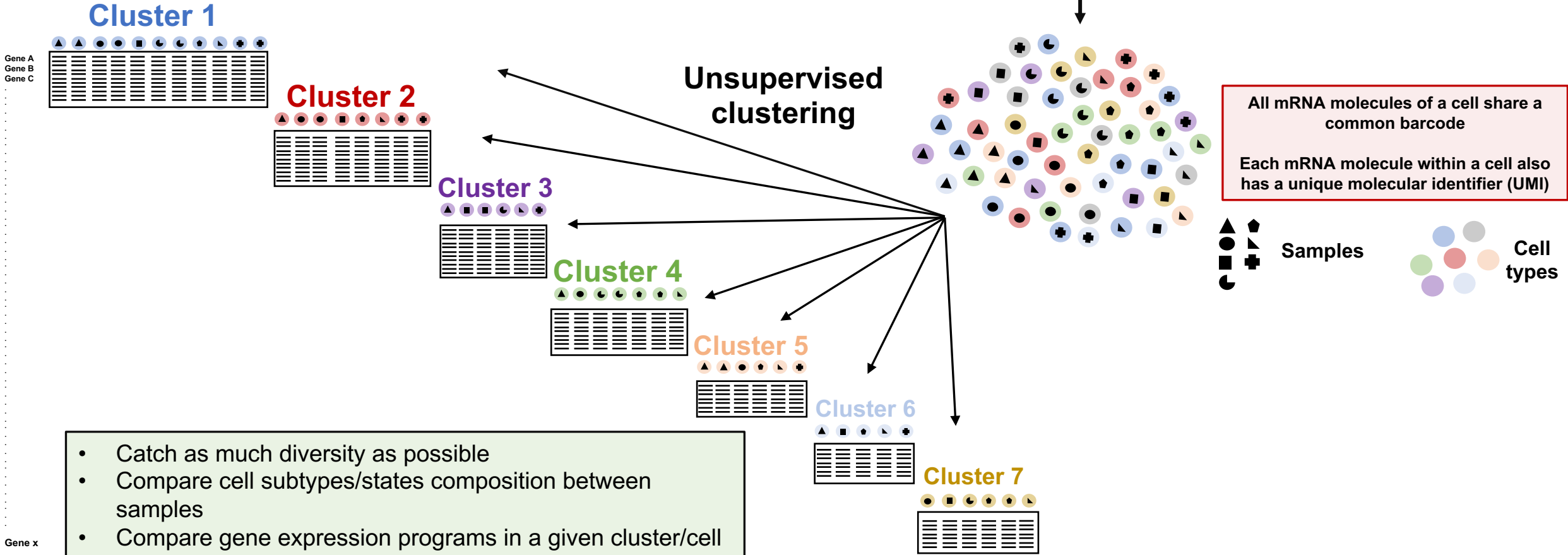
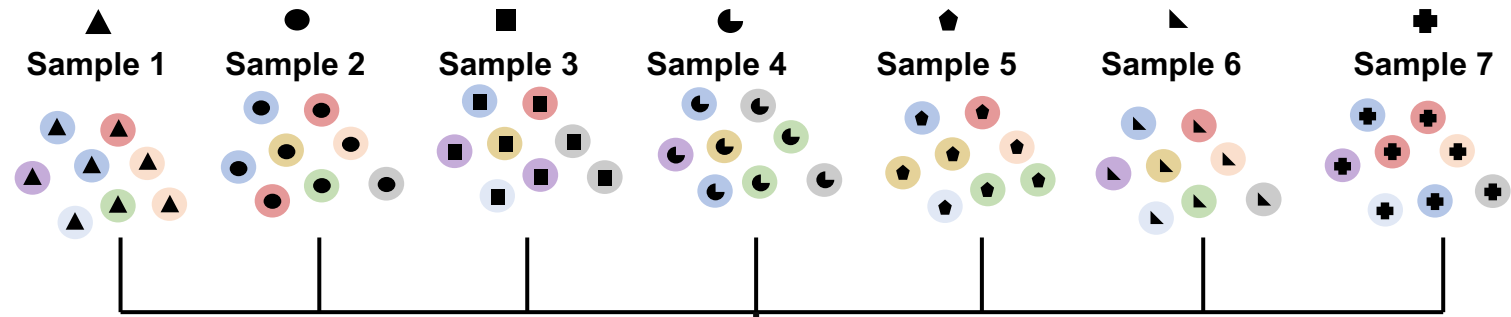


Molecularly defined disease subtypes

Droplet-based single-cell RNA sequencing using the Chromium™ technology (10x Genomics)

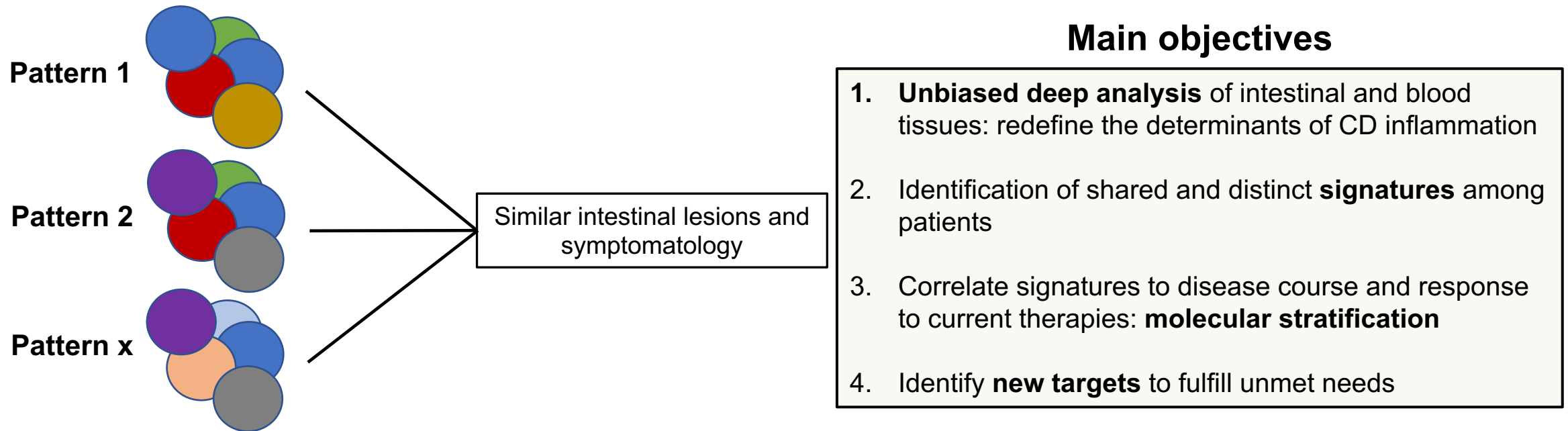


Deciphering cellular heterogeneity within and between multiple samples using scRNAseq

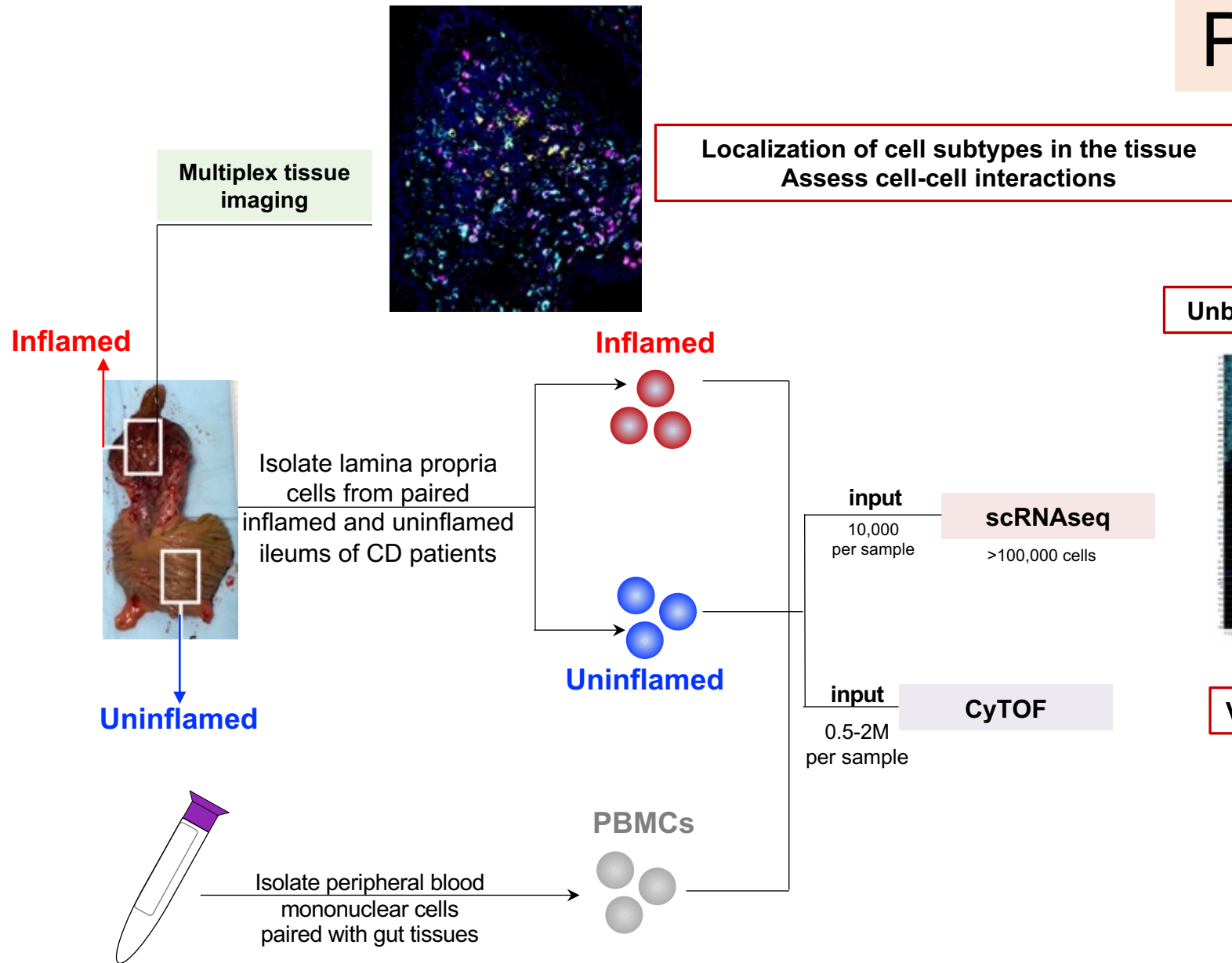


- Catch as much diversity as possible
- Compare cell subtypes/states composition between samples
- Compare gene expression programs in a given cluster/cell subtype between cell from multiple origin

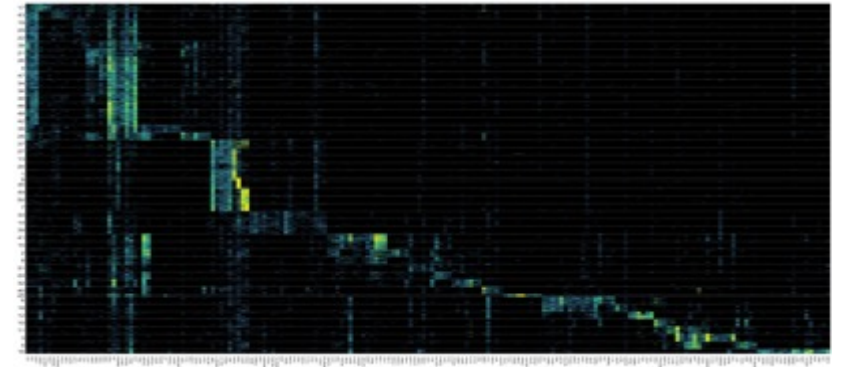
Unraveling ileum CD heterogeneity through high dimensional analysis at the single cell resolution



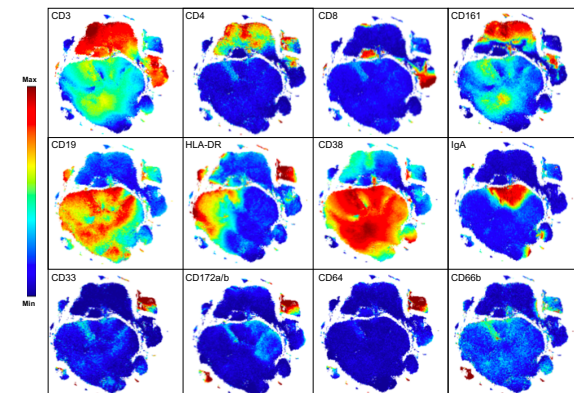
Pipeline of the study



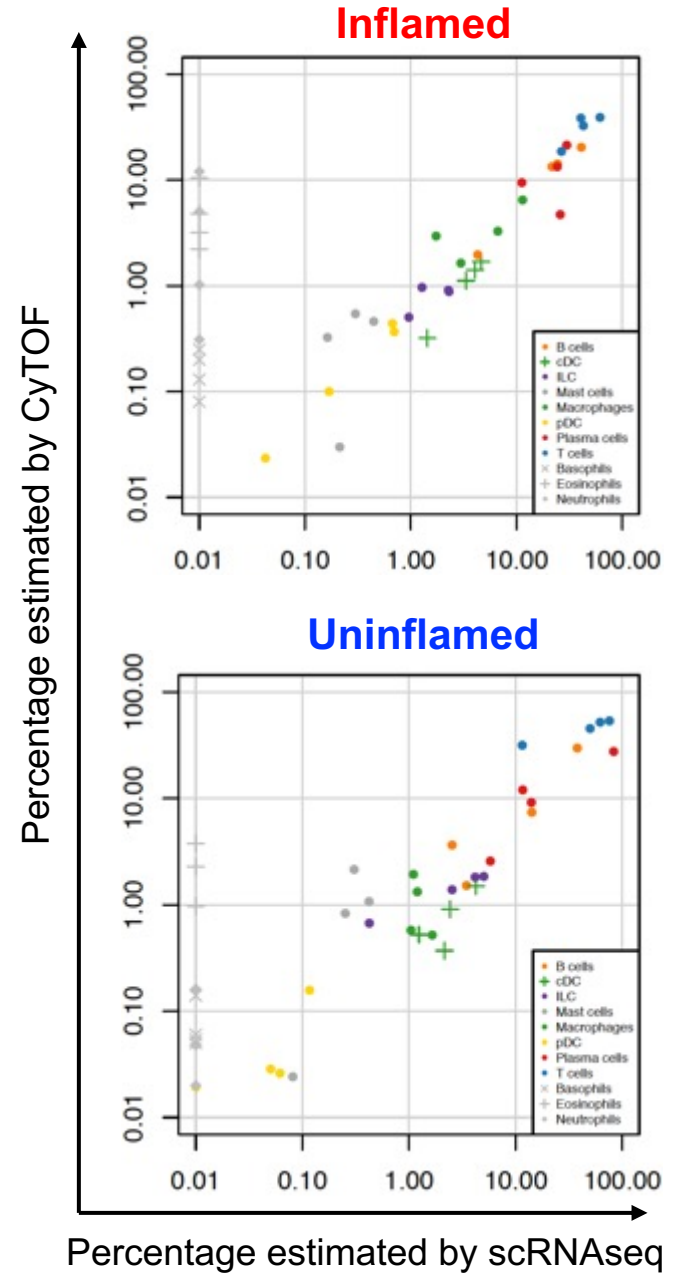
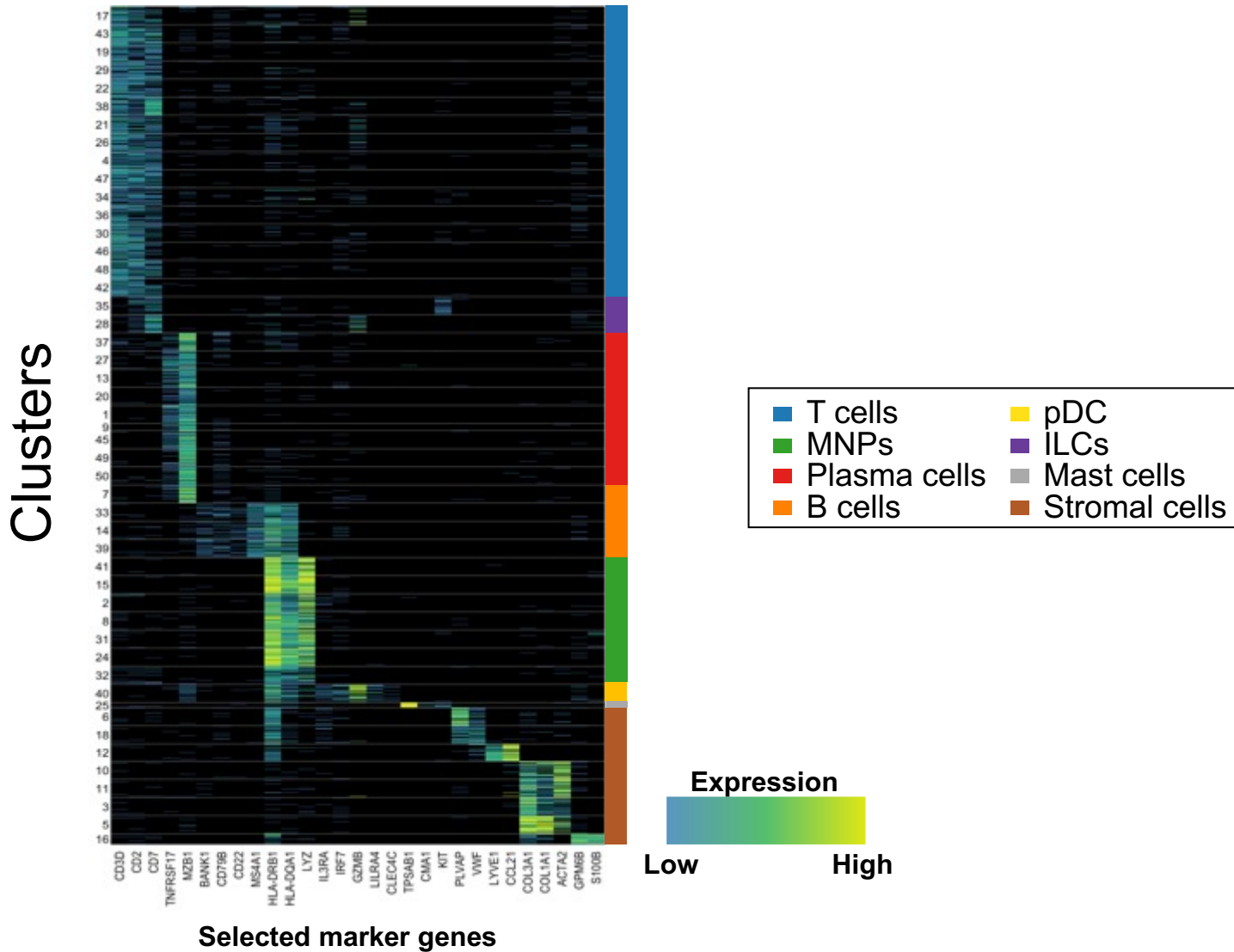
Unbiased deep characterization of CD lamina propria cells



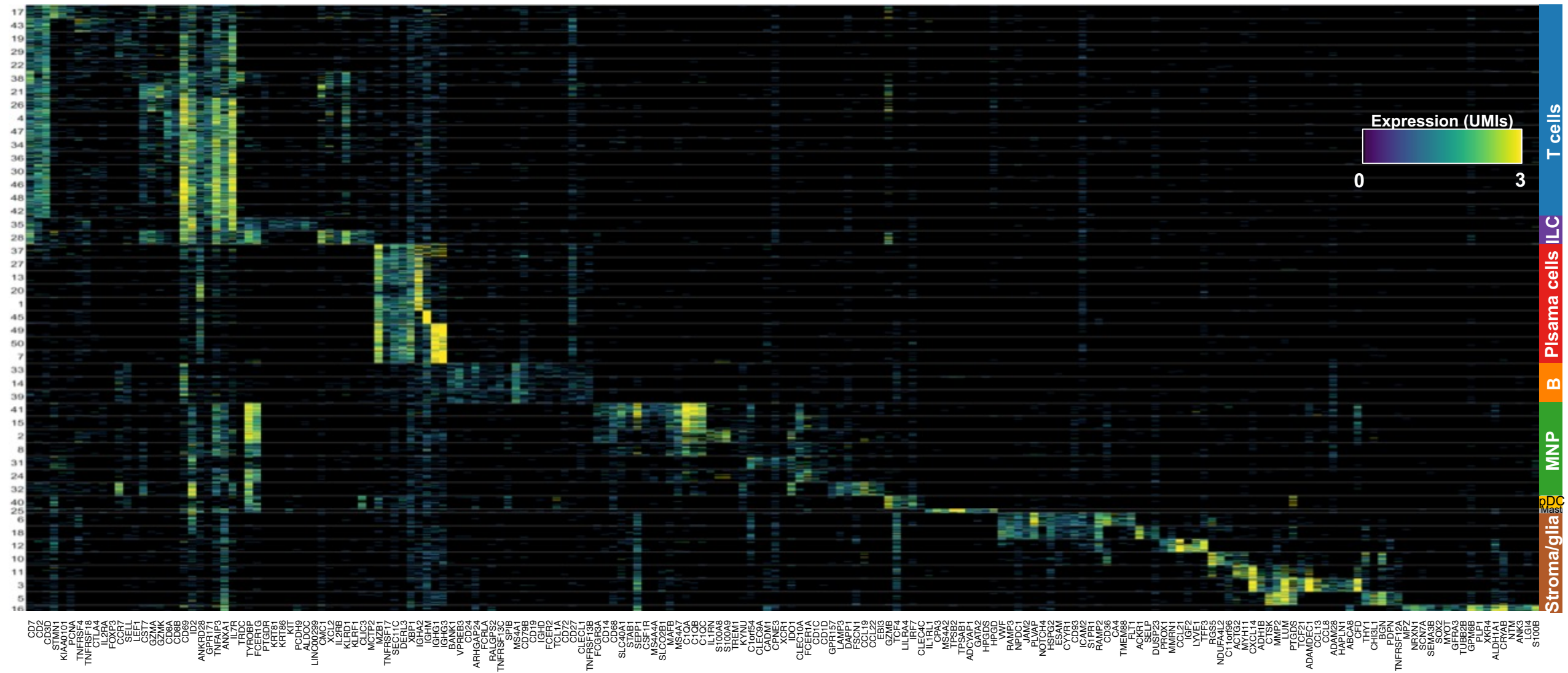
Validation of transcriptomic data at the protein level



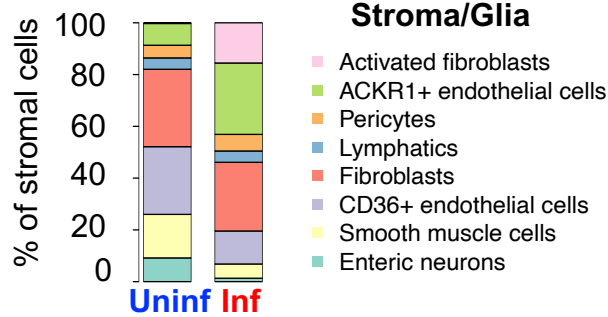
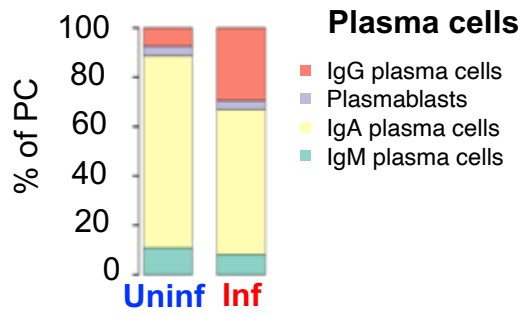
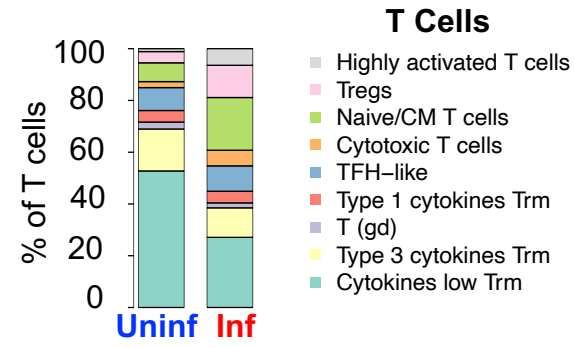
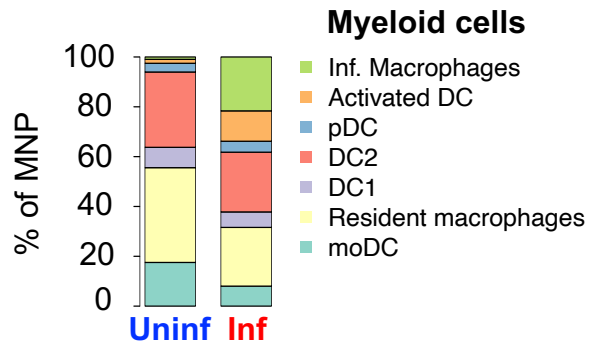
Joint clustering analysis revealed 47 clusters accounting for 8 major cellular compartments



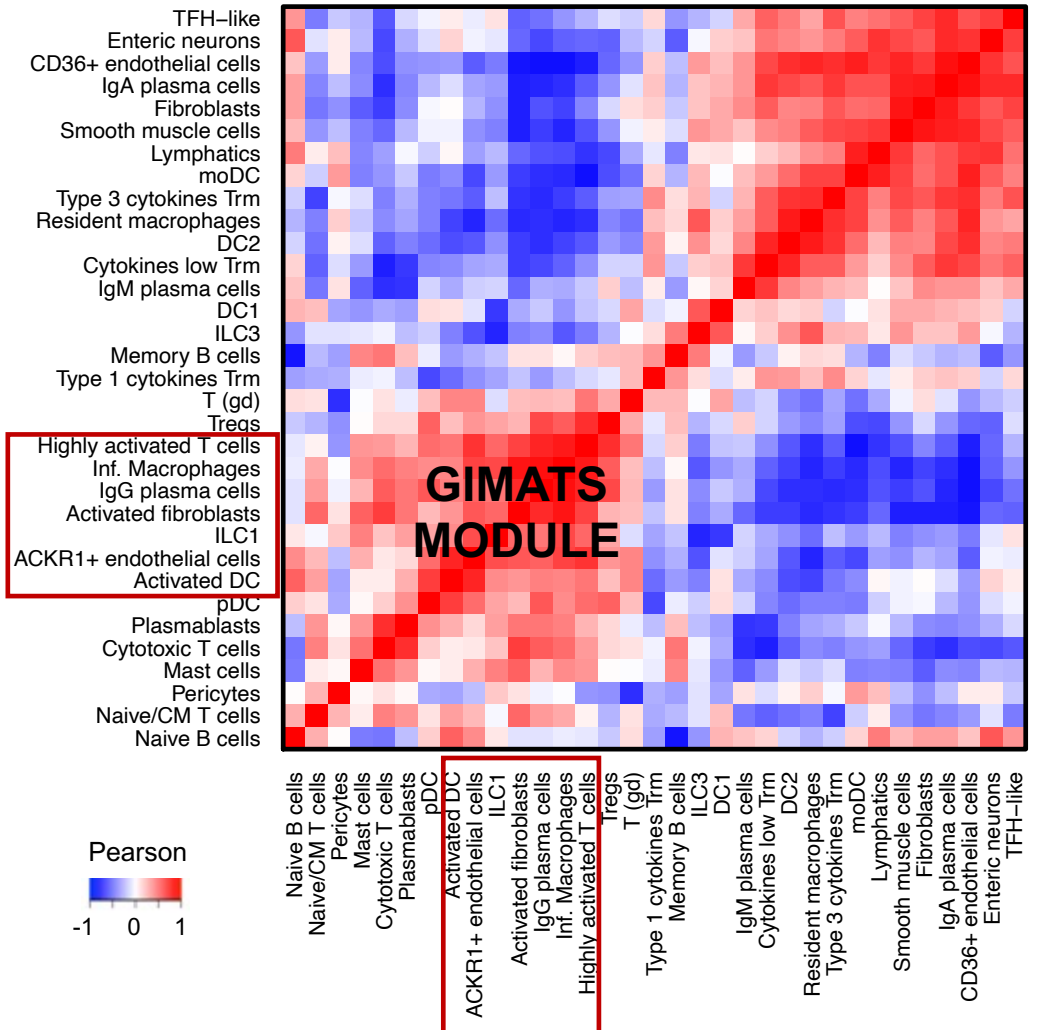
Remarkable transcriptomic heterogeneity exists within 8 major cellular compartments



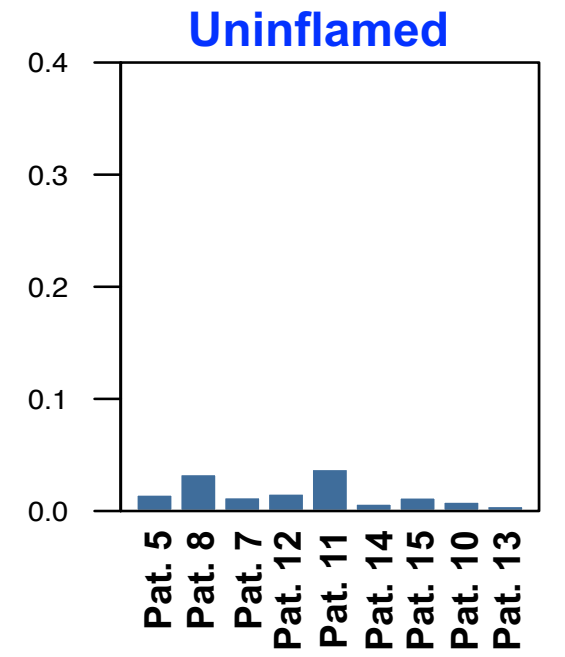
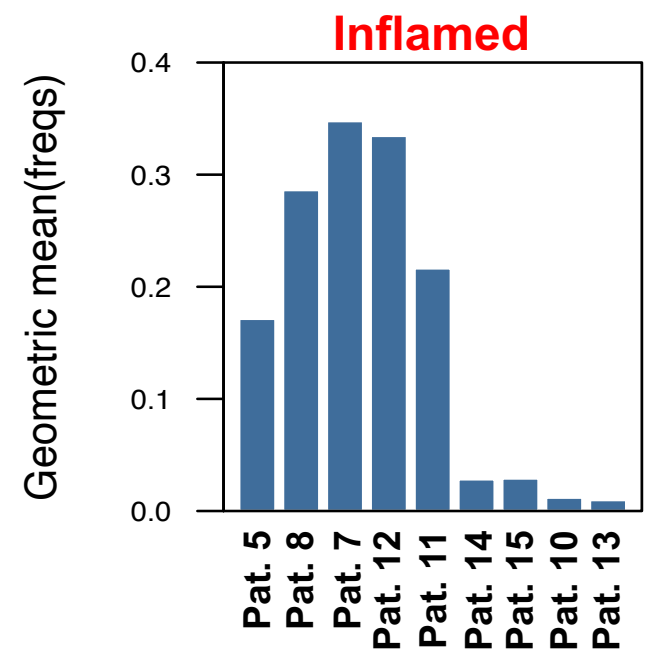
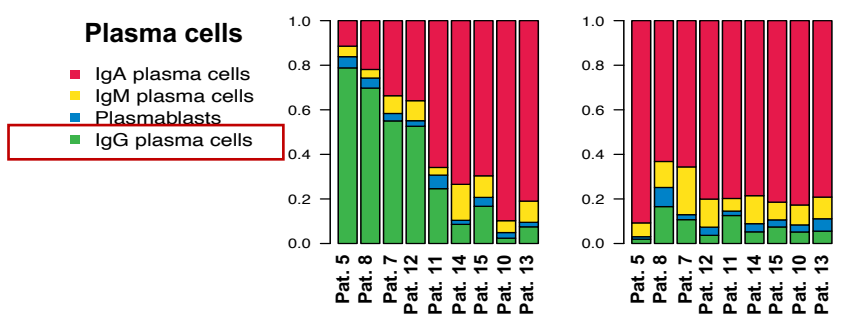
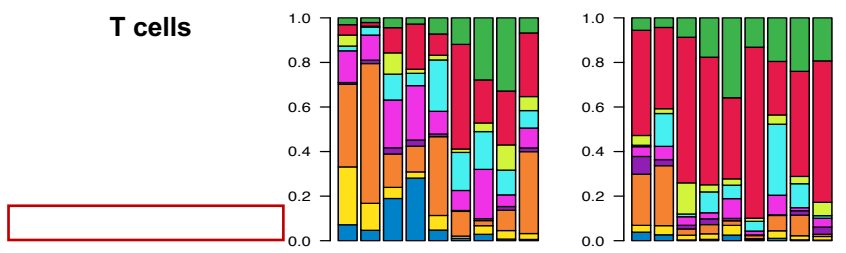
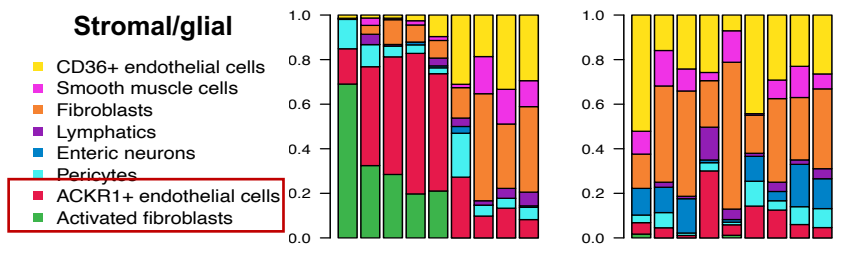
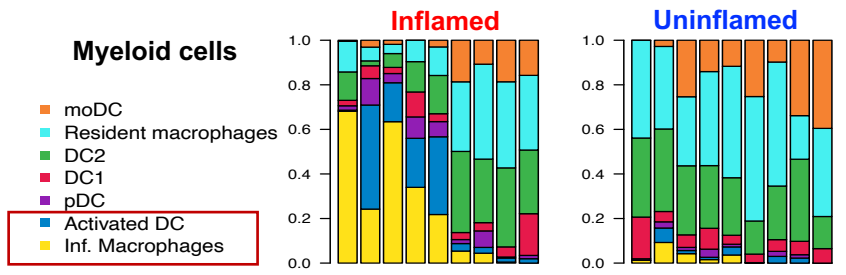
The GIMATS module in inflamed ileums



Correlation between cell subtypes frequencies in inflamed ileums

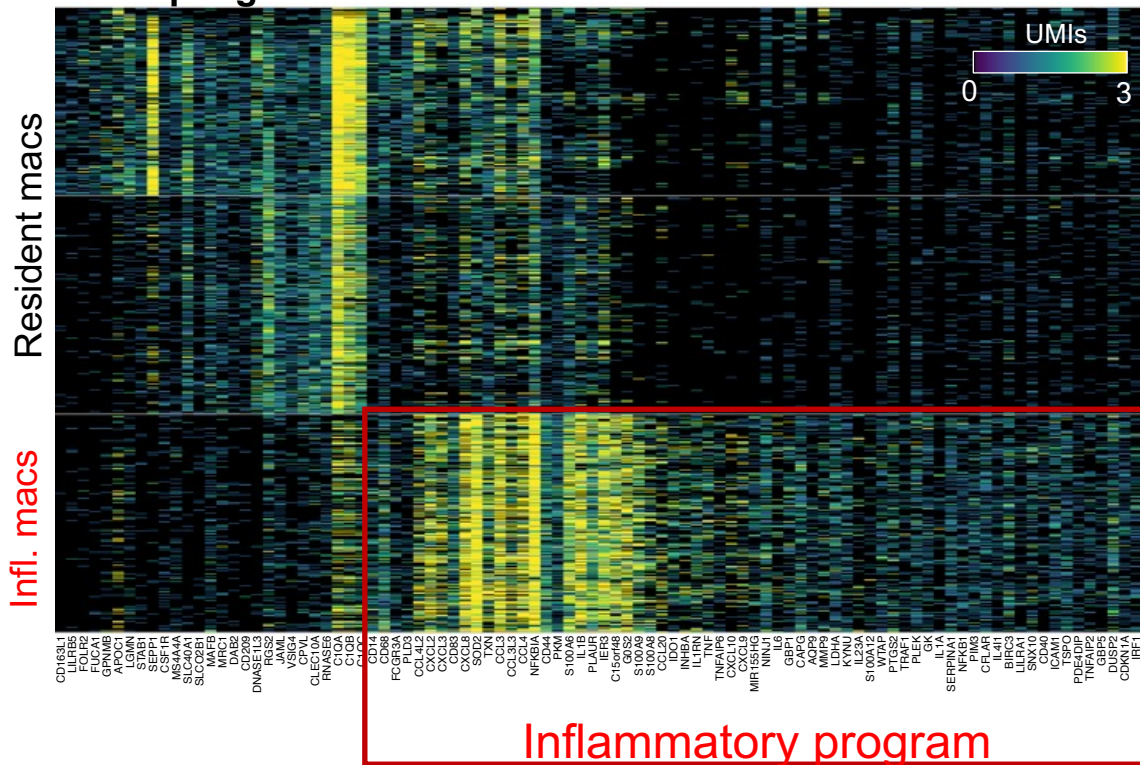


The GIMATS module is enriched in inflamed ileums of a subgroup of patients

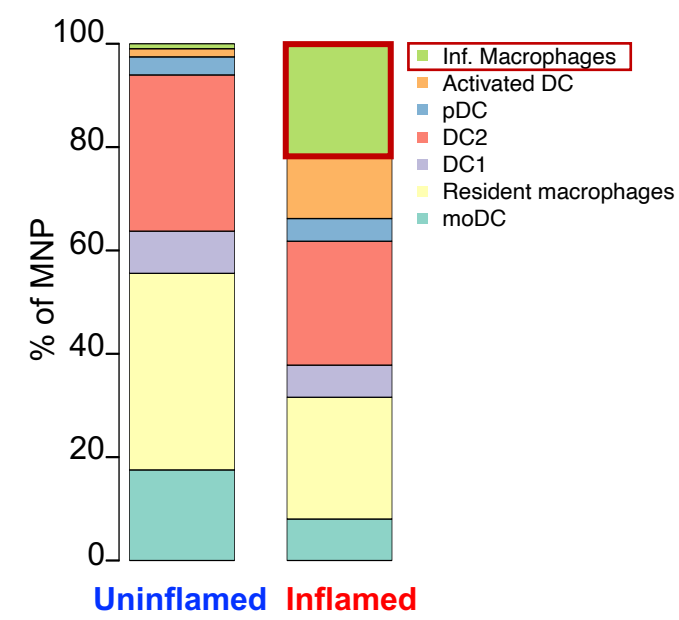


CD14⁺ CD68⁺ CD206⁻ inflammatory macrophages accumulate in CD inflamed ileums

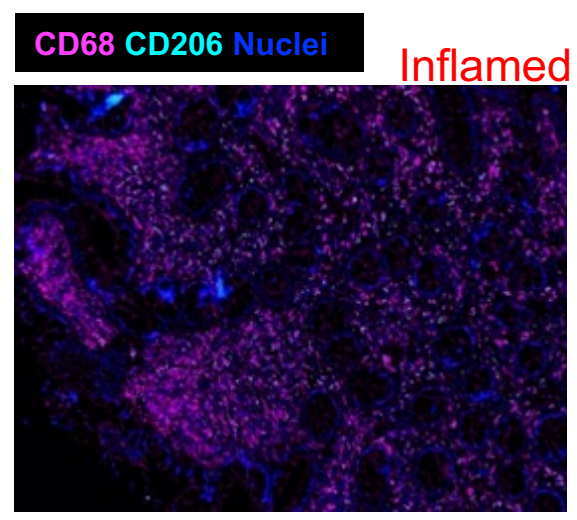
Macrophages



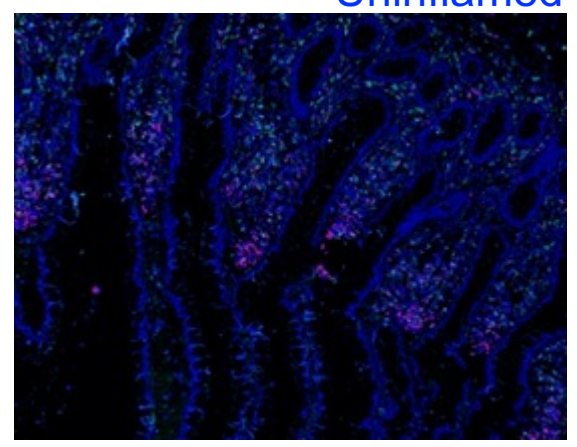
scRNAseq



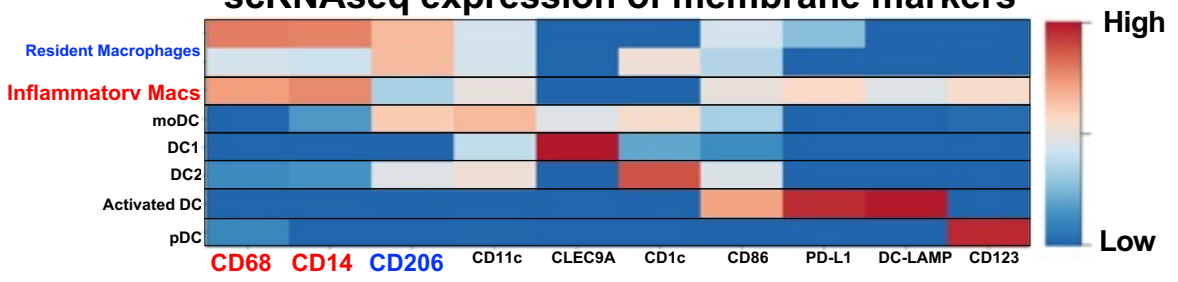
MICSSS



Uninfamed

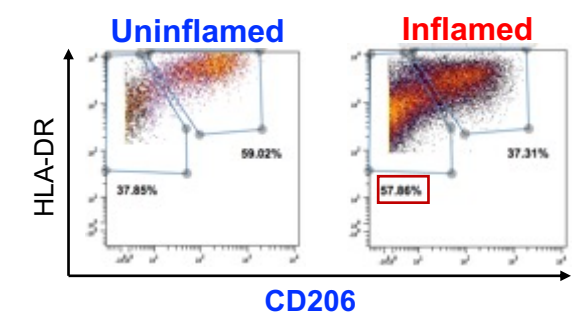


scRNAseq expression of membrane markers



CyTOF

Gated on CD14⁺ Macrophages



CD68⁺ CD206⁻ infl.macs accumulate in the inflamed lamina propria of module-enriched patients

Patient 7

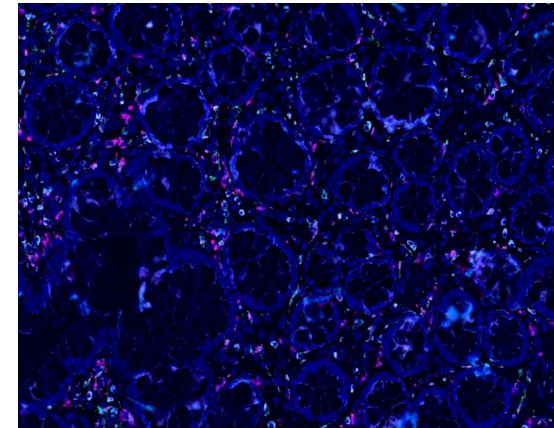
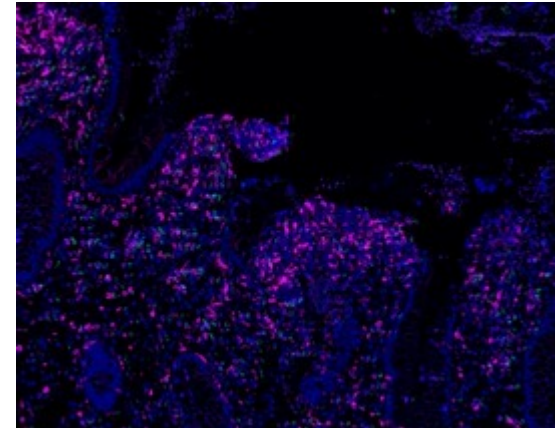
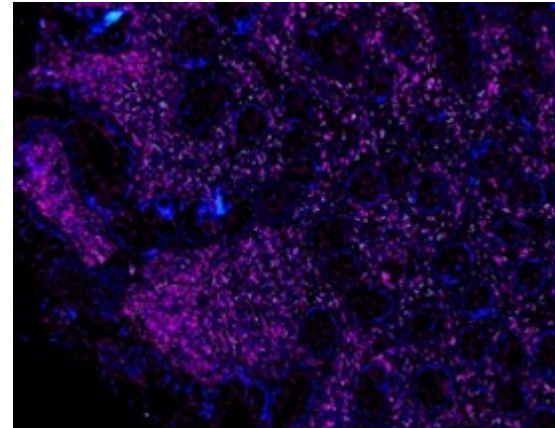
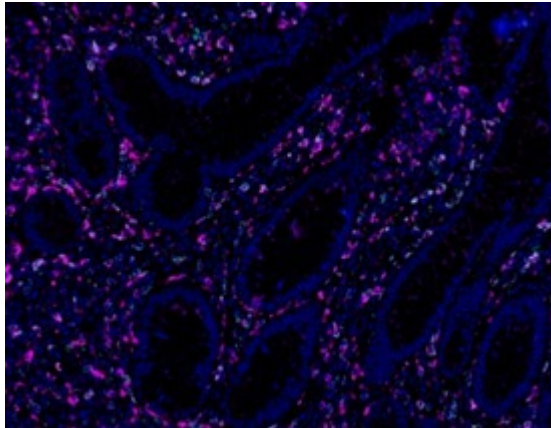
Patient 11

Patient 12

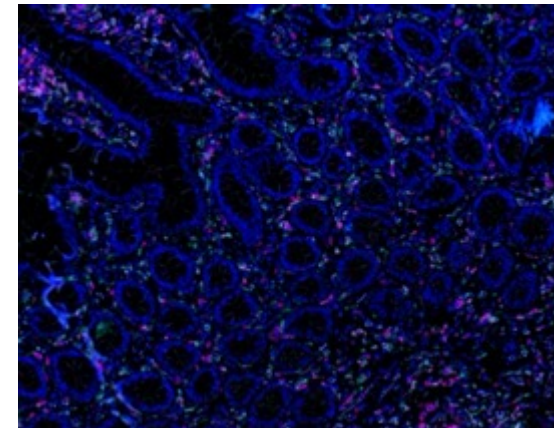
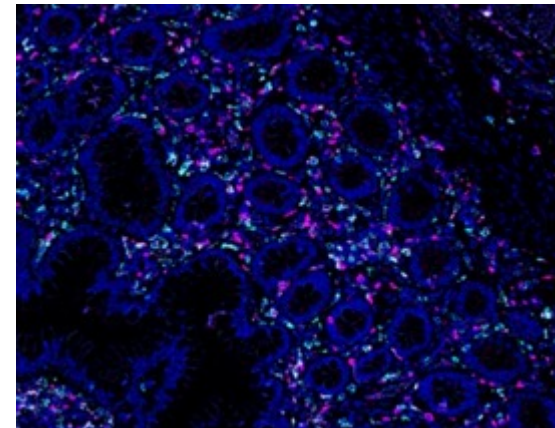
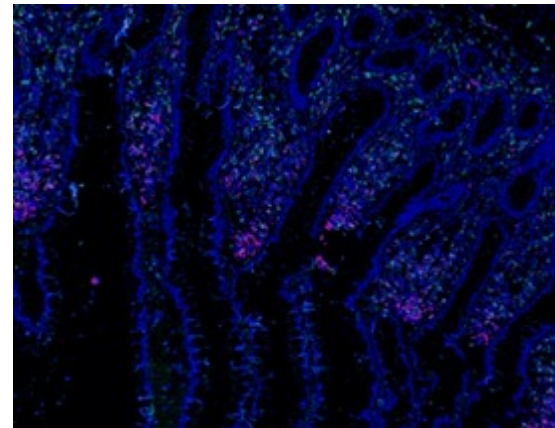
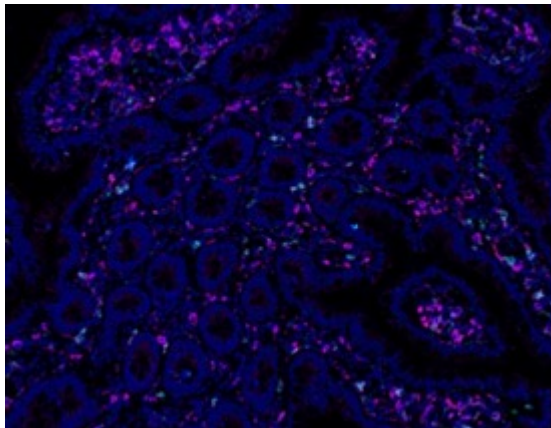
Patient 10

CD68
CD206
Nuclei

Inflamed



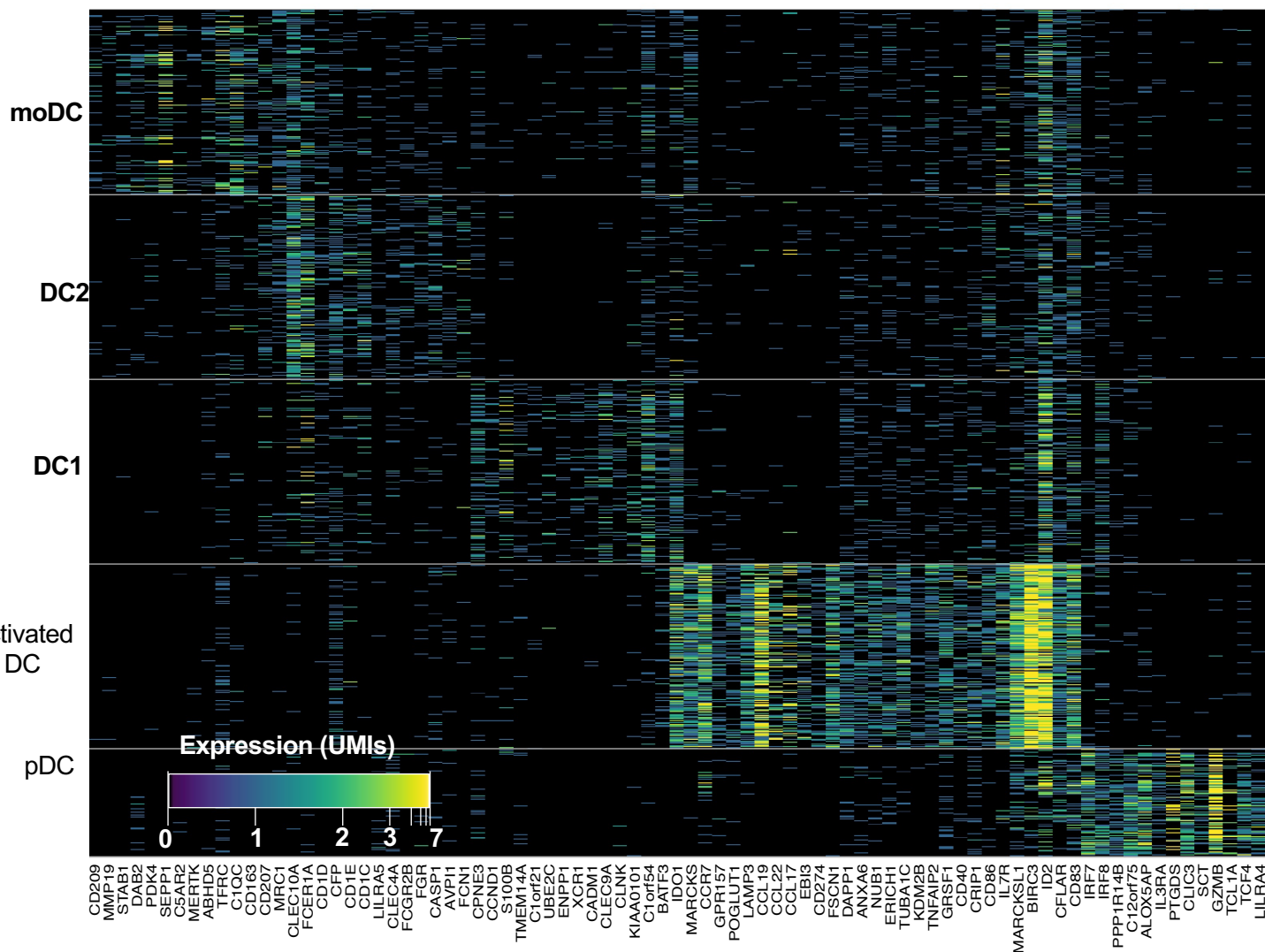
Uninflamed



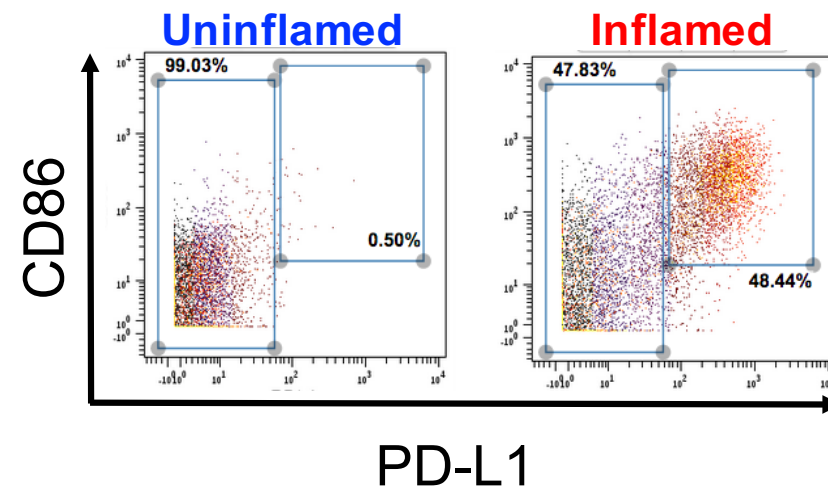
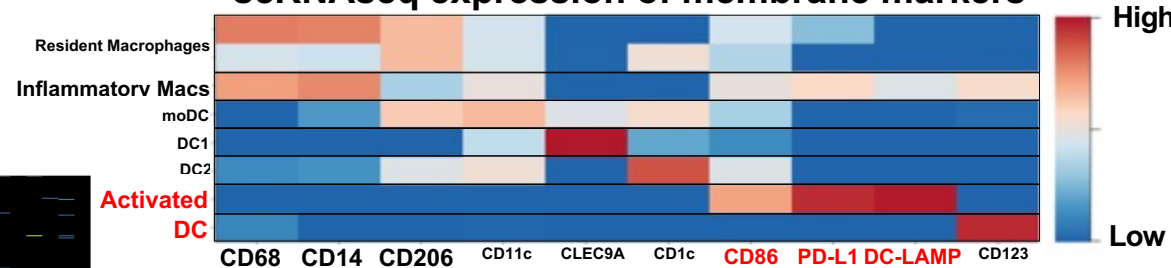
Patients enriched for the module

Patient not enriched for the module

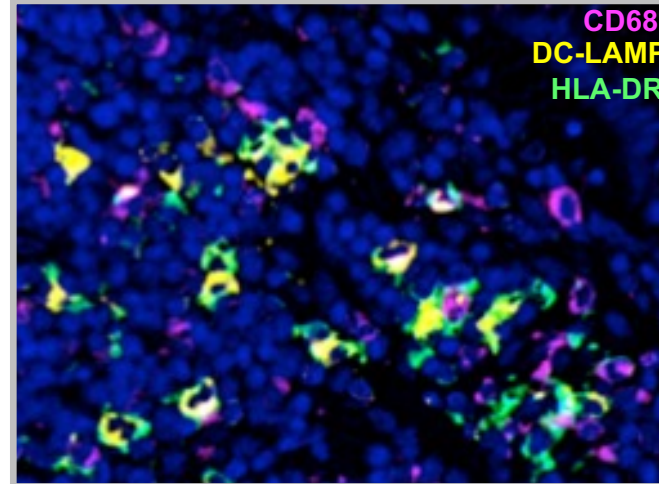
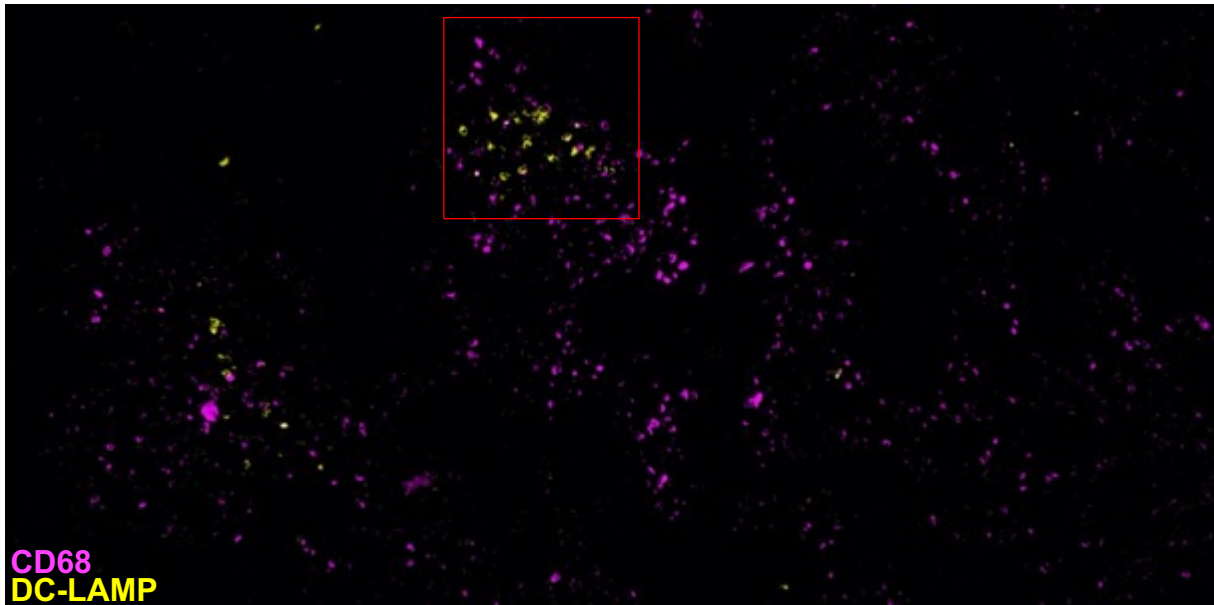
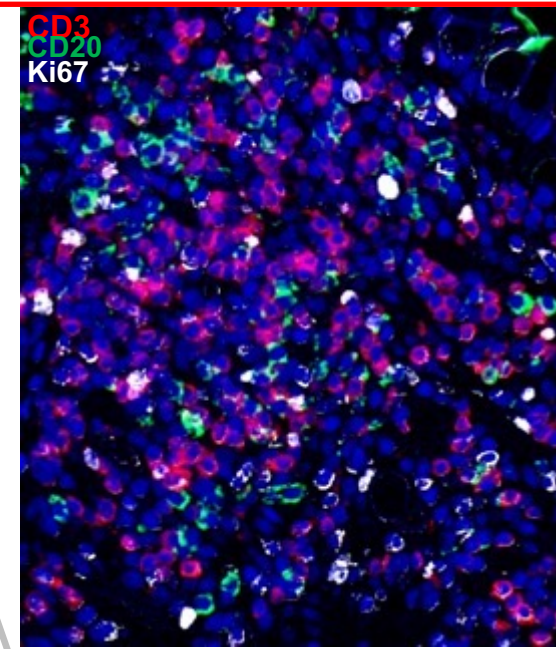
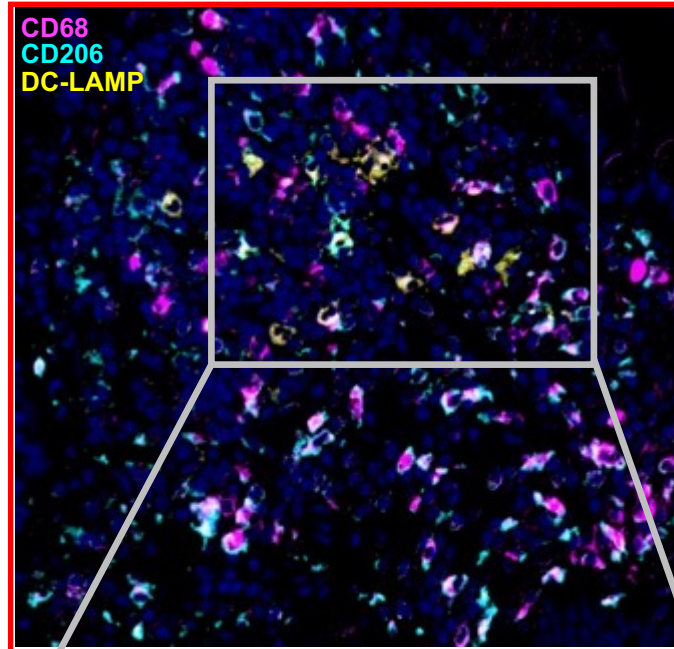
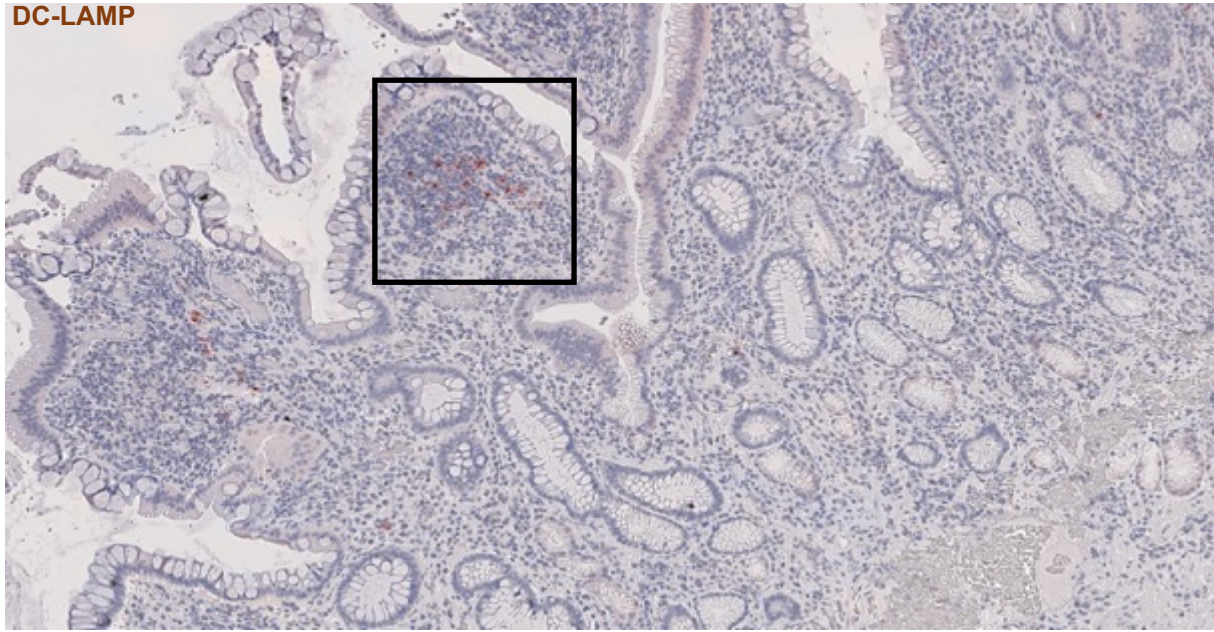
Dendritic cells



scRNAseq expression of membrane markers



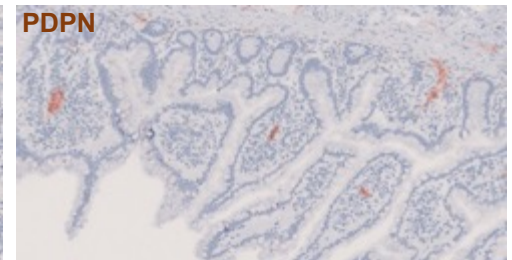
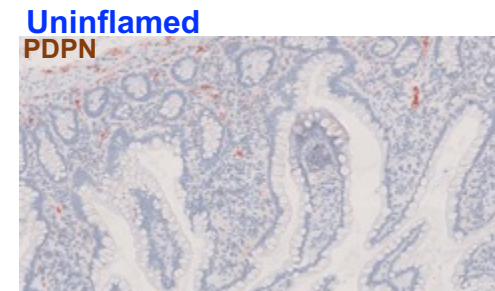
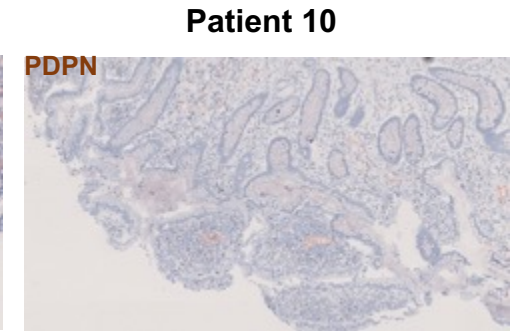
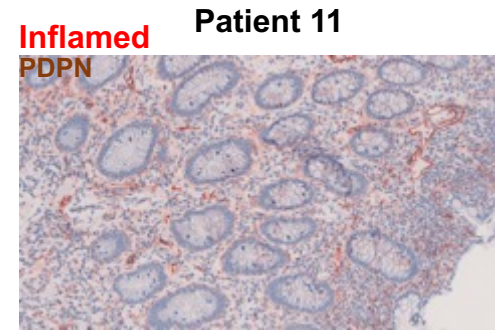
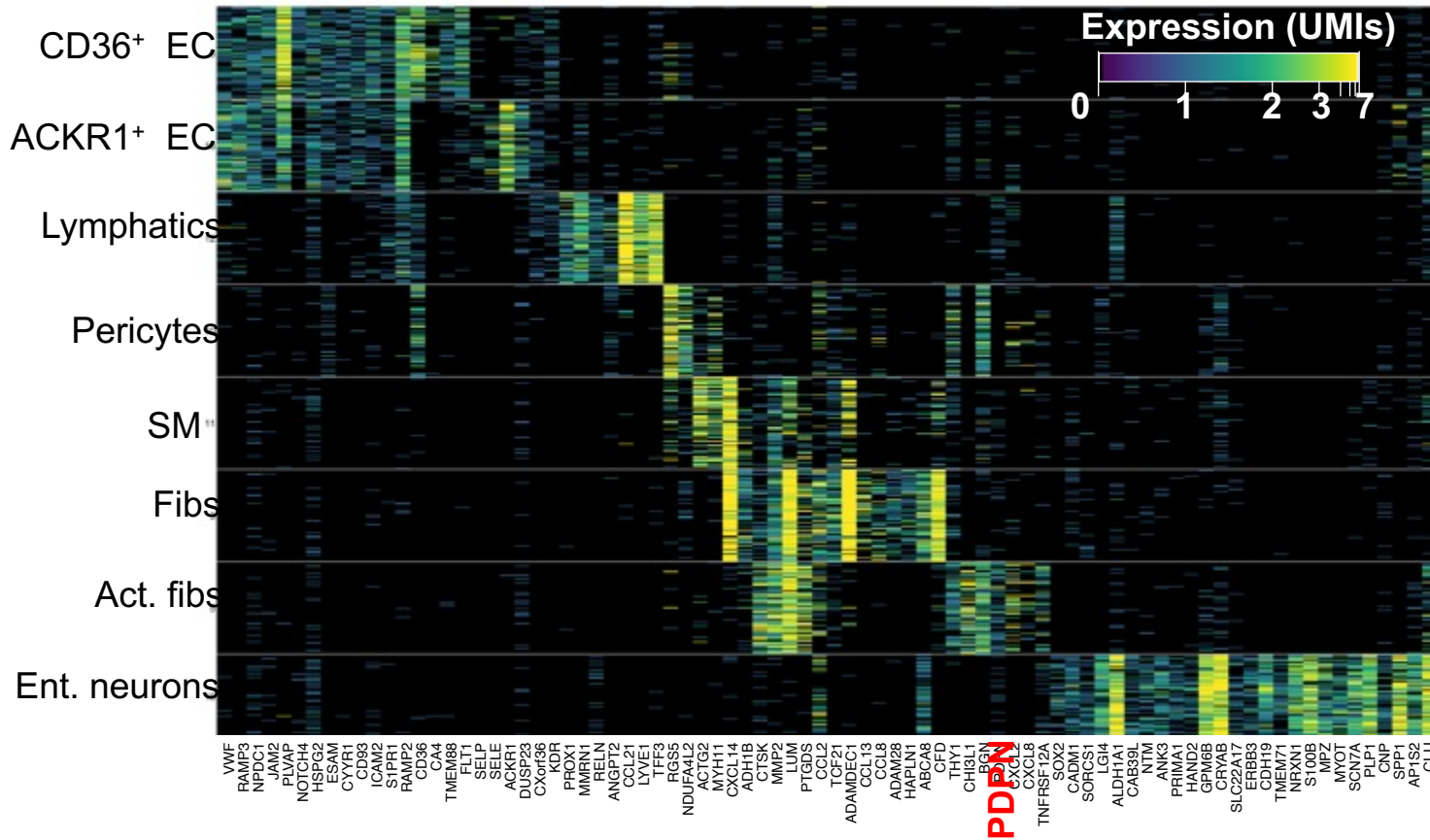
CD68⁻ DC-LAMP⁺ HLA-DR⁺ activated DC in the inflamed lamina propria of module-enriched patients



Activated DC are present in lymphocyte aggregates of T and B cells

PDPN⁺ activated fibroblasts are detected in the lamina propria of patients enriched for the module

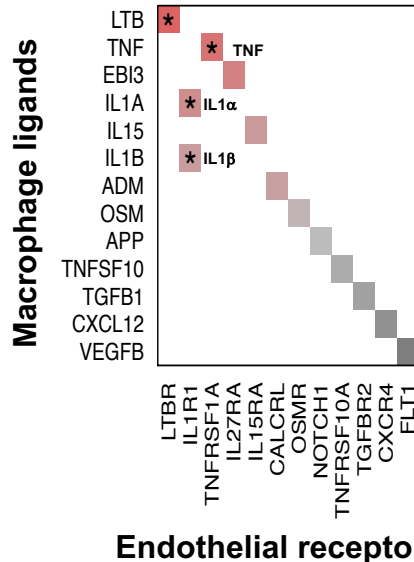
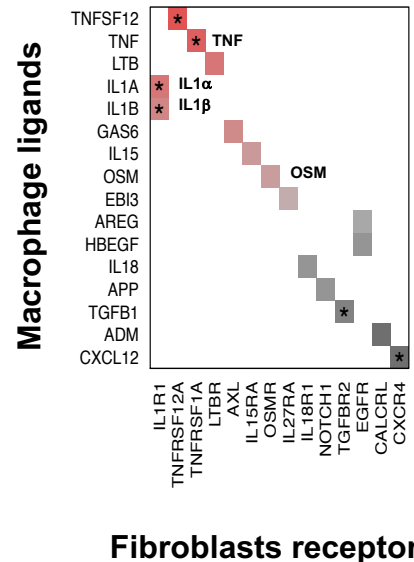
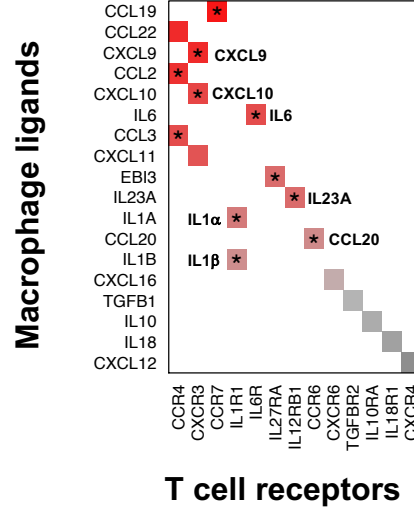
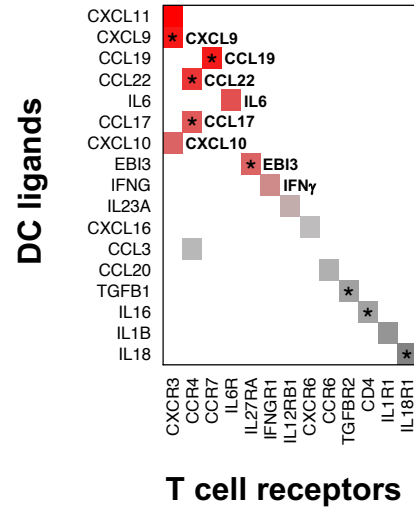
Stromal cells



Not enriched for the module

Monocyte-derived inflammatory macrophages organize pathogenic stromal and T cell responses in inflamed ileums

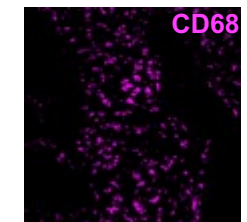
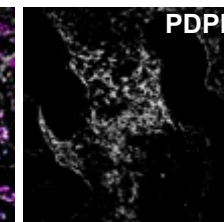
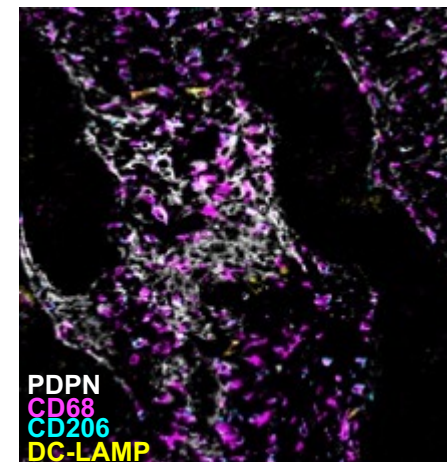
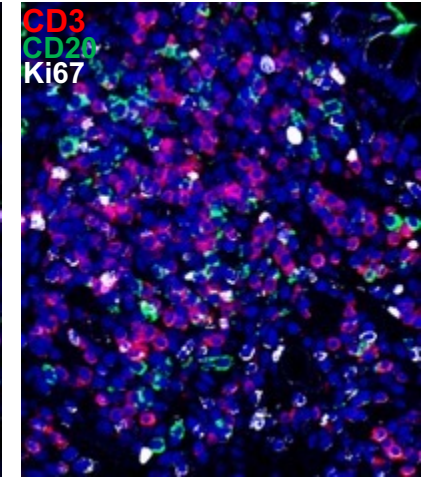
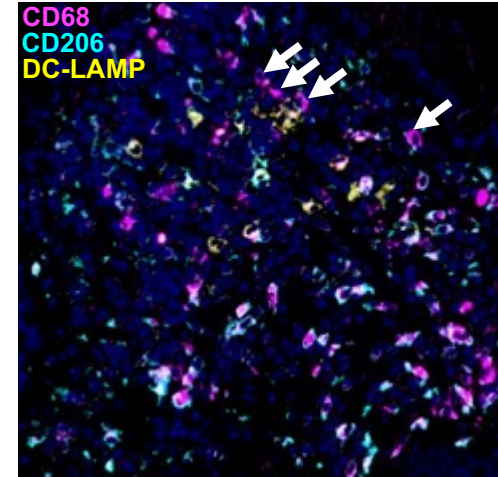
Network analysis



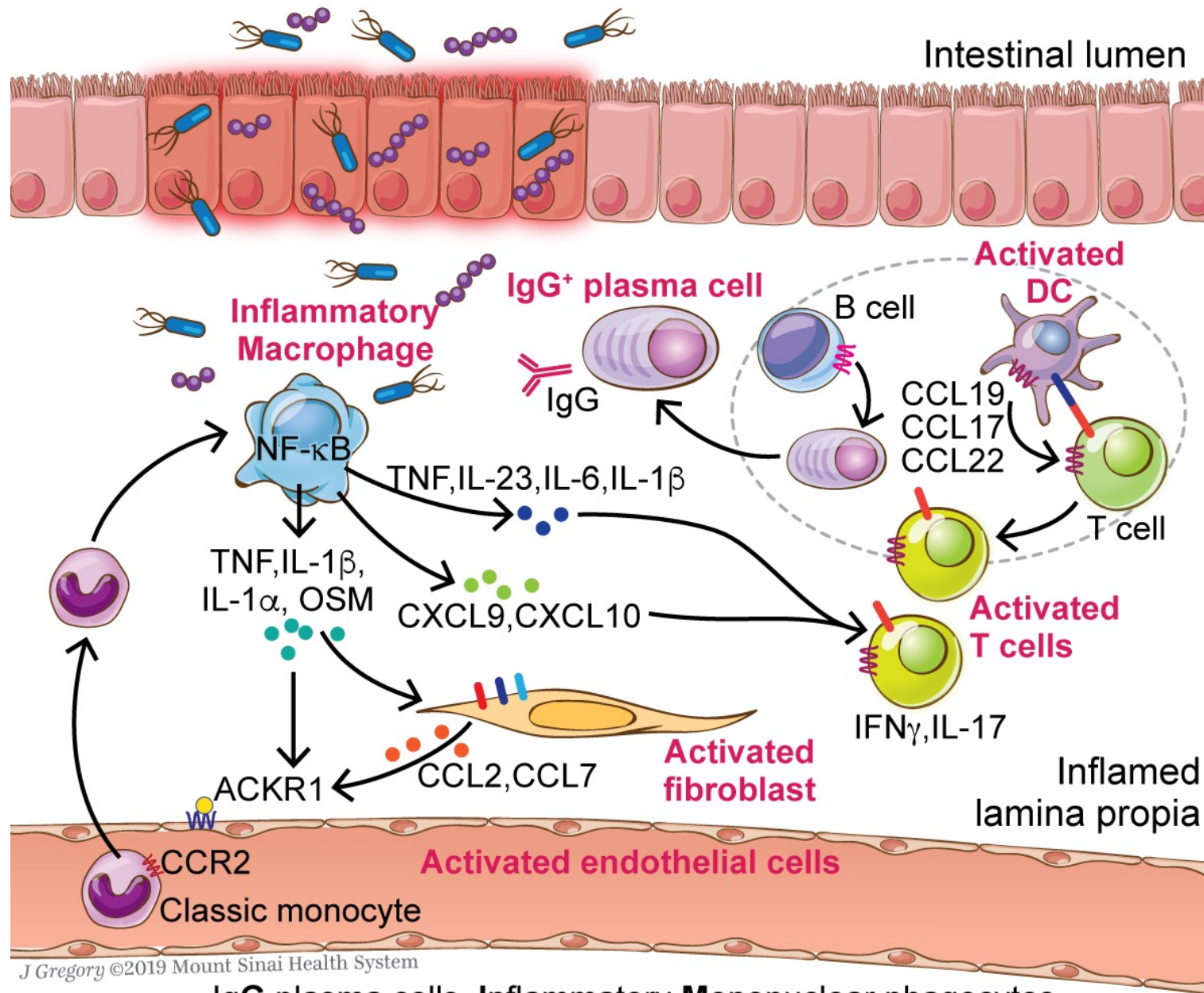
Log₂ FC pair intensity

GIMAT^{low} -2

+2 GIMAT^{high}



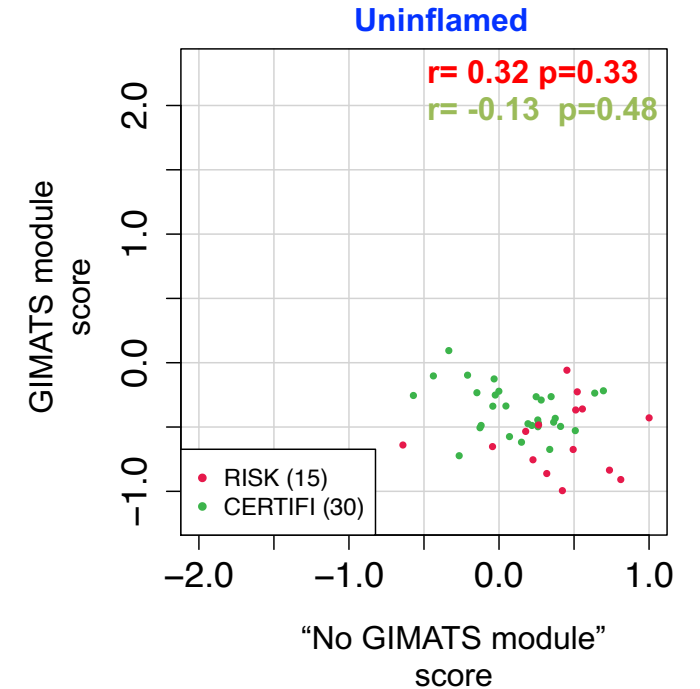
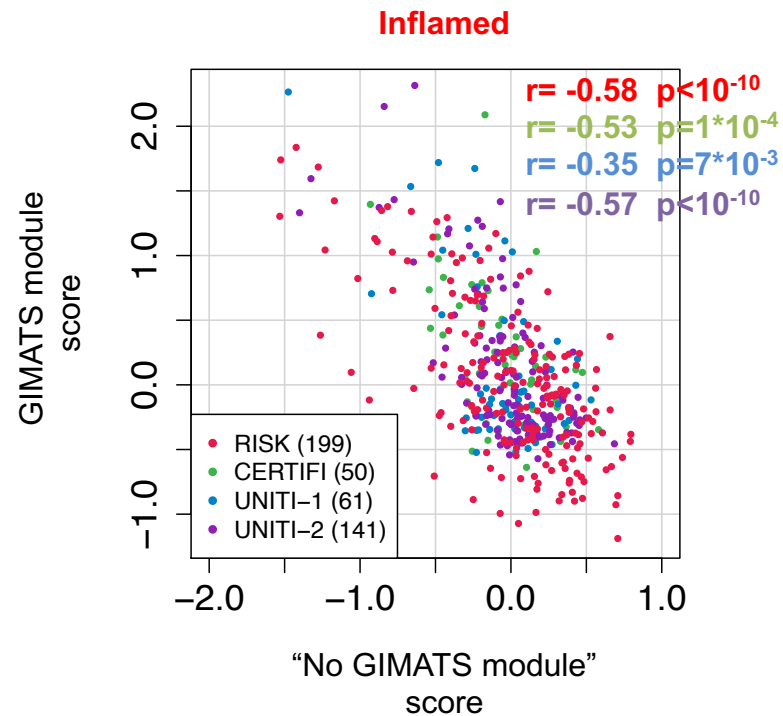
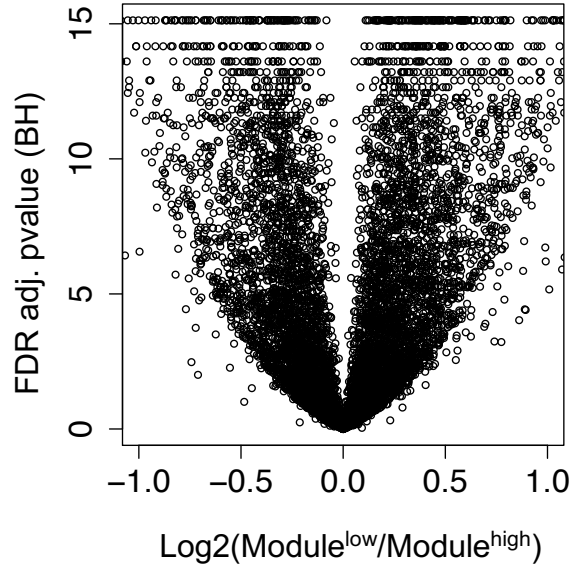
GIMATS module



J Gregory ©2019 Mount Sinai Health System

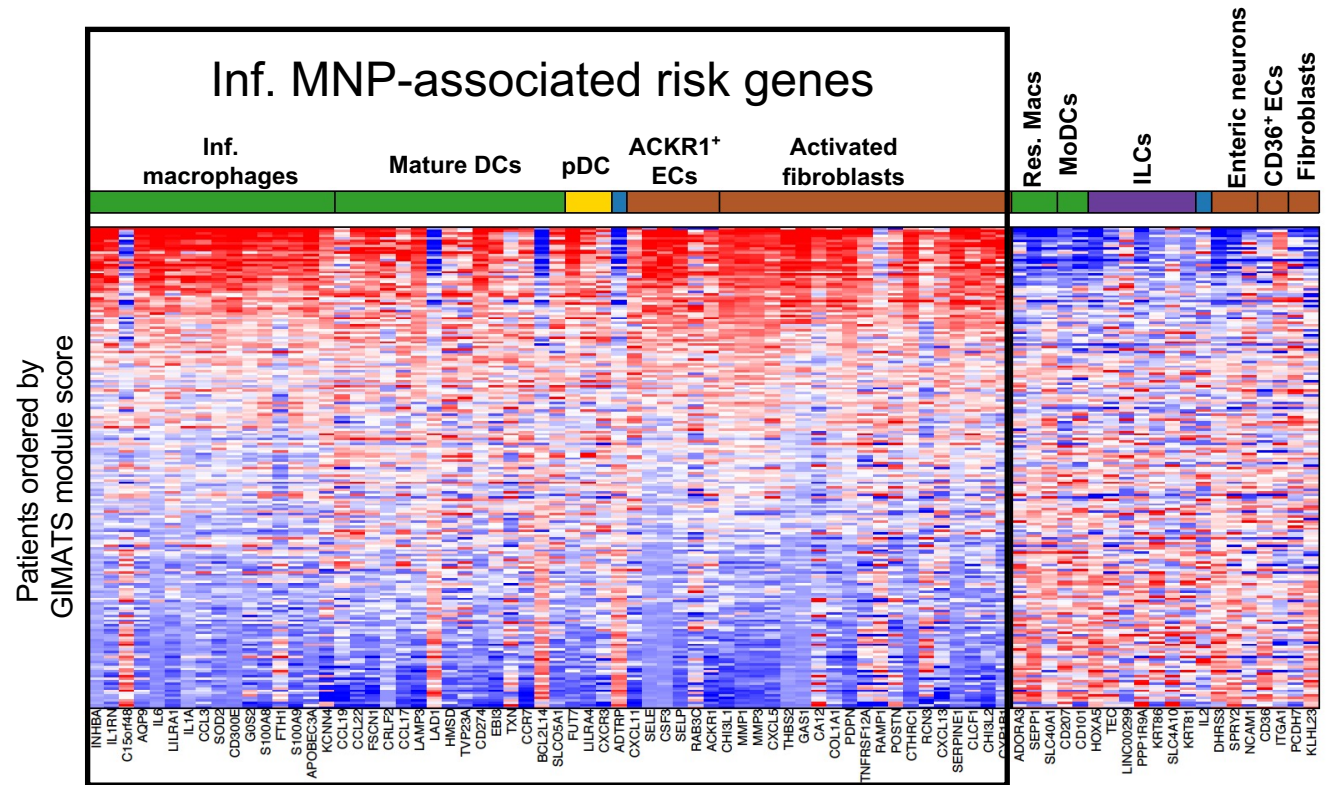
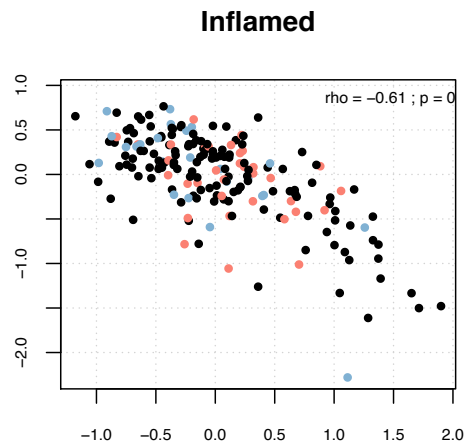
IgG plasma cells, **I**nflammatory **M**ononuclear phagocytes,
Activated **T** cells and **S**tromal cells

Enrichment of the module in a subgroup of patients is a general feature of ileum CD

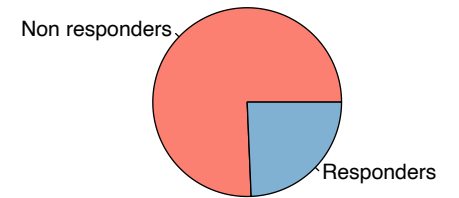


Enrichment of the GIMATS module in early disease correlates with resistance to anti-TNF

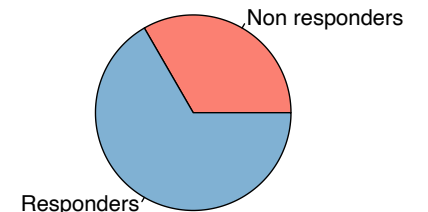
RISK cohort



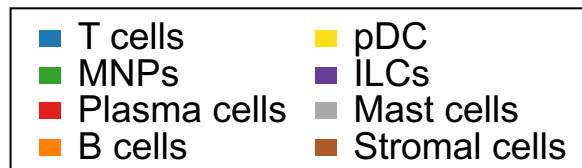
Patients enriched for the GIMATS module



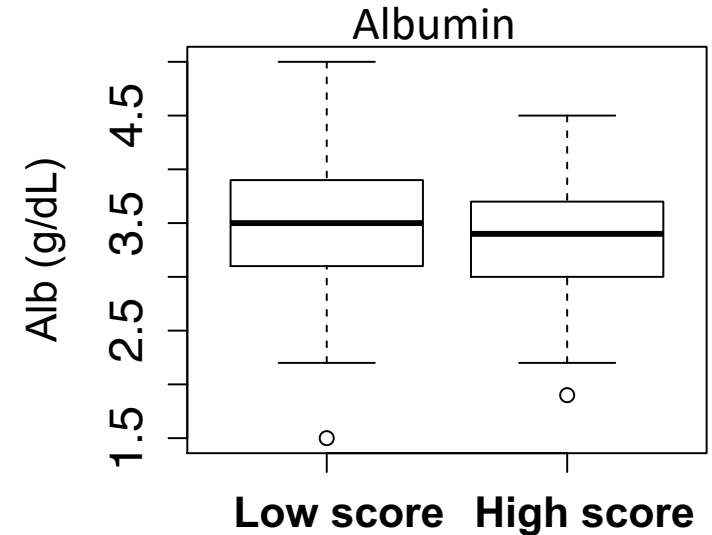
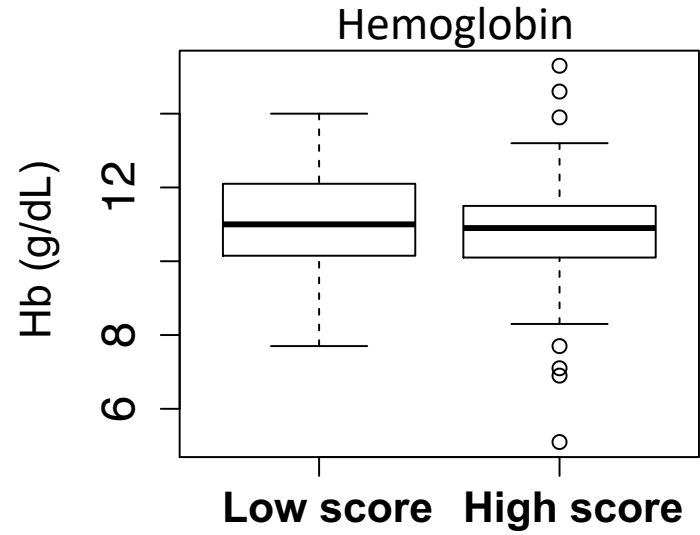
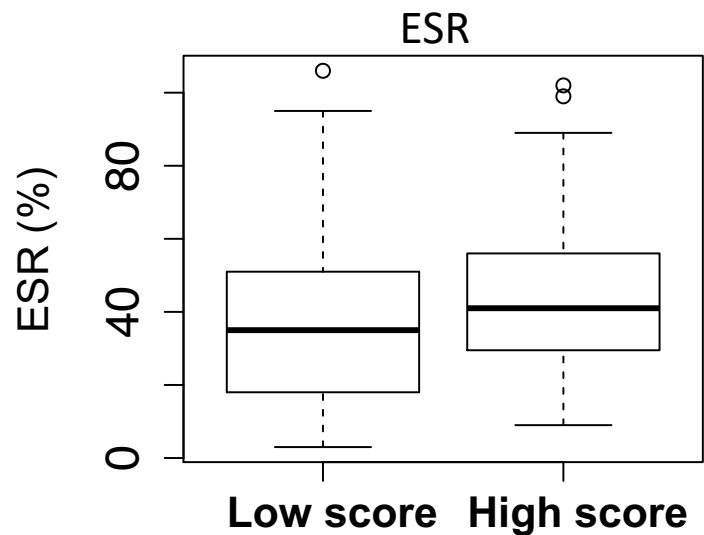
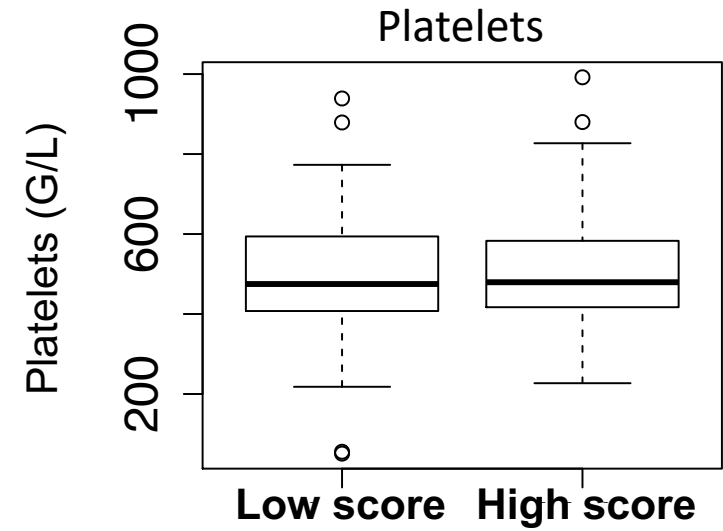
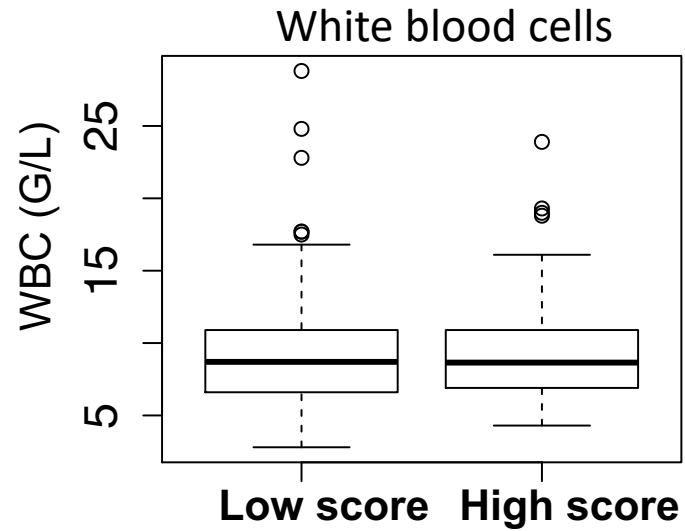
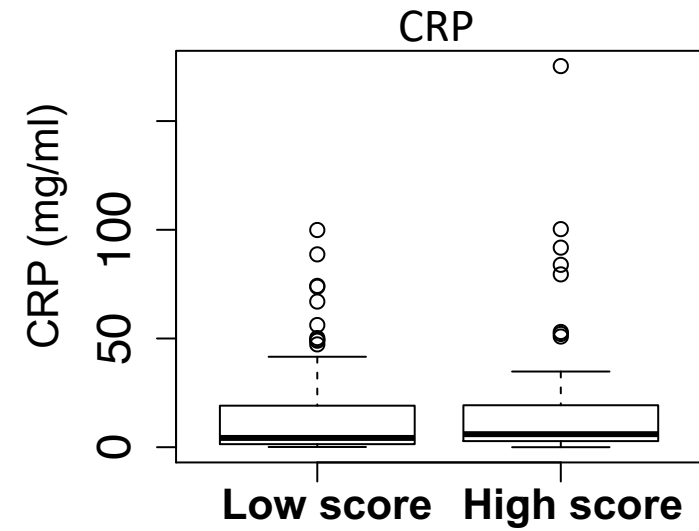
Patients not enriched for the GIMATS module



Responders were defined by long-term (6 months) corticosteroid-free clinical remission (PCDAI<10) during the year following 1st anti-TNF infusion



Enrichment in the GIMATS module is not captured by markers of systemic inflammation



Summary

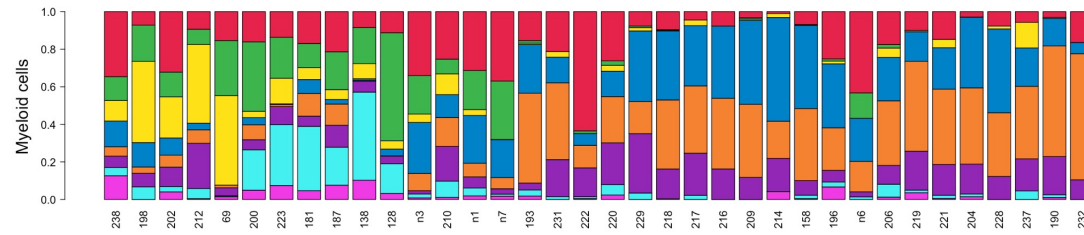
1. scRNAseq analysis identified a pathogenic cellular module in CD inflamed ileum
2. Differential enrichment of the GIMATS module defines two subgroup of patients
3. Marked enrichment of the GIMATS module during early stage of the disease associates with failure to achieve durable CS-free remission during anti-TNF treatment

Single cell mapping of inflammatory lesions provides the opportunity to identify therapeutic targets tailored to anti-TNF non-responders

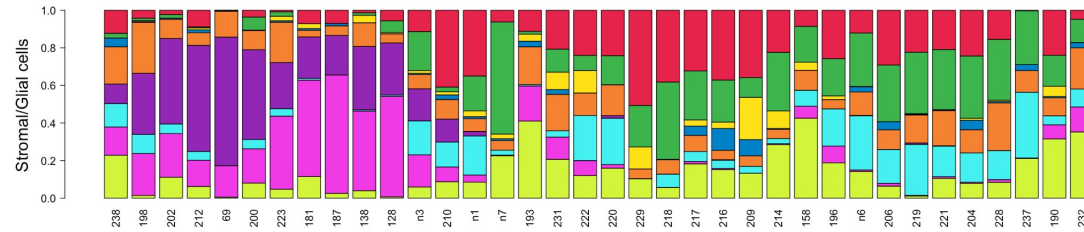
Current directions

1. What drives the GIMATS response ?
2. How are molecular programs defining GIMATS cell types and functions regulated ?
3. Why are GIMATS^{high} patients resistant to anti-TNF?
4. What treatment would benefit GIMATS^{high} patients ?

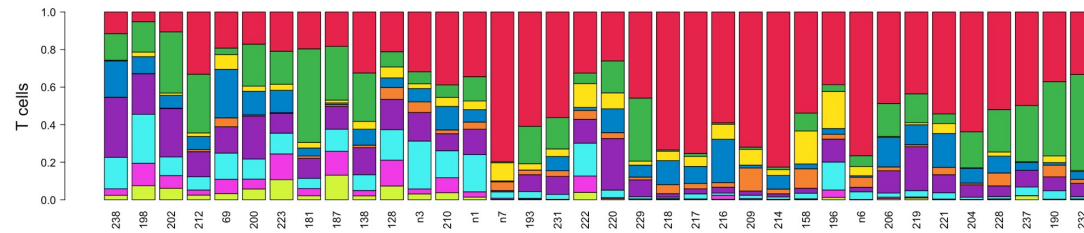
We need to pursue profiling efforts!!



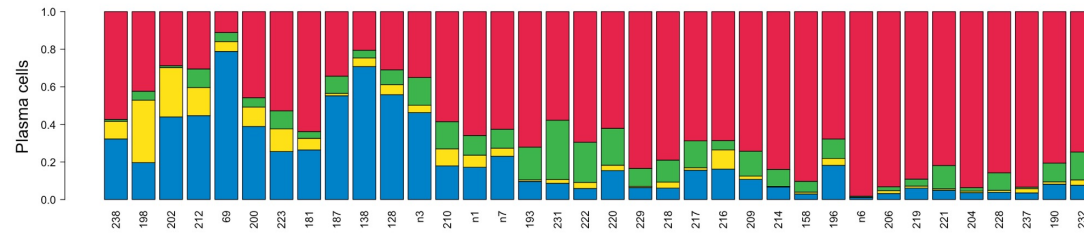
- Macs-1
- Macs-2
- Macs-3
- Macs-4
- DC2
- DC1
- Activated DC
- pDC



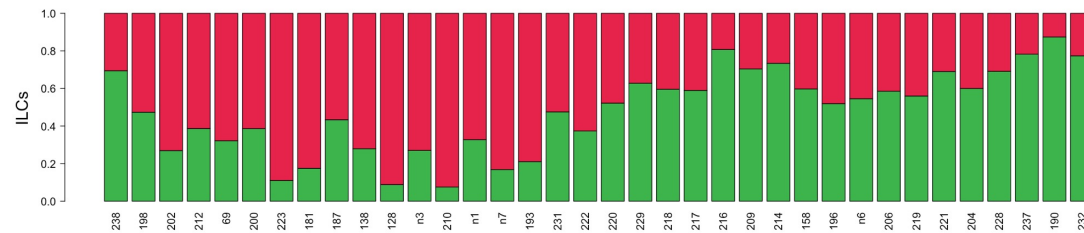
- Fibroblasts -1
- Fibroblasts -2
- Lymphatics
- Glial cells
- SMuscles/Pericytes
- Inf. Fibs
- Mesenchymal niche cells
- ACKR1+ ECs
- CD36+ ECs



- Naive/CM T cells
- Type 3 cytokines Trm
- CTLs
- Type 1 cytokine Trm
- TFH-like
- Tregs
- Activated CD8 T cells
- Activated T cells



- IgA Plasma cells
- IgM Plasma cells
- Plasmablasts
- IgG Plasma cells



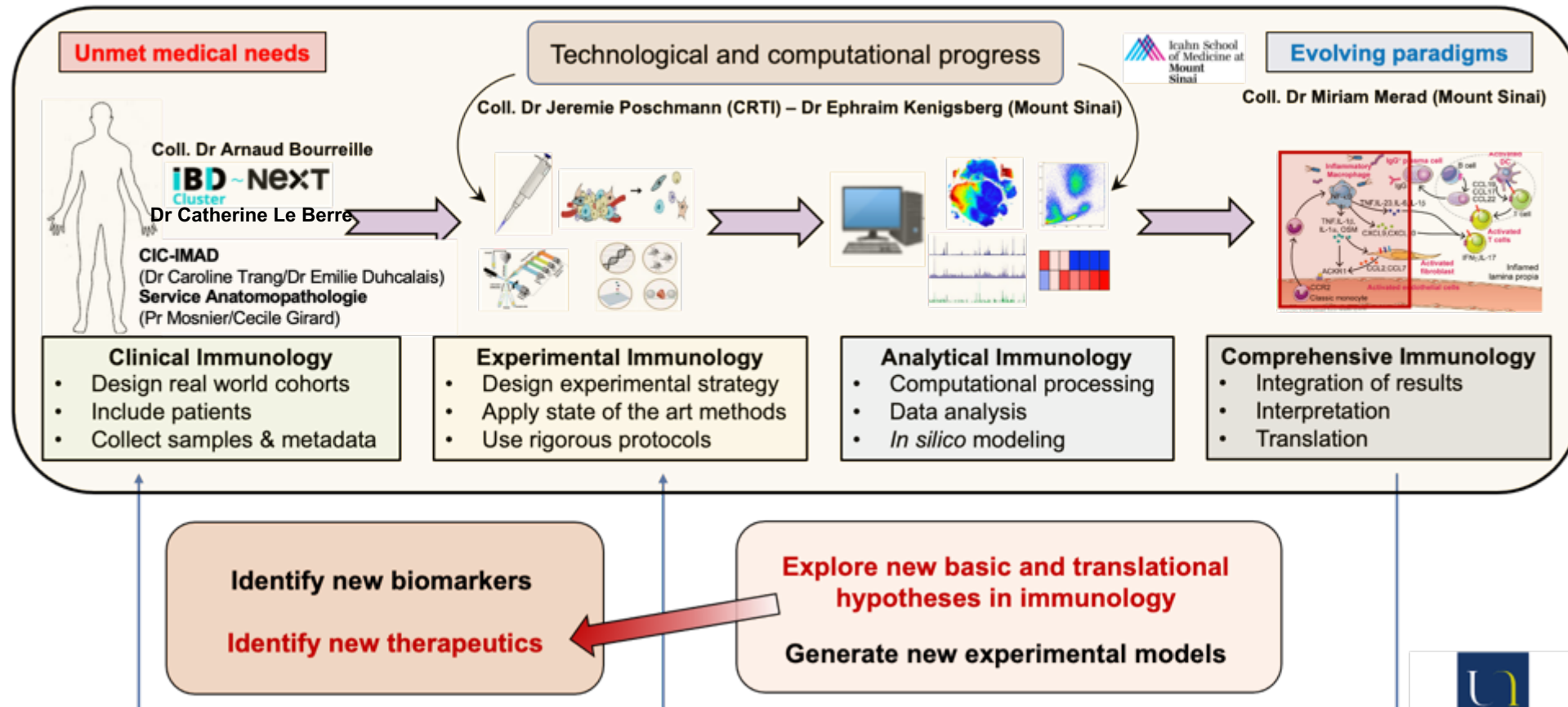
- Group 1 ILC
- Group 3 ILC

Take home message

Only through the study of human tissue lesions at high resolution will be able to understand the organization of immunopathogenic responses, their heterogeneity and the way to therapeutically target them accordingly



Cross-disciplinary efforts at the service of medical research

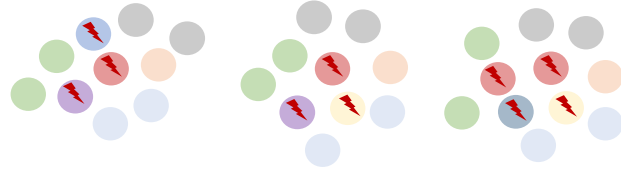


Unraveling immunopathology heterogeneity using single-cell profiling of disease lesions

 Pathogenic cell

a. Cellular and molecular stratification of treatment naïve patients

Signature 1 Signature 2 Signature 3

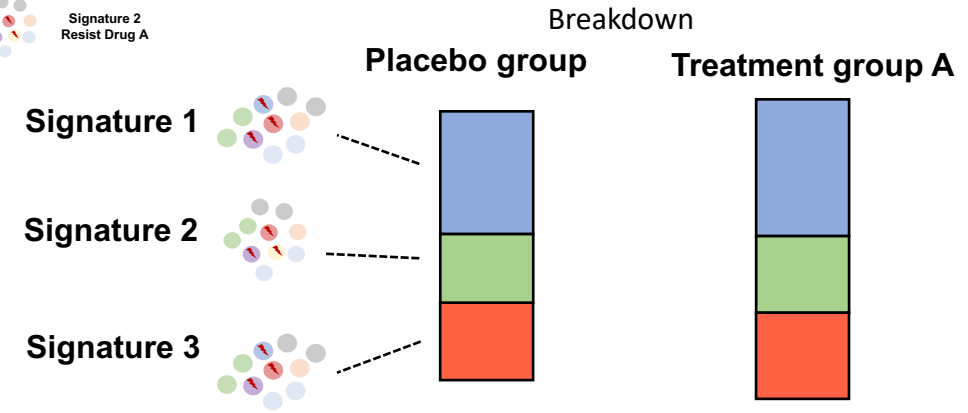


Distinct pathogenic responses between subgroups of clinically identical patients

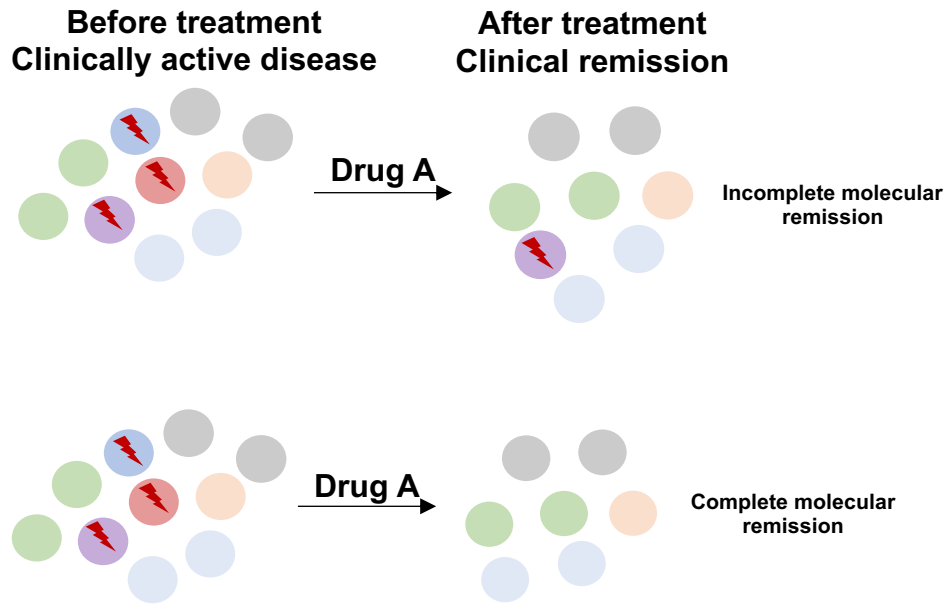
b. Balancing molecular groups in clinical trials

Signature 1
Respond to drug A

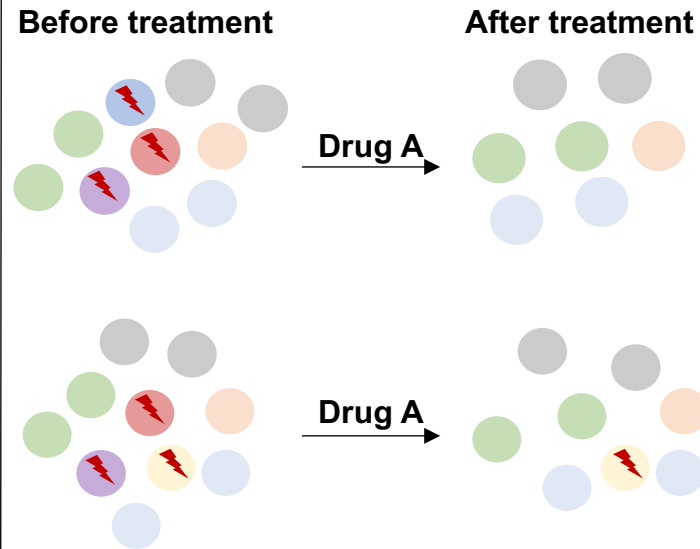
Signature 2
Resist Drug A



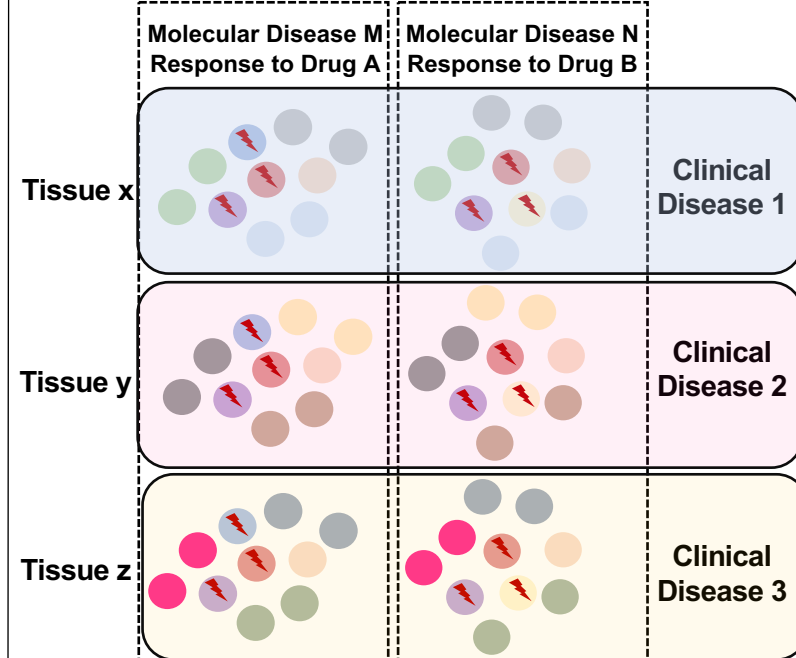
c. Cellular and molecular criteria of remission



d. Identify new targets tailored for non-responders



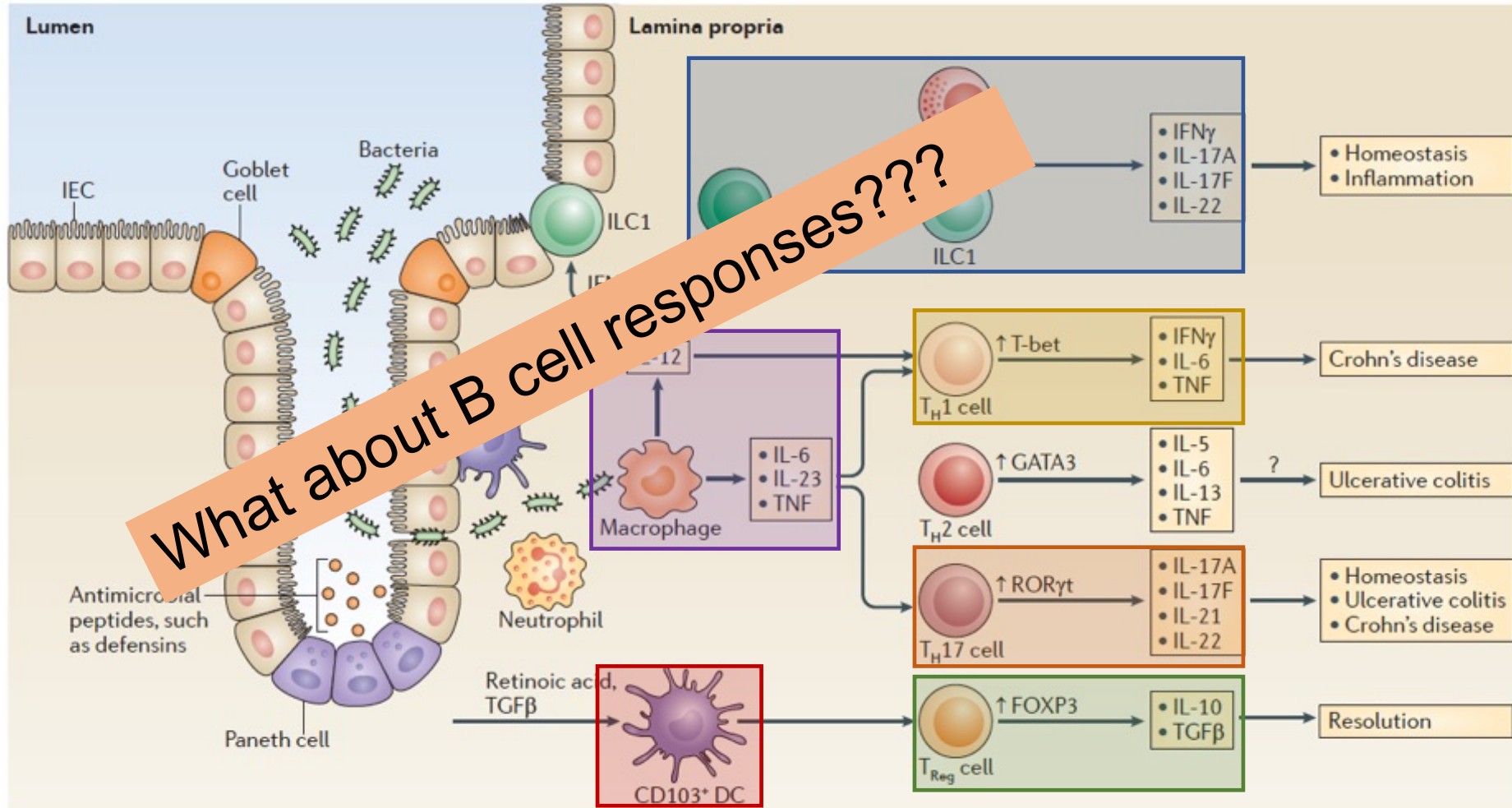
e. Molecular classification of diseases



Is the current pathophysiological model reflecting what really happens in tissues ?

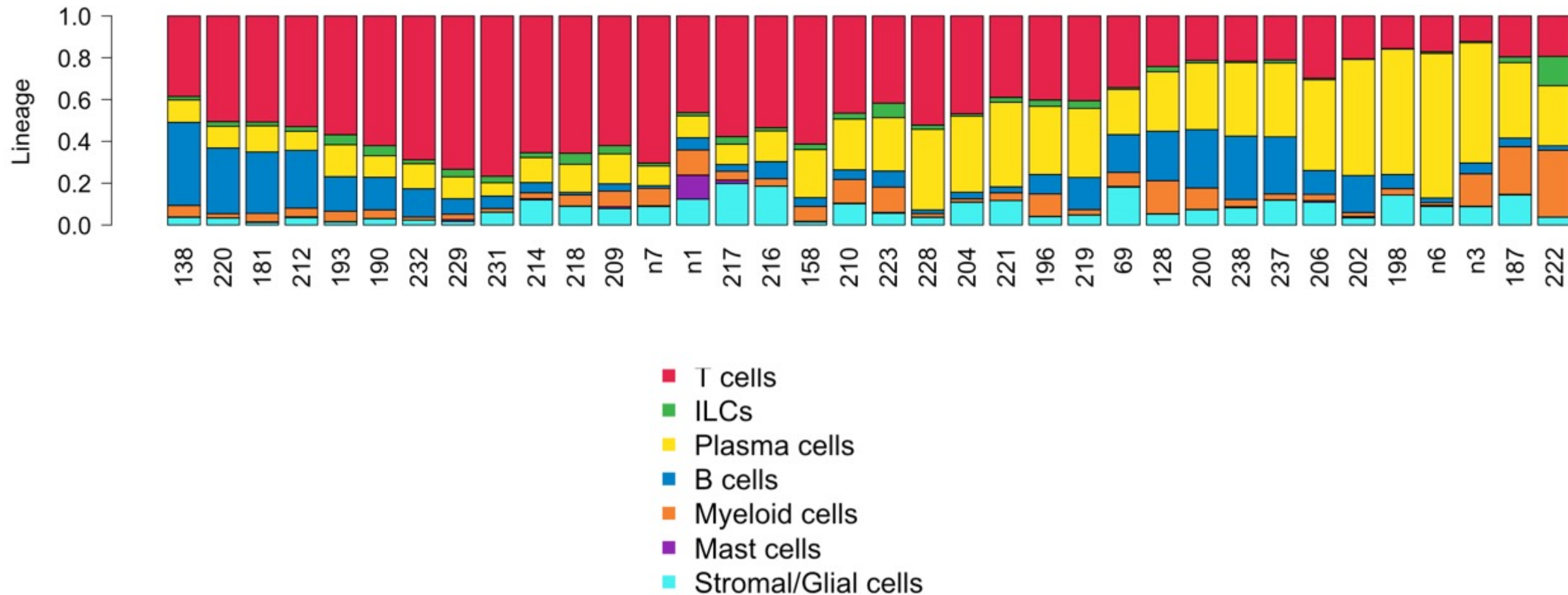
Working model

IBD

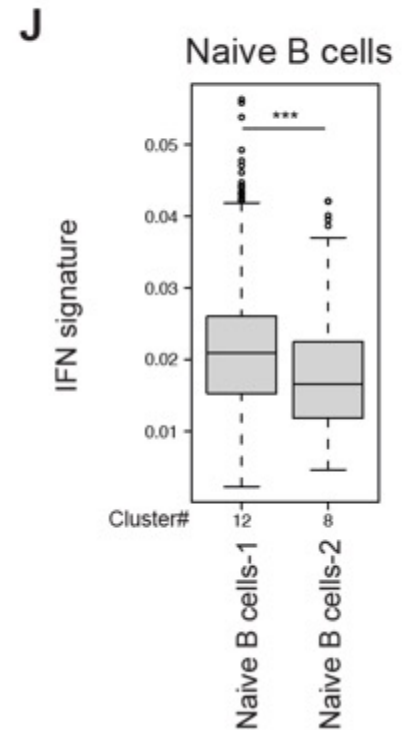
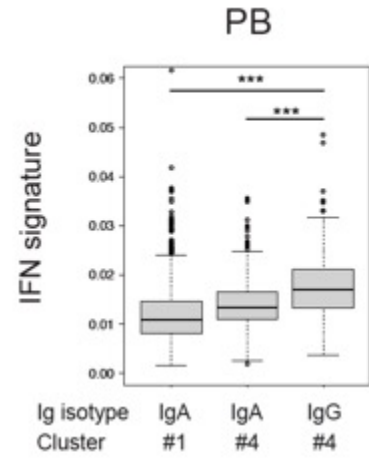
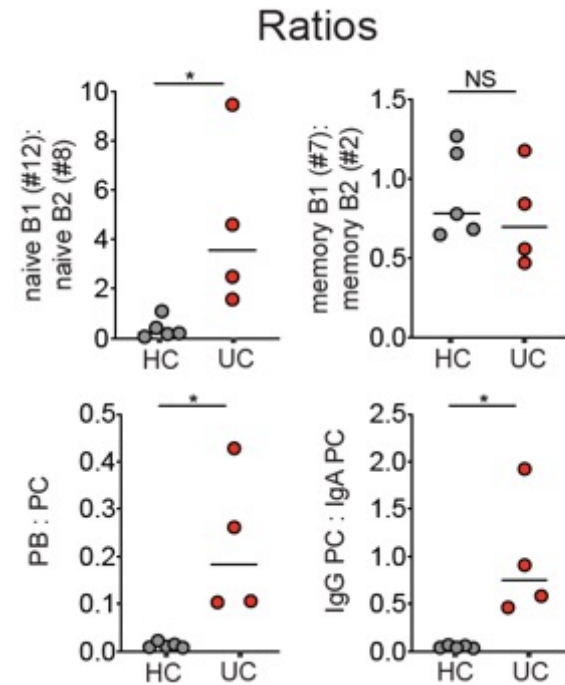
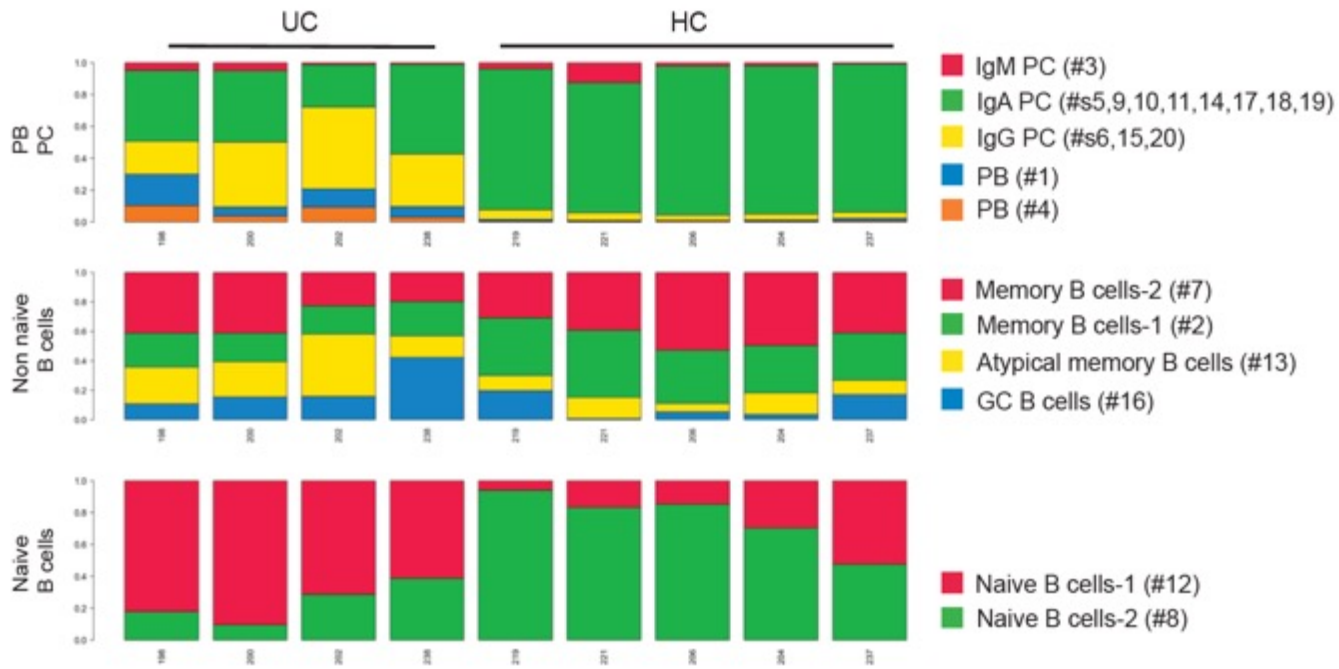


B cell populations dominate the inflammatory immune landscape in subgroup of patients

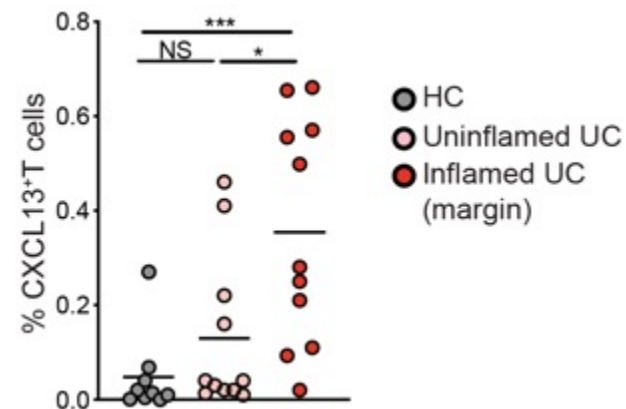
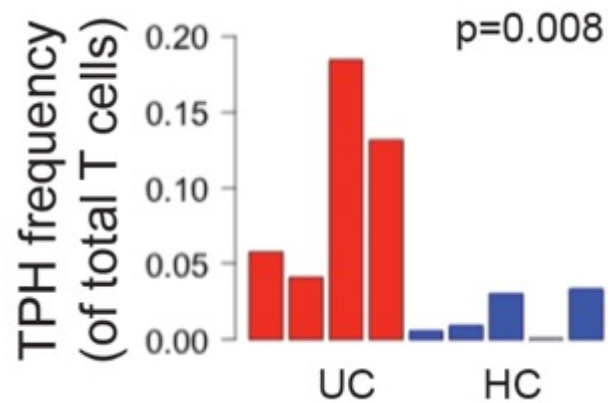
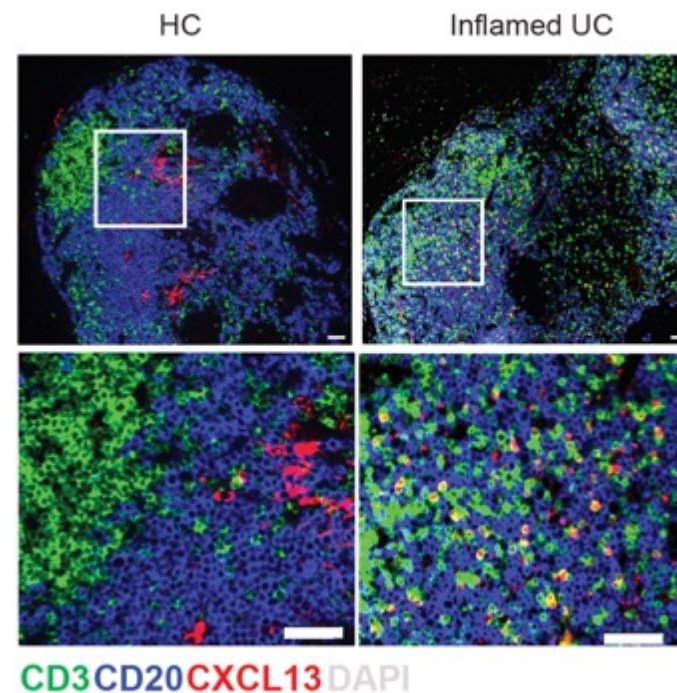
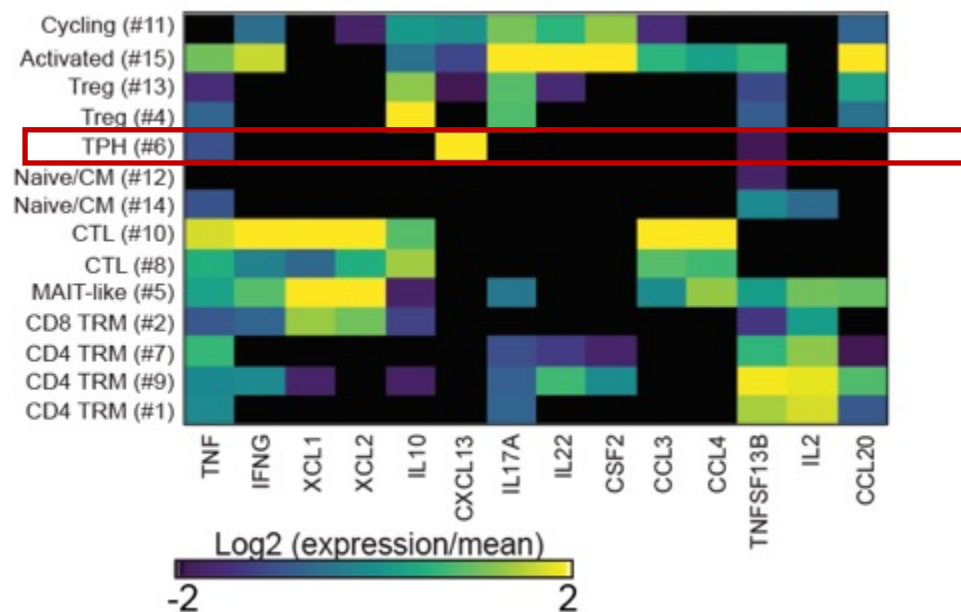
Lineage distribution



A type 1 inflammatory microenvironment reshape the B cell compartment by imprinting naïve B cell molecular programs and skewing part of the PC response toward IgG production



TPH organize B cell responses in inflamed UC colons



Acute B cells coloninc responses translate into increased plasmablast levels in the blood and associate with more severe forms of UC

