RIIP

RENCONTRES en IMMUNOLOGIE & IMMUNOTHERAPIE PRATIQUES

Jeudi 5 et Vendredi 6 octobre 2023

UIC-P - Espaces Congrès
16, rue Jean Rey - 75015 Paris

IMAGE FREEPIK

Sous l'égide de :

Éradiquer les maladies inflammatoires chroniques en partant du modèle MICI

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RIIP Rencontres en Immunologie & Immunothérapie Pratiques
Jeudi 5 et Vendredi 6 octobre 2023
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Institute of Inflammatory bowel disease of Nancy

From cell to environment, we will discover, experiment, and disseminate innovations to cure IBD and allow patients to live a normal life.

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4 Pillars and a triple ambition

01 Research

02 Care

03 Education

04 Innovation

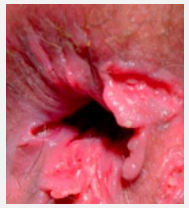
01 Allowing patients to live a normal life

02 Reduce diagnostic delays and medical wandering

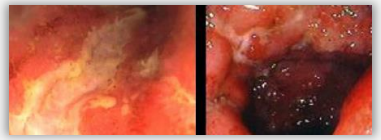
03 Opening up the way to a cure and eradication of the disease

Why an IHU on IBD?

Stoma



Anoperineal lesions



Ulcerations of the colon

- Inflammatory bowel diseases (i.e. Crohn's disease and ulcerative colitis) are **chronic, frequent** (10 million worldwide), **disabling and incurable diseases**.
- They affect **1 in 200 French people**!
- They can occur at any age, with a **peak between the ages of 15 and 35**.
- **Only 1 in 5 patients achieve remission** with current treatments ...

Why establish an IHU for IBD in Nancy?

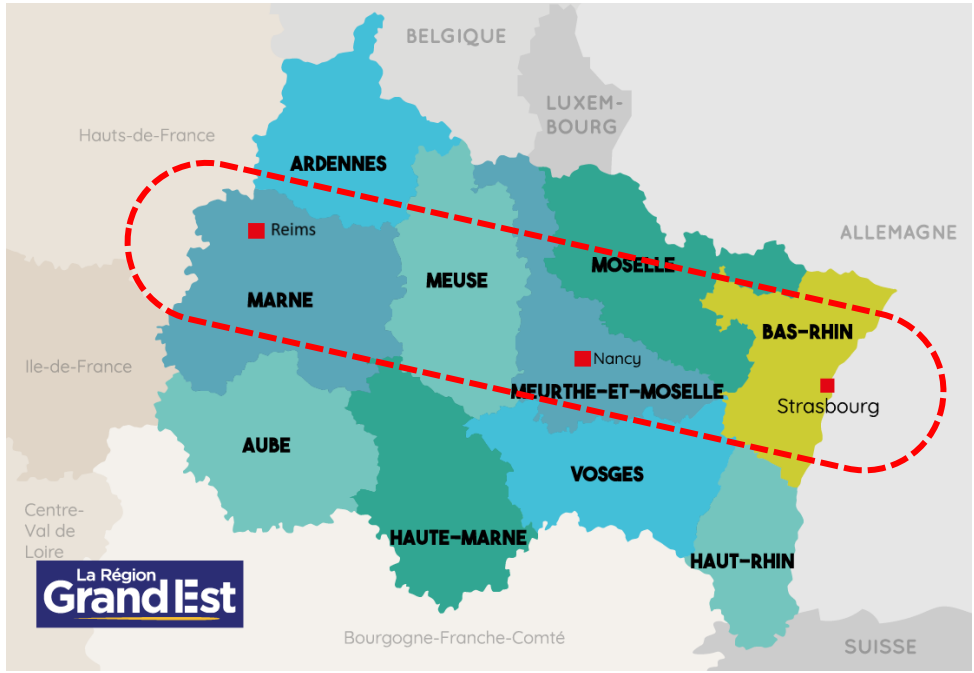
Creation of the FHU CURE “Curing and preventing immune-mediated inflammatory disease” in 2020

Ambition

Create a translational structure of excellence bringing together scientists, clinicians, industry players and cutting-edge technological platforms to create a patient-centered care model.

Cure and prevent inflammatory diseases with an innovative and integrative approach.

FHU CURE led by CHRU Nancy
Coordinator: Laurent Peyrin-Biroulet



Why establish an IHU for IBD in Nancy?

IBD:
A unifying topic in Nancy!

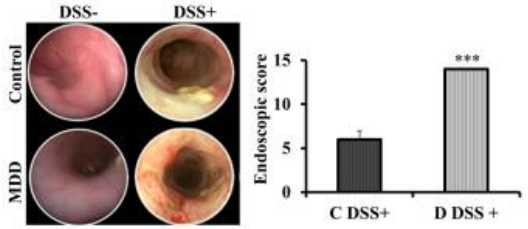
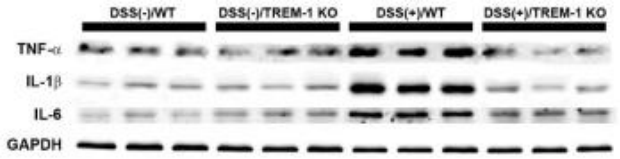
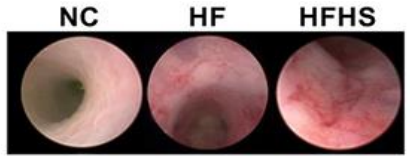
Why establish an IHU for IBD in Nancy?

Some key achievements

Index development	1. **IBD-Disability Index** : Developed and validated with WHO to assess disability in IBD patients (Gower-Rousseau C *et al*. Gut. 2017). 2. **MONITOR Index**: An effective, reliable and easy-to-use tool for predicting postoperative recurrence of CD in routine practice (Schaefer M *et al*. Clin Gastroenterol Hepatol. 2022). 3. **Nancy histological index**: The FDA and EMA have recommended its use in phase II and III trials to assess the impact of new IBD treatments at the histological level (Marchal-Bressenot A *et al*. Gut. 2017).
Consensus	1. **STRIDE** : Treat-to-target strategies for IBD patients (Peyrin-Biroulet L *et al*. Am J Gastroenterol. 2015). 2. **Concept of early CD** (Peyrin-Biroulet L *et al*. Am J Gastroenterol. 2012).
Radiology	**Virtual colonoscopy: MRI without preparation** (Oussalah A *et al*. Gut. 2010).

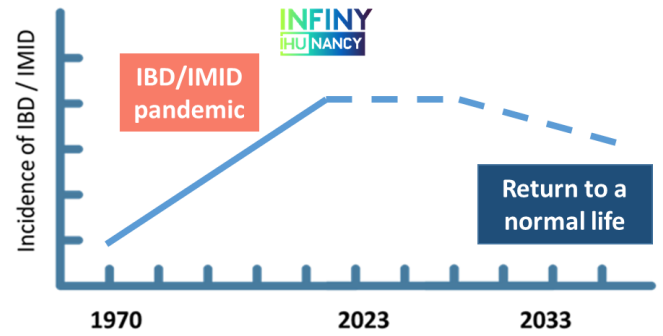
IBD: Inflammatory bowel disease; CD: Crohn's disease; WHO: World Health Organization; FDA: Food and Drug Administration; EMA: European Medicines Agency.

Why establish an IHU for IBD in Nancy?

Experimental research	A low-methyl diet has been shown to promote colitis and SIRT1-mediated endoplasmic reticulum stress (Melhem H et al. Gut. 2016).  ***Figure 1**: Methyl donor deficiency aggravates dextran sulfate sodium (DSS)-induced colitis.*
Early drug development	TREM-1 inhibition has been shown to restore impaired autophagic activity and reduce colitis in mice (Kökten T *et al*. J Crohns Colitis. 2018).  INOTREM control innate immunity ***Figure 2:** TREM-1 deletion in mice prevents colonic inflammation in DSS-induced acute colitis model*
Nutrition and microbiota	Long-term overconsumption of fats and sugars has been shown to cause a partially reversible pre-IBD state (Arnone D *et al*. Front Nutr. 2021).  ***Figure 3:** Effect of a high-sugar, high-fat diet in healthy mice. NC = normal chow; HF = high-fat diet; HFHS = high-fat, high-sugar diet.*

IHU INFINY : Ambition and Objectives

Ambition



Main objectives

Objective 1

Live a normal life with IBD by achieving a disease-free state

Objective 2

Improve and accelerate diagnosis of IBD

Founding members :

CHRU NANCY

Inserm

UNIVERSITÉ DE LORRAINE

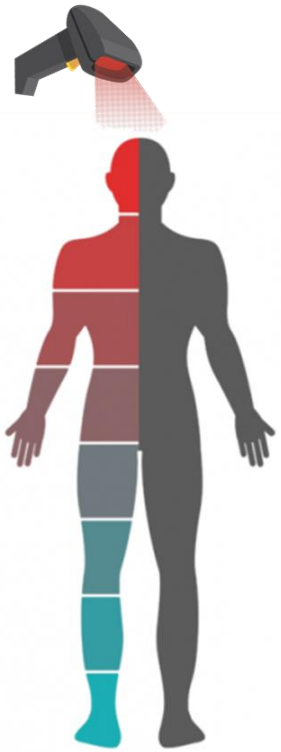
métropole GrandNancy

IHU INFINY : Research program

Objective 1

Comprehensive mapping to identify indicators of normality and of systemic damage

- Social, psychosocial and professional life
- Extra-intestinal damage
- GI physiology
- Biological fluids
- Molecular healing
- Cellular healing



Objective 2

Reversing damage via therapeutic innovations and innovative complex interventions

IHU INFINY : Research program

Main objective 1

Comprehensive mapping to identify indicators of normality and of systemic damage

→ Biological mapping

→ Imaging mapping

→ Electrical mapping

Early detection of flare/intestinal complications

Early detection of extra intestinal damage

Early intervention

Main objective 2

Reversing damage via therapeutic innovations

→ Home-based monitoring tools

→ From drug discovery to early drug development

→ Non-pharmacological approaches

Early drug development

Early detection of treatment failure

Early and full disease control

IHU INFINY : Research program - Comprehensive mapping

Biological mapping - Identification of biological indicators of intestinal and extra-intestinal damage

INFINY Cohort

2.000 IBD patients
1.000 healthy volunteers

1. **Multi-Omics data production** using a broad range of molecular and cellular profiling techniques

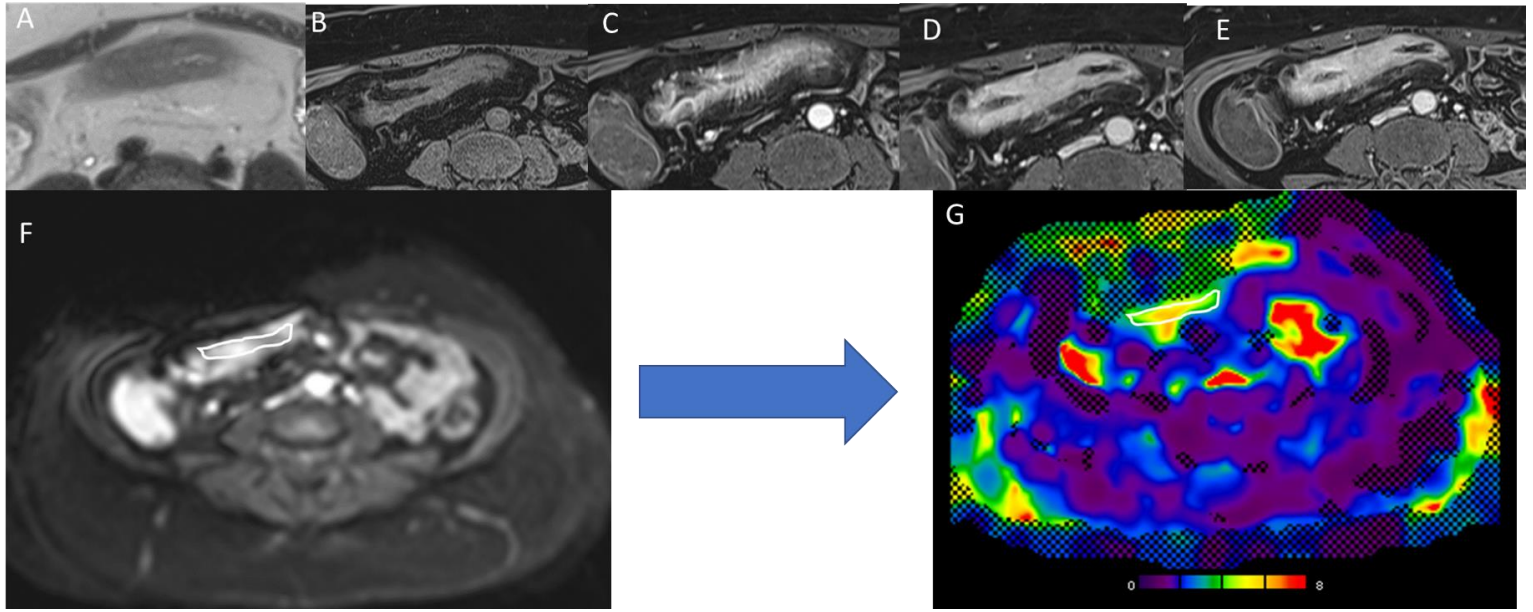
2. **Focus on specific pathomechanism**
   - **Revisiting microbiota analysis** - In depth functional mapping of the intestinal microbiota
   - **Revisiting epigenetics analysis** - Unravel the complex interaction between human health, exposome and epigenome
   - **Revisiting cardiovascular component analysis** - Decipher the mechanisms of immunothrombosis and resolution of inflammation

IHU INFINY : Research program - Comprehensive mapping

Imaging mapping - 3D virtual histology of intestinal lesions by in-vivo and ex-vivo MRI

We aim to develop/provide:

- Specific instrumentation
- Fast and motion-robust acquisition / reconstruction
- Novel contrast mechanisms
- 3D isotropic imaging (e.g. at 1x1x1 mm3 resolution)
- Reference values for validation of the in-vivo measurement methods
- Unprecedented 3D mapping of resected lesions.



Avila F et al. Magnetic Resonance Elastography for Assessing Fibrosis in Patients with Crohn's Disease: A Pilot Study. Dig Dis Sci 2021

IHU INFINY : Research program - Comprehensive mapping

Electrical mapping - Identification of electrical indicators of intestinal damage

Development of an electrointestinogram

Intestinal motility

- Smooth muscle contraction
- Slow waves, pacemaker = Interstitial cells of Cajal

Frequency of slow wave

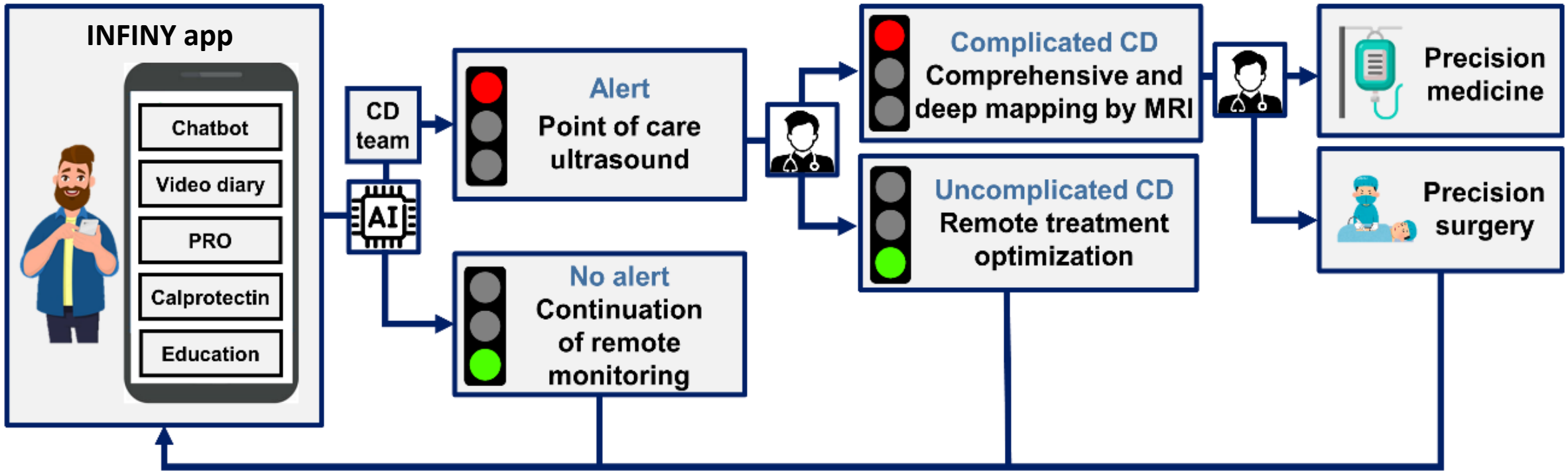
- Stomach: 3 cpm
- Duodenum: 11-12 cpm
- Ileum: 8-9 cpm
- Colon: 3-4 cpm

IHU INFINY : Research program - Comprehensive mapping

Example of a dashboard in urology

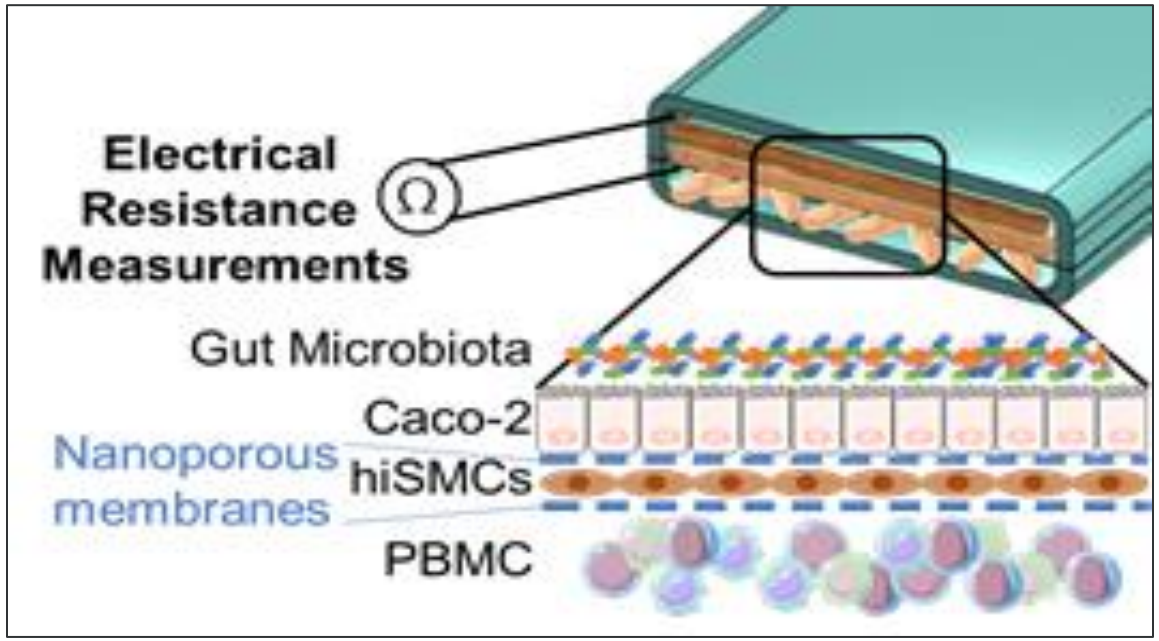
IHU INFINY : Research program - Reversing damage

Home-based monitoring tools



IHU INFINY : Research program - Reversing damage

From drug discovery to early drug development



Schematic representation of our IBD-specific gut-on-chip.

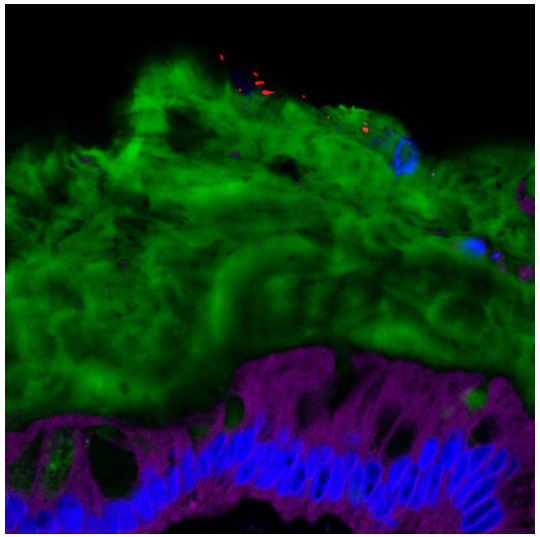
The development of a gut-on-chip could **accelerate pharmaceutical development** and potentially **replace animal testing.**

It will also allow a better management of IBD patients by **selecting the appropriate drug according to their own physiopathology.**

IHU INFINY : Research program - Reversing damage

Non-pharmacological approaches - New targets from translational approach: Example of the study of the microbiota

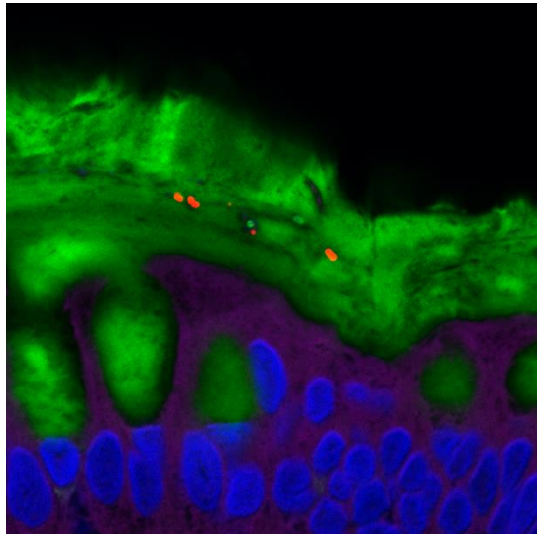
Inner mucus layer - Sterile



Mucus Bacteria
Actin DNA

DIETARY EMULSIFIERS

Microbiota encroachment
Invaders



Intestinal inflammation

IHU INFINY : Research program - Reversing damage

Non-pharmacological approaches - New targets from translational approach: Example of the study of the microbiota

Axis 1 : Identification/ characterization

Material

IBD patients

Stratification criteria
In depth clinical phenotyping

- Disease activity
- Relapse/remission
- Disease history
- Medication
- IBD subtype
- Diet history

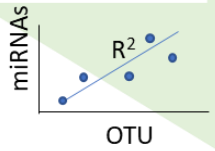
Analyses

Intestinal microbiota composition
- Sequencing (metagenomic, metatranscriptomic)
- High throughput culturomic

Intestinal microbiota function
- Functional investigation
- Metabolomic

Hosts factor involved in microbiota interaction
- Immunophenotyping
- Genome sequencing
- Fecal miRNAs profiling by NGS

Read-out



In depth phenotyping of the disrupted host-microbiota interaction in IBD
- Interactions network
- Validation approach

Outcome

Altered host-microbiota interaction to be therapeutically targeted
Drug, Diet, etc.

Axis 2 : Innovative therapeutic strategies

Microbiota-based modulation of disease activity and disease course

Approach

Modulation of microbiota composition
- Anti-microbial peptides
- CRISPR-Cas9 technology

Modulation of microbiota function
- Targeted immunization

Modulation through hosts factor involved in microbiota interaction
- Exogenous miRNA administration

Outcome

Dampen inflammation, remission, improve response to therapeutics…

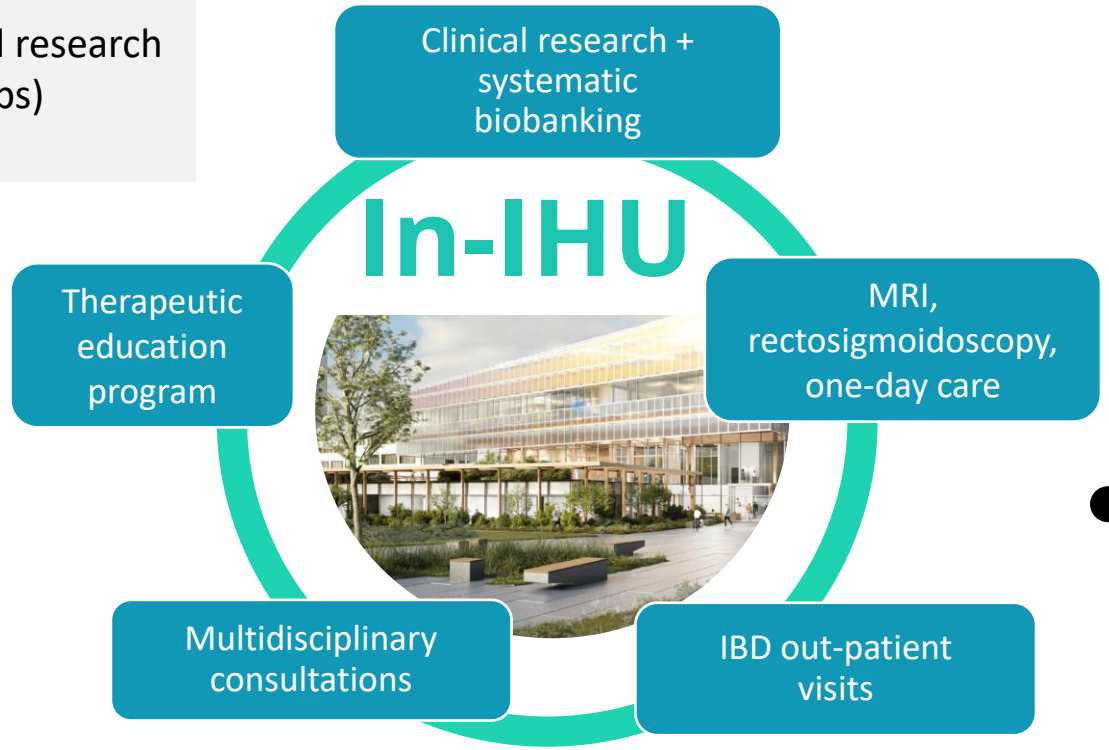
IHU INFINY : Care and prevention program

In-IHU = 3500m² dedicated to :

- Healthcare → Linked to teaching and research
- Development and innovation (startups)
- Conferences and meetings

Primary Prevention

Promoting a healthy lifestyle to protect the intestine



Secondary Prevention

Early detection of IBD

Tertiary Prevention

e-IHU

Personalized home-based follow-up

IHU INFINY: Impact on research, care and patients

Key results for the medical community

- Therapeutic innovation / Drug discovery
- New prevention policy
- Prevention of relapses and extra-intestinal manifestations
- Prediction of relapses and treatment failure
- New care pathway
- Creation of a specific and multidisciplinary teaching program
- Extrapolation to other inflammatory diseases

Direct impact on patients' lives

- ↘ diagnostic wandering
- ↘ 50% appointment
- ↘ 50% colonoscopies
- ↘ 50% hospitalizations
- x 2 deep remission
- ↘ 50% surgeries
- End of short bowel syndrome
- No more stomas
- No more disability

The revolution is underway!
Grand Est region on the road to curing IBD!

IHU INFINY: IBD Research Team