APPEL A PROJETS DE THÈSE 2026
CONCOURS DE L'ED 658 – Sciences du vivant

Formulaire à compléter et déposer par les porteurs du projet de thèse HDR via l'adresse mail suivante :
ed658@univ-amu.fr OU/ET romane.haddadi@univ-amu.fr
MERCI DE METTRE EN SUJET DU MAIL : Concours ED 658 2026 porteur de projet
Ces dossiers seront publiés pour que les candidats postulent.

au plus tard le 3 mars 2026.

INTITULÉ DU PROJET
Role of type III Interferons and Z-form nucleic acids in controlling Enteric repair

1- Directrice ou directeur de thèse HDR			
NOM	Broggi	Prénom	Achille
Téléphone portable	782457461	Courriel	broggi@ciml.univ-mrs.fr
Unité de recherche (UR) de rattachement			
Code (acronyme et n°) de l'UR à AMU :	CIML		
Nom de l'UR :	Centre d'Immunologie Marseille Luminy		
Directrice ou directeur de l'UR			
Nom	Milpied	Prénom	Pierre

2- Codirectrice ou codirecteur de thèse, le cas échéant			
NOM		Prénom	
Téléphone portable		Courriel	
Unité de recherche (UR) de rattachement			
Code (acronyme et n°) de l'UR à AMU :			
Nom de l'UR :			
Directrice ou directeur de l'UR			
Nom		Prénom	

SPECIALITE : (Rayer les mentions inutiles)

Bio-informatique et ~~Génomique / Biochimie Structurale / Biologie du Cancer / Biologie du Développement / Biologie Végétale / Biotechnologie~~ / Immunologie / Microbiologie et interactions hôte-pathogènes / ~~Neurosciences~~

SOUS JURY POUR LE CONCOURS : (Rayer les mentions inutiles)
JURY 1 : BIOLOGIE CELLULAIRE
JURY 2 : ~~MICROBIOLOGIE – GENOMIQUE~~
JURY 3 : ~~NEURSOCIENCES~~

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MERCI DE REMPLIR TOUTES LES INFRORMATIONS EN FRANÇAIS ET EN ANGLAIS

Description de la problématique de recherche - Project description

This project investigates how elevated type III interferons (IFN-III) in IBD patients inhibit mucosal healing by increasing Z-form nucleic acid (Z-NA) sensing and inducing epithelial cell death. Using clinical samples, human organoids, and mouse models, the study aims to define the molecular mechanisms of IFN-III activity in humans, identify microbial and host factors driving its upregulation, and characterize the origin and regulation of Z-NA.
IFN-III delays epithelial repair by promoting ZBP1-mediated cell death in intestinal stem cells, but the specific pathways triggered in humans, the source of IFN-III, the stimuli that induce its upregulation, and the source and regulation of Z-NA remain unclear.
Using clinical samples, human organoid models, and mouse models of IBD, we will:
a) extend our mechanistic findings to on IFNs' role in inducing epithelial cell death and impeding repair and translating it to the human system,
b) investigate microbial and host factors driving IFN-III augmentation in IBD patients' mucosae, and
c) characterize the nature and regulation of Z-NA that trigger epithelial cell death.
This translational research project will inform of novel therapeutic targets to enhance tissue repair in IBD patients.

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Mots clés – Keywords

Interferon
IBD
MICI
Z-NA
Cell death
Innate immunity

Thématique / Domaine / Contexte - Theme / Field / Context

In IBD patients' intestinal mucosa, the balance between the immune response, the epithelia, and the microbiota is dysregulated and leads to inflammation and tissue dysfunction. Current therapies, focus on reducing inflammation, however despite good results on clinical remission, endoscopic remission is achieved only in 50% of patients. Therefore, a major clinical goal is to promote mucosal healing and decrease relapse. Intestinal epithelial cells (IECs) are key players in mucosal healing, but their physiology is affected by their interaction with immune cells, and microbes.

In this context we are interested by the role of type III interferons (IFN-III), also known as IFN-lambda(Broggi, Granucci, and Zanoni 2020)They activate antiviral interferon stimulated genes (ISGs) upregulation, through the same intracellular pathway governing type I IFN responses. However IFN-III primarily affect epithelial cells due to the sIFN-III maintains basal antiviral states in the gut and is elevated in IBD patients.

We found IFN-III delays mucosal repair in mouse colitis and irradiation models by inducing IEC death. This occurs via ZBP1 upregulation—a sensor of Z-NA (Z-conformation nucleic acids)—triggering CASP-8 activation and GSDMC cleavage, causing pyroptosis in reparative stem cells. Deleting ZBP1, GSDMC, or inhibiting CASP-8 rescues repair defects.(Jena et al. 2024)

In IBD patients, the IFN-III/ZBP1/CASP-8/GSDMC axis is activated, with ZBP1/GSDMC transcripts and CASP-8 activation correlating with IFN-III levels. However, IFN-III alone doesn't induce IEC death; Z-NA binding to ZBP1 is required. During colitis/irradiation, Z-NA levels rise, and ZBP1^ΔZα2 mutants (lacking Z-NA binding) show improved repair.

Using ALI-cultured organoids, we confirmed IFN-III induces death only during simulated damage/repair—conditions where Z-NA levels peak.

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Objectives

We have recently demonstrated that IFN-III is elevated in the mucosae of IBD patients and can inhibit mucosal healing by promoting the sensing of Z-NA and inducing epithelial cell death. In this study we aim to explore three main questions that have arisen thanks to our initial study: 1) Are the mechanisms by which IFN-III inhibits repair in mouse models conserved in humans, and do they differ in homeostatic and pathological contexts? (2) What are the specific cell types, host mechanisms, and microbial stimuli driving IFN-III production in IBD? (3) What is the nature and regulation of Z-NA required for IFN-III–dependent cell death and repair inhibition? These insights aim to extend mechanistic understanding and uncover potential therapeutic targets in humans.

We propose to address these questions with the following specific aims:

Aim1. Define the microbial stimuli and immune recognition pathways stimulating IFN-III upregulation in IBD, and the responsible cell types.

Aim 2: Define how Z-NA formation is regulated in IBD, and how the interplay between IFN signaling and Z-NA recognition regulates intestinal repair

Méthode – Method

Aim 1: Define the microbial stimuli and the immune recognition pathways stimulating IFN-III upregulation in IBD, as well as the cell types responsible for its production

Basal levels of IFN-III were described to be dependent on the intestinal microbiome, and there are reports of their production in response of commensal viruses in the context of immunodeficient mice (REFs). However, in the context of IBD, the microbial stimuli and the immune recognition pathways stimulating IFN-III production, as well as the cell types responsible for its production are unknown. Commensal viruses have been shown to induce IFN-III production in the gut (REF), and analyses of the virome of IBD patients compared to controls has shown an enrichment in eukaryotic commensal viruses that correlates with disease manifestations an IFN responses (REFs). We thus hypothesize that intestinal damage causes reactivation of commensal eukaryotic viruses, which leads to the production of IFN-λ. In addition, the combination of viral reactivation and barrier breakage might allow viral components to stimulate lamina propria phagocytes to induce IFN-λ production. We will use a combination of microbiome manipulation, mouse genetics, *in vitro* organoids and phagocyte models to investigate the microbial stimuli as well as the cellular source of IFN-III.

Aim 2: Define how Z-NA formation is regulated in IBD, and how the interplay between IFN signaling and Z-NA recognition regulates intestinal repair.

Our preliminary work represent strong evidence to further study Z-NAs in the context of IBD, however we still don't know: Aim 2.1) the nature (DNA or RNA) and origin (sequence) of the NAs that are upregulated during disease; and in the different models (patients, mouse models, human and mouse organoid models); and Aim2.2) how is their upregulation regulated during disease.

In different disease models Z-NA can originate from mitochondrial DNA under oxidative stress (REF), double stranded RNA from endogenous retroelements (REF), telomeric repeat containg RNA. We will leverage the availability of the Z-NA specific Z-22 antibody to bind both DNA and RNA in the Z conformation, and ZBP1 specific antibodies to perform RNA Immuno Precipitation, Chromatin immunoprecipitation (ChIP), and co-IP of mitochondrial DNA (REF). This will allow us to identify the totality of Z-NAs and the one bound to ZBP1 and will allow us to formulate hypotheses on the molecular origin of the Z-NAs.

Based on these results, we will thus explore the molecular mechanisms that regulate Z-NA upregulation, leveraging the availability of patients samples, mouse models and *in vitro* model that allow us to discriminate the mechanisms involved in Z-NA upregulation during damage and repair.

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Références bibliographiques

Broggi, Achille, Francesca Granucci, and Ivan Zanoni. 2020. "Type III interferons: Balancing tissue tolerance and resistance to pathogen invasion." *The Journal of Experimental Medicine* 217 (1). https://doi.org/10.1084/jem.20190295.

Jena, Kautilya K., Julien Mambu, Daniel Boehmer, Benedetta Sposito, Virginie Millet, Joshua de Sousa Casal, Hayley I. Muendlein, et al. 2024. "Type III Interferons Induce Pyroptosis in Gut Epithelial Cells and Impair Mucosal Repair." *Cell*, November. https://doi.org/10.1016/j.cell.2024.10.010.

Conditions scientifiques matérielles et financières du projet de recherche - Scientific, material, and financial conditions of the research project

This pronect is fina nced by an A*midex chair of excellence until the end of 2026 and is object of two grant proposals that are currently pending and will ensure funding until 2029

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Profil et compétences recherchées - Profile and skills required

The student will be familiar with innate immunity, mucosal immunity and epithelial cell biology and will preferentially have skills in manipulation of intestinal organoids.

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