**Master 2 internship project**

**Year 2025-2026**

**Laboratory/Institute:** Institute for Advanced Biosciences **Director:** C. Arnoult

**Team:** [Novel Drug Targets in Human Diseases](https://noveltargets-palencia.com/) **Head of the team:** A. Palencia

**Name and status of the scientist in charge of the project:** A. Palencia, G. Hoffmann

 **HDR: yes x no ☐**

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**Program of the Master’s degree in Biology:**

 **x** Microbiology, Infectious Diseases and Immunology **x** Biochemistry & Structure

**☐** Physiology, Epigenetics, Differentiation, Cancer **☐** Neurosciences and Neurobiology

**Title of the project:**

**Characterization of Novel Boron-based Compounds Targeting Bacterial Leucyl-tRNA Synthetase**

Objectives (up to 3 lines):

Following the discovery of a novel benzoxaborole active against Gram-positive bacteria, the primary objective is to characterize its interaction with leucyl-tRNA synthetase using a biophysical approach, and to leverage this data for the structure-guided design of derivatives with improved antimicrobial properties.

Abstract (up to 10 lines):

Benzoxaboroles are a novel class of antimicrobials with potent activity against a variety of pathogens. They are known to inhibit leucyl-tRNA synthetase in complex with its cognate tRNA, a critical enzyme in protein synthesis. A screening of a compound library against several pathogenic bacteria led to the identification of the first benzoxaborole with promising activity against Gram-positive bacteria. Preliminary data confirmed that this compound targets leucyl-tRNA synthetase through novel interactions distinct from those observed with previously known benzoxaboroles. We aim to further characterize this drug–target interaction using a biophysical approach, including microcalorimetry, X-ray crystallography, and cryo-electron microscopy. Novel AI-tools will be used to predict structures and complexes with inhibitors. The resulting data will be used to guide structure-based optimization of the compound to enhance its activity and support the design of novel derivatives against emerging pathogens, and improve existing lead compounds targeting Gram-negative species. This stage requires the interaction (in English) with academics, clinicians and pharma.

Methods (up to 3 lines):

The project involves the production and purification of protein using a bacterial expression system, as well as the *in vitro* synthesis and purification of RNA. Drug–target interactions will be characterized primarily through X-ray crystallography, cryo-electron microscopy, microcalorimetry and thermal shift assays.

Up to 3 relevant publications of the team:

- Hoffmann et al., 2024. Targeting a microbiota Wolbachian aminoacyl-tRNA synthetase to block its pathogenic host. Sci. Adv.10: eado1453. DOI:10.1126/sciadv.ado1453

- Hoffmann et al., 2023. Adenosine-Dependent Activation Mechanism of Prodrugs Targeting an Aminoacyl-tRNA Synthetase. J. Am. Chem. Soc. 145(2): 800–810. DOI:10.1021/jacs.2c04808

- Lukarska & Palencia. 2020. Aminoacyl-tRNA synthetases as drug targets. Enzymes. 48: 321-350. DOI: 10.1016/bs.enz.2020.07.001.

Requested domains of expertise (or willingness to learn those) (up to 5 keywords):

Protein production

RNA production

X-ray crystallography or cryo-electron microscopy

Structure-guided drug design

AI-tools in structural biology and ligand identification