RÉPUBLIQUE FRANÇAISE
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Université de Toulouse

Approbation de la cotutelle de l'UMR INTHERES.

Conseil d'administration du 6 octobre 2025

Délibération 2025/10/CA-008

LE CONSEIL D'ADMINISTRATION,

Vu le code de l'éducation, notamment ses articles L. 712-1, L712-3 ;

Vu les statuts de l'université de Toulouse ;

Considérant les cotutelles ENVT et INRAE de l'UMR INTHERES ;

APRES EN AVOIR DELIBERE,

- **APPROUVE la cotutelle de l'UMR INTHERES par l'Université de Toulouse.**

Toulouse le 6 octobre 2025,

La Présidente de l'Université de Toulouse,

Date de transmission à la Rectrice de Région académique et publication :
13 avril 2025

Odile RAUZY

Délibération adoptée à l'unanimité des votes exprimés

Nombre de membres en exercice : 40
Nombre de membres présents ou représentés : 37

Nombre de voix favorables : 36
Nombre de voix défavorables : 0
Nombre d'abstentions : 1

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PROJET DE TUTELLE UT
PRESENTATION DE L'UMR INTHERES

Introduction au document.
Le document est organisé à partir d'éléments du DAE rédigé en anglais, sélectionnés et adaptés.
Dans les sections 1-4, les informations sur les données/projets relatifs aux recherches en santé humaine, ainsi que les compétences mobilisées pour ces recherches, sont présentées en rouge.
Les sections 5-6 sont dédiées totalement aux activités des personnels hospitalo-universitaires de l'unité.

Ce document ne développe par l'implication d'InTheRes dans les formations de 3ème cycle universitaire. Elle sera présentée oralement.

1 Unit Identification

Unit name: Innovations thérapeutiques et résistances

Acronym: InTheRes

Label and number: UMR 1436

Main scientific field:

SVE: Life, Health and Environmental Sciences

Scientific panels (in the Hcéres classification) in decreasing order :

Panel 1

SVE2: Plan and Animal Production (Agronomy), Plant and Animal Biology, Biotechnology and Biosystems Engineering

Panel 2

SVE3: Living Molecules, Integrative Biology (From Genes and Genomes to Systems), Cell and Development Biology for Animal Science

Panel 3

ST1: Mathematics

Panel 4

SVE7: Prevention, Diagnosis and Treatment of Human Diseases

Executive team:

- Alain Bousquet-Mélou: Director, ENVT
- Anne Lespine: Deputy Director, INRAE

List of the research unit's supervisory institutions and bodies:

- French National Research Institute for Agriculture, Food and the Environment – INRAE
  - Affiliation to the Animal Health Division of INRAE
- National Veterinary School of Toulouse - ENVT

Doctoral/Graduate school(s) of affiliation:

- « Sciences écologiques, vétérinaires, agronomiques et bio ingénieries » – **SEVAB**.
  Speciality: Infectiology, Physiopathology, Toxicology, Genetics and Nutrition
- « Biologie, Santé, Biotechnologies » – **BSB.** Speciality: Pharmacology
- « Mathématiques, Informatique, Télécommunications de Toulouse » - **MITT**

2 Presentation of the unit

2.1 History, location of the unit:

The Joint Research Unit (UMR 1436) **InTheRes** has been created on January 1st 2018, as a joint decision of our two supervisory institutions, INRAE and ENVT.

The objective of this creation - proposed in a former Self-assessment Report of the Animal Health Division of INRAE - was to develop a multidisciplinary strategy to address identification of improved therapeutic practices allowing the reduction of spread of antimicrobial resistances in farm animals, and to stimulate therapeutic innovations in the field of antibiotherapy.

InTheRes was created from two research teams that formerly belonged to the Joint Research Unit **Toxalim** (UMR 1331):

- Former team E6: Membrane Transporters and Resistances
- Former team E7: Pharmacokinetics, Pharmacodynamics and Modelling.

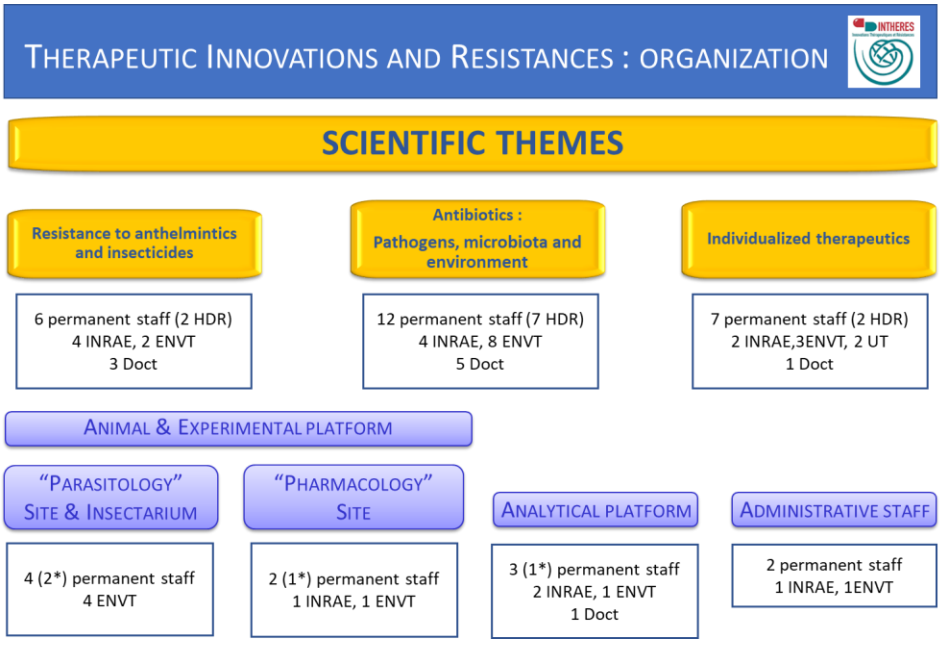
The scission met the objectives of improving the coherence and visibility of Toxalim that focuses on food contaminants toxicology, and of E6 and E7 teams that worked in a One-health perspective on resistances issues associated to the major classes of veterinary drugs, antimicrobial resistance and anthelmintic resistance. In addition, E6 and E7 teams already shared common disciplinary and methodological background.
This restructuration was announced in an evaluation report of Toxalim, with the objective to prepare and finalize the project during the contract corresponding to the period [2016-2020].

At its creation in January 2018, the **InTheRes's** staff was initially located on two sites; the campus of the ENVT (4/5 of the staff), and the facilities of the research unit Toxalim (1/5 of the staff).

Thanks to the support of the ENVT that allowed re-affectation of buildings and facilities, the entire InTheRes's staff is located at ENVT **since January 2021**.

2.2 Structure and organization of the unit:

The organization of the unit on December 31st 2024 is presented in the figure below.



The numbers in bracket with asterisk refer to people who supervise the platform and are already counted in a scientific theme

Teams, platforms, shared services, etc.:

The unit is organized as follows:

- Three scientific themes: Resistance to anthelminthics and insecticides
  Antibiotics; pathogens, microbiota and environment
  Individualized therapeutics
- Two internal platforms: Animal & experimental platform (2 sites in the campus of ENVT)
  Analytical platform
- One administrative team

The unit organization around scientific themes instead of teams was discussed at the creation of the unit and resulted in a consensus that it better fitted with our scientific organization at this stage. The management of the unit with a shared budget has facilitated such organization.
The three scientific themes were present at the creation of the unit in 2018, and were subject to evolutions according to the progressive development or reinforcement of the scope of the research activities, and in link with the arrival of several researchers in 2021.

	2018	**2021**
Theme 1	Resistance to anthelmintics	Resistance to anthelmintics and insecticides
Theme 2	Resistance to antibiotics	Antibiotics: pathogens, microbiota and environment
Theme 3	Individualized therapeutics	Individualized therapeutics

The research activities are supported by two internal platforms located on the campus of ENVT:
- One platform dedicated to analytical chemistry (drug and xenobiotic quantification)
- One platform dedicated to animal models and facilities, including an insectarium.

Size and composition of the teams (if applicable) on 12/31/2024:

On 31st December 2024, InTheRes is composed of **32 permanent people**, affiliated to INRAE (13 people), ENVT (17 people) or the Toulouse University (2 people).

Theme 1 – Resistance to anthelminthics and insecticides
This theme hosts **6 permanent people**: 2 researchers (INRAE), 2 teacher-researchers (ENVT), 1 engineer (INRAE), 1 assistant engineer (INRAE). Three PhD students are present on December 31st, 2024.
Within the [2019-2024] period, the staff was **increased by 2 people**:

Theme 2 – Antibiotics: pathogens, microbiota and environment
This theme hosts **12 permanent people**: 2 researchers (INRAE), 6 teacher-researchers (ENVT), 2 engineers (1 INRAE, 1 ENVT), 2 technicians (1 INRAE, 1 ENVT). Five PhD students are present on December 31st, 2024.
Within the [2019-2024] period, the permanent staff was **increased by 3 people**:

Theme 3 – Individualized therapeutics
This theme hosts **7 permanent people**: 1 researcher (INRAE), 4 teacher-researchers (2 ENVT, 2 UT3), 1 engineer (ENVT), 1 assistant engineer (INRAE). One PhD student is present on December 31st, 2024.
Within the [2019-2024] period, the permanent staff was **increased by 3 people.**

Analytical platform
The Analytical platform hosts **3 permanent people**: 2 engineers (INRAE), 1 of whom supervisor of the platform, 1 engineer (ENVT). One PhD student is present on December 31st, 2024. One PhD student is present on December 31st, 2024.
Within the [2019-2024] period, the permanent staff was **unchanged**:

Animal & experimental platform
The Animal & experimental platform hosts **5 permanent people** who are located at two different sites located in the campus of ENVT.
Within the [2019-2024] period, the permanent staff of the platform was **reduced by 2 people**:

Administrative staff
The Administrative staff is composed of **2 permanent people:** 1 assistant engineer (INRAE) and 1 administrative agent (ENVT)
Within the [2019-2024] period, the permanent staff was **reduced by 1 people**:

Considering permanent staff, 10 people left the unit during the 2019-2024 period, 8 were recruited on **open permanent positions** (INRAE or ENVT) and 7 joined the unit by **mobility** (INRAE or ENVT). The positive balance is the consequence of the support by our supervisor institution (open positions) and of our attractivity (mobility).

Considering **PhD programs**, we significantly increased the number of funded PhD fellows between Mid-2019 and 2024: from 5 to 11 who were present in the staff in 2024; in addition,11 PhD were completed (defense) during the 2019-2024 period.

Financial resources

The **recurrent resources** coming from our supervisory organisms (INRAE, ENVT) have **grown from 61 k€ in 2019 to 138 k€ in 2024**, representing a 122% increase. This increase was of 80% of ENVT resources and 144% for INRAE resources.

During the [2019-2024] period, the amount of **non-recurrent financial resources (grants/contracts)** was about **800-1100 k€ per year** (in average). The recurrent resources (INRAE/ENVT) represented for the period about 8-10% of the total budget. The total amount of financial resources allows the unit to develop its scientific strategy, and to maintain internal solidarity.

2.3 Scientific orientations of the unit and its teams (if applicable):

Context and missions

The main mission of the unit is to produce scientific knowledge that contributes to the development of a prudent and responsible use of anti-infectious drugs, with a special focus on antibiotics and anti-parasitic drugs (anthelminthics and insecticides). Through this mission, our ambition is to address the multiple challenges of: (i) minimizing the risks for Humans linked to the emergence and spread of antimicrobial resistances, (ii) ensuring animal health and welfare by combating diseases of bacterial and parasitic origin while respecting environmental ecosystems, (iii) preserving the effectiveness of antibiotics and anti-parasitic drugs.

Because of the multidisciplinary competences and methodological skills of our group, which transversally cross the human and animal sectors, we develop our projects for animals – including food-producing animals and companion animals - as well as for human medicine.

Scientific objectives

The projects developed in the scope of our scientific themes aim at producing innovations, in the field of **therapeutic solutions** for Themes 1 and 2, and in the field of **therapeutic interventions** – more individualized and personalized treatments – for Theme 3.

Strategy

The strategy developed since the creation of the unit was established after careful analysis of our competences and skills.

Since many years, the competences in pharmacology and **pharmacokinetic/pharmacodynamic (PK/PD) modelling** constitute a hallmark of our laboratory, in the veterinary pharmacology community and beyond. The PK/PD approach allows the characterization and understanding of the Dose-Concentration-Effect relationship, and offers an invaluable framework for the development of optimal dosage regimens of compounds combating bacterial infections or parasitic infestations.

The competences in **analytical chemistry** are crucial for our strategy. They are present since many years in the lab and were continuously reinforced (equipment and human resources).

The progressive development of projects exploring mechanistically the interactions between the anti-infectious drugs and their targets has been permitted by the implementation of competences in **microbiology**, **parasitology**, **cellular biology**, **genomics**.

The other historical and fruitful competences of our group are in **mathematics/statistics**. The importance of sustaining these competences to support our researches was highlighted by our supervisor institutions. These competences were progressively oriented to the development of **Artificial Intelligence**.

An important feature of our group lies in its long-standing links with the pharmacology of human drug and colleagues from the Faculty of Pharmacy, which was further reinforced at the creation of the unit through the recruitment of a medical pharmacologist (PU-PH). It legitimized and supported the development of researches in the human sector in our unit.

Scientific orientations

The scientific orientations of each research themes are briefly described below.

Theme 1 – Resistance to anthelminthics and insecticides
The researches conducted in this theme are at the intersection of pharmacology and parasitology, focusing on the mechanisms underlying resistance to anthelmintics and insecticides in parasitic nematodes and insect vectors of veterinary importance. The "insecticide" theme was initiated in 2021 thank to the mobility of 2 teacher-researchers of ENVT.

Theme 2 – Antibiotics: pathogens, microbiota and environment
Since the creation of InTheRes (2018), the theme 2 has developed researches on the optimization of therapeutics against bacterial pathogens in animals or humans, based on modelling approaches.
At the beginning of the current contract (2021), 2 new scientific orientations were developed under this theme:

- Exploration of the dissemination of both antimicrobial resistant bacteria (and resistance genes) and antibiotic residues, from gut microbiota to environmental compartments.
- Exploration of the mechanisms of antimicrobial resistance gene transfer in *Staphylococcus aureus*.

Theme 3 – Individualized therapeutics
The theme 3 is dedicated to researches applying to both animal and human sector. Indeed, since the creation of InTheRes (2018) it hosts a medical/pharmacist people (PU-PH). Through advanced mathematical modelling and Artificial intelligence, researches in theme 3 aims at developing precision livestock farming in the animal sector and precision medicine in human health.

3 Research environment

InTheRes benefits of the activities of GenoToul (https://www.genotoul.fr/en/l, the network of technological platforms of Toulouse.

InTheRes interacts with the INRA-Occitanie-Toulouse Center, and with the network of its research units. We had collaborations with teams of the Units Toxalim, IRSD (Digestive Health Research Institute), IHAP (Host-Pathogens Interactions), GenPhySE (Genetics, Physiology and Farming Systems).

InTheRes is member of the " Structure Fédérative de Recherche Biologie et Biotechnologie pour la Santé " (SFR-B2S). This structure was created in 2023 with the objective of disseminating knowledge and information between the various research units in Toulouse.

InTheRes is member of the Carnot Institute "Franc Futur Elevage" (FFE), led by the Animal health Division of INRAE. Several research programs have been founded by the Carnot-FFE, including projects co-funded by the Carnot Pasteur Microbes&Santé.

In continuity with Carnot Institutes, InTheRes interacted with transfer structures: (i) the SATT of Toulouse (TTT, Toulouse Tech Transfert) with a project initiated in 2017 that cancelled in the early 2020, and (ii) more recently the structure "INRAE transfert" through the submission of a project to the "Challenge Astragale" (early 2025).

InTheRes has historically strong interactions with the University of Toulouse, in particular with the Faculties of Medicine and Pharmacy in the field of Pharmacology, and with the Toulouse Mathematics Institute. These interactions are related to both research and teaching, through a strong involvement in master degrees (participations, co-responsibility of master degree).

The most recent concretizations for teaching/training are:

- The co-responsibility of a Master degree – M2 Pharmacokinetic and pharmacodynamic modelling – for which the ENVT has a co-habilitation
- The association of InTheRes is the recent EUR UNITEID (University of Toulouse graduate school on Emerging Infectious Diseases).

The two internal platforms

- The Animal & experimental platform of InTheRes has links with other structures, at local and national levels. It is Integrated into the INRAE Animal Welfare Structure's network since 2020. At Toulouse, the Anexplo platform (https://anexplo.genotoul.fr/) is specialized in the housing and development of animal models. We initiated in 2024 the project of integrating Anexplo, consisting in proposing our platform to the scientific community for the housing of porcine species and the development of biomedical models in pigs.

- The platform is organized in two sites located on the campus of ENVT: The "Physiology site" and the "Parasitology site" which hosts an **insectarium**.

- The Analytical platform has strong collaboration with the team "EXPER" of the research unit Toxalim (which is hosted on the premises of InTheRes). In addition, the platform is developing a partnership with the laboratory of Pharmacokinetics and Toxicology of Toulouse's hospitals (https://www.chu-toulouse.fr/-pharmacocinetique-et-toxicologie-), through the co-development and validation of analytical techniques for anti-infectious drugs in human sample (CHU laboratory) or experimental (animal, *in vitro*) samples (InTheRes platform).

Links with clinical research: continuum between research laboratories and care structures

The interactions with the University hospital (CHU) of Toulouse have been strongly reinforced because of the arrival in the staff of the Head of the laboratory of Pharmacokinetics and Toxicology of Toulouse's hospitals (https://www.chu-toulouse.fr/-pharmacocinetique-et-toxicologie-), recently joined by another UT3 agent (PHU).

Through the activities of the laboratory of Pharmacokinetics and Toxicology, we interact with several hospital services - Intensive Care Unit, Infectious Diseases Unit, Respiratory Disease Unit (adult and pediatric) – as well as with the Hematology Unit of the Cancer Institute of Toulouse. Therapeutic drug monitoring (TDM) and research activities focus on antibiotics, antifungal drugs, and antiretroviral drugs.

4 The research themes

The research themes tackled by InTheRes over the reference period are organised under 3 thematic axes.

Theme 1 – Resistance to anthelminthics and insecticides

The research conducted in this theme are at the intersection of **pharmacology** and **parasitology**, focusing on the mechanisms underlying resistance to **anthelmintics** and **insecticides** in parasitic nematodes and insect vectors of veterinary importance.
They aim to decipher the adaptive processes driving drug resistance in parasites under pharmacological pressure, and by understanding these mechanisms, to identify targets for sustainable solutions allowing to slow resistance development and establish early detection of pharmaco-resistance in livestock.
The resistance to anthelminthics is investigated using ***Caenorhabditis elegans*** as genetically tractable model. The targeted clinically relevant parasites are *Haemonchus contortus* in ruminants, and *Dirofilaria immitis* in companion animals. Two insect species are used as models to investigate the insecticide resistance mechanisms: the cat flea, *Ctenocephalides felis*, major ectoparasite of companion animals, and its resistance to fipronil, and the stable flies, *Stomoxys calcitrans*, major ectoparasite of large animals, and its resistance to pyrethrinoids.

Theme 2 – Antibiotics: pathogens, microbiota and environment

Since the creation of InTheRes (2018), the theme 2 has developed researches focusing on:
- The **optimization of therapeutics against bacterial pathogens in animals or humans**, with special focus on old antibiotics, based on **PK/PD approach, population pharmacokinetics** and relevant models to explore optimal dosing and to identify alternative solutions to critically important antibiotics. We use *in vitro* models/methods (time-kill studies, Hollow-Fiber Infection model (HFIM)) that are used for investigating PK/PD of bug-drug couples from both animal and human sectors.
- In-field evaluation of collective treatments of food-producing animals (metaphylaxis) especially those distributed by drinking water, through the investigation of pharmacokinetic variability and variability of individual drinking behaviour.

At the beginning of the current contract (2021), theme 2 was enriched by the development of two other topics. One consists in **exploring the dissemination of both resistant bacteria, resistance genes and antibiotic residues, from gut microbiota to environmental compartments**.
The other topic investigates two bacterial mechanisms related to the development of antimicrobial resistance: bacterial tolerance and persistence in *Escherichia coli*, and the dynamics of **antimicrobial resistance gene transfer in *Staphylococcus aureus***.

Theme 3 – Individualized therapeutics

The theme 3 denomination as "Individualized therapeutics" attempts to encompass the **projects of precision medicine in human health** and those related to precision livestock farming in the animal sector.
For livestock, theme 3 develops projects that include individual behavioural monitoring through sensors:

- the individual drinking behaviour as a major driver of drug ingestion by the animals (in link with theme 2),
- any other behaviour aiming at early detecting specific diseases, or at identifying welfare impairments.

In addition to the monitoring technologies using sensors, large-scale video tracking now enables, using **Artificial intelligence,** real-time and individualized heath/welfare assessment in farm settings.

In human health, researches focus on individualized drug dosages for specific subpopulations (eg. obese patients, breastfeeding women…) to optimise efficacy. Again, population pharmacokinetic modelling is used to account for inter-individual variability and optimize treatment strategies.

Together, these efforts underscore precision medicine as a driver of improved outcomes in both animal and human health.

The outcomes for international, national an local calls for projects

During the 2019-2024 period, InTheRes members obtained grants in the following projects (excepting human clinical research, described in section 5).

International projects: 8
2 as leader (1 **EU_ICRAD**, 1 **JPIAMR**), 5 as partner (1 **H2020**, 1 **EU_PAHW**, 2 **JPIAMR**, 2 **Interreg-POCTEFA**)
InTheRes members were also partners in 3 **COST Actions**.

National projects: 22
ANR: *3 as leader* (1 PRC, 1 JCJC, 1 PRME). **ANSES/PNR-EST**: 2 as leader, 1 as partner.
PEPR MIE: 1 as partner
Carnot FFE: 5 as leader, 1 as partner. **EcoAntibio** (ANSES): 1 as leader, 1 as par partner.
CASDAR : 3 as partner (CASDAR project are mandatory led by Agricultural technical institutes, but InTheRes was the scientific leader)
IFCE (horse sector): 4 as leader.
SANBA (INRAE "Metaprogam"): 1 as partner

Grants at local level: 5
They are mainly associated with the **Region Occitanie funded RIVOC project** ("Risques infectieux et vecteurs en Occitanie"), supporting our researches on insecticides.

Focus on human health sector projects managed under theme 2.
In some projects, IntheRes was partner/leader of consortiums aiming at developing antibacterial solutions for human health.
Two European JPIAMR projects (InTheRes partner)

- **Developing combinations of CO-ACTIVE antimicrobials and non-antimicrobials – CO-ACTION**
  InTheRes contribution: Animal model to investigate the impact of minocycline on the gut microbiota (Vallé et al, 2021)
- **Flavodoxin inhibitors to kill resistant bacteria – FLAV4AMR**

InTheRes contribution: *In vitro* PK/PD models to investigate antibiotic/flavodoxin inhibitor combination against *Helicobacter pylori* (Beyria et al, 2023)
One National Inter-Carnot (with PastersMS) project (InTheRes leader)

- **Bacteriophages/antibiotic combinations to prevent resistances in *Pseudomonas aeruginosa* – PHAGODRUG**

InTheRes contribution: *In vitro* dynamic PK/PD model - Hollow-fiber Infection Model (HFIM) to investigate the combination of ciprofloxacin (systemic) and phages (loavby mimicking systemic and local routes lavodoxin inhibitor combination against *Helicobacter pylori* (Beyria et al, 2023)

5 Focus of Peggy Gandia's projects within InTheRes (Theme 3 – Human sector)

5.1 Past and present activities

Human clinical research is organized around three themes characterizing subpopulation needing **individualized drug dosage strategies**: (i) medication use during breastfeeding and its accumulation in the breast milk ingested by the infant; (ii) the influence of obesity on the pharmacokinetics of drugs and dosing adjustments; (iii) the pharmacokinetics of antimalarials consumed as herbal tea by local populations.

Exploration of drug diffusion into breast milk

Since 2018, Peggy Gandia has been a member of the European Consortium CONCEPTION. The European Consortium CONCEPTION was created in 2018 with the goal of documenting the transfer of drugs into breast milk and the risks to the breastfed infant when the mother is on medication. The project, with a planned duration of 4 years, consists of several work packages (WP). Peggy Gandia was involved in two WPs (WP3 and WP4) with a total funding of €200k. The project began in April 2019. In WP3, Peggy Gandia participated in the development of physiologically-based pharmacokinetic (PBPK) models for a broad range of medications prescribed to varying extents in different countries. The proposed PBPK models, created using *in vitro* and *in vivo* data, aim to predict the absorption, distribution, metabolism, and excretion (ADME) of chemical substances in humans, based on pathophysiological variables. In WP4, Peggy Gandia's role was to document the transfer of amoxicillin into breast milk through a multicenter clinical study, which Peggy Gandia coordinated. The clinical research protocol was submitted in July 2021 to the Ethics Committee and received approval in September 2021. The analysis of blood samples (n=75; maternal samples only) and milk samples (n=75) collected from 25 mothers, along with the pharmacokinetic interpretation conducted using a population-based approach, were carried out at the Pharmacokinetics and Toxicology Laboratory (Toulouse University Hospital) in collaboration with UMR1436-INTHERES. The article is finalized and is currently undergoing approval by the WP4 members. The scientific output for Peggy Gandia consists of 10 articles published in international journals.

Influence of lean body mass on the pharmacokinetics of drugs administered to obese patients

According to the WHO, the number of obese individuals is expected to reach 50% of the global population by 2035. Obesity (BMI > 30 kg/m²) is a chronic disease. When these patients receive drug treatments, their dosing regimens have been determined for non-obese patients with a BMI between 20-30 kg/m². However, for non-obese patients (BMI between 20-30 kg/m²), the ratio of lean mass to total mass remains generally constant. Moreover, eliminating organs (i.e., kidney/liver) have an elimination capacity proportional to lean mass and thus to total mass. This justifies adjusting dosages based on total mass for non-obese patients.
In obese individuals, the increase in total mass reflects an increase in fat mass without a proportional increase in lean mass, suggesting that elimination capacities do not increase proportionally to total weight. In the absence of documented dosing regimens for obese individuals, it is logical to question the relevance of adjusting dosages based on total weight in these patients.

The lack of data on medications prescribed for obese patients is particularly pronounced for less commonly used drugs like acyclovir, an antiviral active against certain Herpesviridae. In 2021, the ACICLOPTIM project "Individualization of Dosing Regimens in Obese Patients: Application to acyclovir" received funding (€30k) from the Toulouse University Hospital as part of the ARI 2021 project call. The protocol received approval from the ethical committee in June 2022. Due to administrative delays, patient inclusions began in March 2024. Sarah Baklouti (PharmD with a PhD in Pharmacokinetics and Modeling) is PI of this project. The analysis of blood and urine samples, along with the pharmacokinetic interpretation conducted using a population-based approach, will be carried out at the Pharmacokinetics and Toxicology Laboratory (Toulouse University Hospital) in collaboration with UMR1436-INTHERES.

Pharmacokinetic Exploration of Antimalarials in Endemic Regions

In December 2020, at the request of Jean-Christophe BARALE (Research Director of the "Malaria Target Biology and Antimalarials" group at UMR CNRS 3528) and Professor Antoine BERRY, Peggy Gandia joined the recently established KARMA Consortium, coordinated by Jean-Christophe BARALE. This consortium aims to document the therapeutic interest and risks associated with the consumption of herbal tea made from *Artemisia annua*, administered for preventive or curative purposes. Peggy Gandia is the reference person for pharmacokinetic and pharmacodynamic exploration in the clinical projects led by the consortium (The clinical studies are ongoing).

5.1 Future activities / Trajectory

Personalized drug dosage

The dosage regimens applied in anti-infectious therapy are usually defined for a population without taking into account all the characteristics of the patient (age, sex, weight, renal and hepatic functions, co-prescriptions ...). This "one size" approach may lead to patient under- or overexposure, resulting in inefficacy or toxicity. In hospital, dosage regimen individualization is achieved through therapeutic drug monitoring (TDM), which consists in measuring blood concentrations of drugs in treated patients and comparing the value to recommended levels. These recommended levels are intervals in which the concentrations must be at a given moment of the PK profile, most often a few minutes before drug re-administration. In theory, a patient with a concentration in this range should have a global exposure that ensures both efficacy and limited toxicity. In practice, these intervals lead to erroneous conclusions for a large number of patients. This is due to an insufficient correlation between these measured concentrations and the global exposure, to allow an accurate PK interpretation and an effective dosage adjustment. The Bayesian approach allows to more accurately inform about the patient's PK profile, by using a population PK model (PK-POP) and patient-specific information, such as plasma concentrations, and/or individual characteristics (weight, height, sex, creatinine clearance ...).

Pharmacokinetic/pharmacodynamic and medical imaging

Today, investigating drugs pharmacokinetics and pharmacodynamic through imaging approaches is particularly valuable in the context of **precision medicine**, as medical imaging is non-invasive and provides access to deep tissues that are inaccessible through conventional matrices such as blood and urine.

- ***Drug pharmacokinetics and tissue identification***

Modern medical imaging techniques, such as PET scans (Positron Emission Tomography coupled with CT scans), allow for the *in vivo* study (i.e., in animals) and in patients of the distribution of radiolabeled drugs at the level of the different tissues in each organ. These approaches are particularly relevant because they allow to document the kinetics of a drug depending on the nature of the tissues it distributes into. This approach is mainly applied in oncology (identification of healthy, inflammatory, tumor, and necrotic tissues). We already published 2 articles on this topic in 2017 in collaboration with the IUCT-Oncopole (PMID: 27995528; PMID: 27395047). In connection with new ongoing collaborations with the University of Caen, we are considering evolving our approach.

- ***Pharmacokinetic/pharmacodynamic exploration of biotherapies***

The emergence of biotherapies (monoclonal antibodies and related structures), whose pharmacokinetics are very different and much more complex than conventional drugs (i.e., small chemical structures), necessitates a review of preclinical and clinical exploration approaches for these new drugs prescribed for a wide range of indications (cancer, inflammatory, infectious diseases, etc.).

As mentioned above, imaging techniques allow for precise documentation of the pharmacokinetics of these biotherapies in the different compartments of the body, as well as the relationship between exposure and response (efficacy and toxicity). Understanding the PK/PD relationship of these new drugs is essential to optimize dosing regimens on an individualized basis.

A project was submitted to the AAP (Inserm) titled "Interdisciplinary Approaches to Oncogenic Processes and Therapeutic Prospects: Contributions of Physics, Chemistry, and Engineering Sciences to Oncology," in collaboration with the University of Caen (GANIL, CERMN, UMR 6030, Centre François Baclesse, LPC).

Early detections

- ***Multidimensional analysis of medical biology data for human health***

In human health, the multidimensional analysis of medical biology data constitutes a powerful yet underexploited resource for early disease detection. These data, routinely generated in university hospital laboratories and private diagnostic networks, contain latent signals of pathophysiological change. However, when interpreted in isolation from clinical diagnoses, their potential to inform early interventions remains limited. To unlock this potential, we are developing integrative models that combine laboratory data with information from the **French National Health Data System (SNDS)**, which infers diagnostic intent through prescription patterns and specialized testing. The convergence of these datasets creates the foundation for **artificial intelligence algorithms allowing identifying early warning signs of diseases, before they become clinically apparent**.

This work was initiated in 2024 through a collaboration with SNDS and Cerballiance laboratories. It is currently focused on overcoming regulatory and ethical hurdles, particularly those related to **General Data Protection Regulation (GDPR)**, in order to establish a shared and secure framework for data use. Once in place, this infrastructure will support scalable, high-impact research in preventive and personalized medicine.

As part of this work, we recently published a study in *Scientific Reports* introducing a new method to define more accurate biological reference regions and decision boundaries using multidimensional data. Applied to **a large American dataset of over 20,000 individuals**, our approach demonstrated superior sensitivity and specificity compared to traditional methods. This study underscores the importance of analysing a broad panel of biological variables to enhance early disease detection and characterization.

6 Publications track record (Theme 3 – Human sector)

2019-2024 period

En rouge : les noms des personnels hospitalo-universitaires de l'unité

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7 Tableau personnels InTheRes – Convention d'UMR INRAE / ENVT

Contrat quinquennal 2021-2026 (vague A)

La liste des personnels Statutaires est actualisée au **1er janvier 2025**
Seuls les personnels permanents sont listés
Titulaires = Fonctionnaires
Non-titulaires = CDI / fonctionnaires stagiaires / PHU

Personnels statutaires de l'UMR ***(inclure les personnels statutaires des établissements partenaires mais non tutelles de l'UMR)***

			Civilité	Nom	Prénom	Grade ou qualité
Chercheurs et Enseignants -Chercheurs *(Rajouter autant de lignes que nécessaire)*	**INRAE**	Personnels titulaires Effectif = **5**	M	BETOUS	Rémy	CR
			Mme	DORDET-FRISONI	Emilie	CR
			M	GIRAUD	Etienne	CR
			Mme	HERNANDEZ	Noslen	CR
			Mme	LESPINE	Anne	DR
		Personnels non titulaires				
	ENVT	Personnels titulaires Effectif = **10**	Mme	BIBBAL	Delphine	MC
			Mme	BOULLIER	Séverine	PR
			Mme	BOUHSIRA	Emilie	MC
			M	BOUSQUET-MELOU	Alain	PR
			M	CONCORDET	Didier	PR
			Mme	FERRAN	Aude	PR
			M	IMAZAKI	Pedro	MC
			Mme	LALLEMAND	Elodie	MC
			Mme	LAVOUE	Rachel	MC
			M	LIENARD	Emmanuel	MC
		Personnels non titulaires				
	UT3	Personnels titulaires Effectifs = **1**	Mme	GANDIA	Peggy	PU-PH
		Personnels non titulaires Effectifs = **1**	Mme	BAKLOUTI	Sarah	PHU
Personnels statutaires ITA et IATOS *(Rajouter autant de lignes que nécessaire)*			**Civilité**	**Nom**	**Prénom**	**Corps**
	INRAE	Personnels titulaires Effectif = **8**	Mme	ALBERICH	Mélanie	IR
			Mme	ARPAILLANGE	Nathalie	TR
			M	BOURDAUD'HUI	Pascal	AI
			Mme	CLAUSTRE	Lucie	IE
			M	FACCINI	Julien	AI
			M	GIMENO	Rémi	AI
			Mme	LACROIX	Marlène	IR
			Mme	ROQUES	Béatrice	IR
		Personnels non				
	ENVT	Personnels titulaires	Mme	DUPOUY	Véronique	IR
			Mme	GOUNAUD	Sonia	AT
			Mme	GOURBEYRE	Ophélie	TR

		Effectif = **7**	Mme	LACOMBE	Marine	IE
			M	RAMON PORTUGAL	Felipe	IR
			M	REYNOLDS	Brice	IR
			Mme	ROQUES	Martine	AT
			Mme	GUTIERREZ	Lis	SA CDI
		Personnels non titulaires Effectif = **1**				