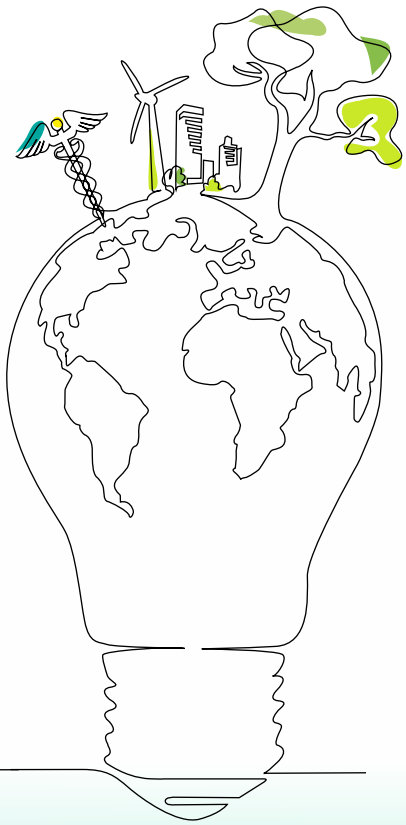
BIOHEALTH WHITE PAPER

MONTPELLIER UNIVERSITY OF EXCELLENCE



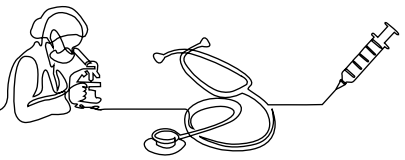
BIOMARKERS & 6P MEDICINE

PERSONALIZED
PREVENTIVE
PREDICTIVE
PARTICIPATORY
PATIENT-CENTERED
PRECISE

MUSE
BIOHEALTH DEPARTMENT
MONTPELLIER UNIVERSITY OF EXCELLENCE

MUSE BIOHEALTH WHITE PAPER
Biomarkers and 6P Medicine
Author and coordinator: Brigitte Couette

Publication director: Philippe Augé
Design: MUSE Communication



foreword

by Philippe Augé
President, University of Montpellier

Jacques Mercier
Vice-president of Research
University of Montpellier

François Pierrot
I-SITE Executive Director
Montpellier University of Excellence

Pierre-Emmanuel Milhiet
Director of BioHealth Department
Montpellier University of Excellence

Philippe Van de Perre
President of the Research Committee
on Biomedical and Public Health Issues (CBRSP)

One of the major challenges for tomorrow's health and medicine, especially in fast changing environments, is to provide medical solutions that continually become more predictive and personalized, from prevention to treatment.

Inseparable from diagnostic and prognostic biomarkers, and therapeutic choices, targeted therapies represent a path for the future that simultaneously takes pathology sub-types as well as the patient's physiological characteristics into account in a given treatment protocol, thus offering the potential for more effective personalized treatment.

To help move this public health challenge forward, the Montpellier-Nîmes BioHealth Department has written its first white paper, entitled: **Biomarkers and 6P Medicine** (Personalized, Preventive, Predictive, Participatory, Patient-centered, Precise). Produced as part of the MUSE project, this white paper is designed for the entire community, territorial authorities, companies in the sector. It is also intended to be distributed internationally.
The result of a collective effort by the entire BioHealth community, Biomarkers and 6P Medicine is divided into thematic topics related to seven research axes: quantitative biology, oncology, genetics-epigenetics, infectiology and immunology, experimental and regenerative medicine, neurosciences, and technologies for health and bioengineering.

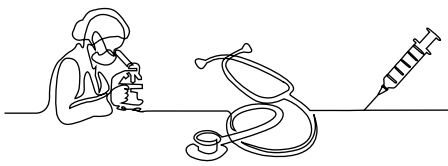
It also presents some of the main success stories that have led to fundamental discoveries and the development of innovative technologies created at our site. The encouraging successes offer further motivation to continue along this path.

Finally, group thinking brought about by writing this White Paper has turned out to be key for evaluating needs and defining actions to carry out over the coming years in academic and clinical research on biomarkers and 6P Medicine.

One benefit of the cross-functional expertise united in this work is that it highlights the intertwined relationship between care, research, and innovation in supporting people's health and quality of life. In particular, it successfully reveals the strengths of the Montpellier-Nîmes site in terms of fundamental and clinical research, and education, while highlighting the strong potential for developing partnerships with companies.

Similar initiatives on cross-functional themes covered by other research departments at our target university are certain to emerge and demonstrate the vitality of research within each of our communities. Destined to be updated regularly, this white paper represents a true space for collaborative work efforts and dialog among all partners and players in the socio-economic world, a tool to promote and communicate on biology and health science research. It helps generate recognition for the Montpellier-Nîmes site as a reference in France and internationally in the field of biomarkers and personalized medicine, thus also contributing to the exposure of research efforts in our region.

Created in December 2017 as part of the Montpellier University of Excellence Foundation, the BioHealth Department is one of five key research departments representing the future target university, the ultimate result of the MUSE I-SITE.



introduction

A white paper on bio-health?

The BioHealth community at the Montpellier-Nîmes site wanted to create a white paper to help a synergetic research program emerge on a topic that is situated at the crossroads of all BioHealth Department disciplines.

"Biomarkers and 6P Medicine" was chosen as the theme. This white paper looks at existing resources, success stories, and prospects, as well as the main actions that need to be implemented to reach objectives. The community is therefore considering the most effective ways to increase its attractiveness with respect to academic, clinical, and industry partners as well as local authorities.

The long-term goal is for our identity to be well-recognized locally, nationally throughout France, and internationally.

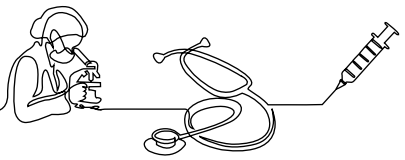
General biomarker context

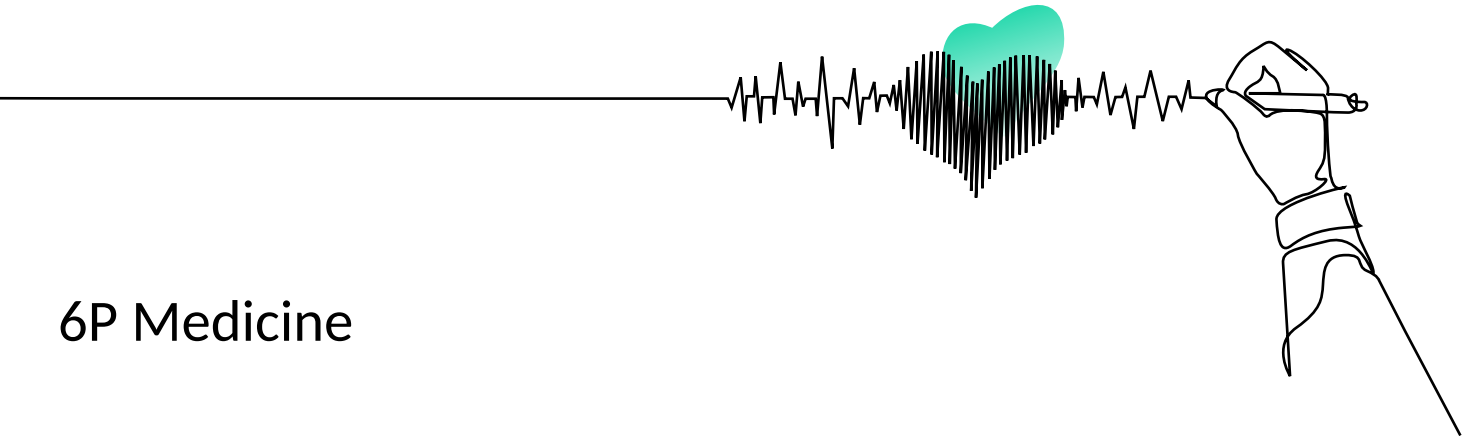
The concept of biomarkers is not new, as some biomarkers have been used for many years, such as for glycemia in diabetes, carcinoembryonic antigen, and prostate antigen specific to some types of cancer. On the other hand, the development of high-throughput approaches, known as "omics", has emerged over the past twenty years and contributed significantly to accelerate research in this area, ranging from molecular biology using massive genome sequencing and data expression using Next Generation Sequencing or RNA sequencing, to biochemistry using proteomics and metabolomics. Automation of these new analysis and collection techniques, combined with high-throughput bioinformatic and biostatistical analyses have further encouraged the emergence of this notion of biomarkers.

Biomarkers are defined as quantifiable biological characteristics related to a normal or pathological process. They must be measured and evaluated objectively in order to be used as reliable direct or indirect indicators for pathological biological processes or responses to treatment. Depending on their functions, biomarkers are used to evaluate the risk of developing a pathology (risk biomarkers), predict or track pathology evolution (prognostic biomarkers), establish a precise diagnosis (diagnostic biomarkers), or predict therapeutic response (predictive biomarkers).

Biomarkers are associated with "companion" diagnostic tests as tools for therapeutic orientation.

One of the main challenges in current translational research is to identify the appropriate biomarker(s) that will enable clinical practitioners to understand and monitor a disease's progression or response to treatment as early as possible in the process. Early detection also represents a key factor. Essential prerequisites for developing personalized medicine, or 6P medicine, the discovery and validation of new biomarkers will no doubt lay the foundation for medicine in the XXIst century.





6P Medicine

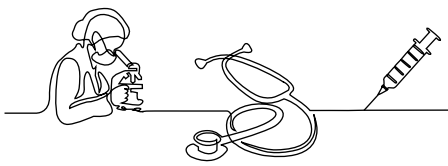
The expression "personalized medicine" was first used in the United States in 2000. In 2008, the President's Council of Advisors on Science and Technology (PCAST) defined personalized medicine as follows:

"Personalized medicine is the tailoring of medical treatment to a patient's individual characteristics. This customization does not mean that drugs are created for a single individual. Rather, it is the ability to classify individuals into sub-populations characterized by their predisposition to certain diseases or by responses to a particular treatment. Preventive or therapeutic measures are therefore prescribed to patients who will benefit from them while avoiding imposing side effects on individuals who will not benefit from them. The costs associated with these side effects are also avoided."

In 2013, Leroy Hood of the Institute for Systems Biology (ISB) defined personalized medicine as "4P Medicine", with four main features:

4P medicine is personalized, as it takes the individual's genetic or protein profile into account; preventive, as it considers health problems by focusing on wellness rather than the disease; predictive, by indicating the most appropriate treatment(s) for the patient and trying to avoid the side effects of drugs; participatory, leading patients to become more responsible concerning their own health and care.

More recently, notions of patient-centered care and precise medicine have emerged. This is referred to as 6P Medicine.



Strategic and economic stakes

At an international level, the United Nations' Sustainable Development Goal 3 is entitled: "Ensure healthy lives and promote well-being for all at all ages"

In France, the CoVAlliance permanent committee is in charge of coordinating research promotion, under the leadership of the Aviesan Alliance, that brings together aviesan's member organizations and their valorization departments.

For France's Occitanie region, 6P Medicine is included in one of the seven Strategic Activity Domains of the Regional Innovation Strategy for Intelligent Specialization. Entitled "Health and Medicine of the Future", the domain focuses on: (1) becoming the "Diagnostics Bay" of southern Europe to provide visibility for diagnostics companies in Europe and abroad; (2) serving as a reference region for developing the "Health Journey"; and (3) promoting the development of targeted therapy and personalized medicine.

It is also important for Montpellier Métropole, which is the only one of fifteen metropolises in France to focus on health as part of its State-Metropolis Pact. The Montpellier project is entitled: "Montpellier France Health Hub". This innovative and unifying initiative brings together health stakeholders, such as those involved with education, research and care, companies, and local authorities, to develop major projects and highlight Montpellier on a European scale.

MUSE I-SITE is also involved, as the 6P medicine approach fits perfectly into one of the foundation's main themes, "Care".

Lastly, the economic stakes are key for companies in the health sector. According to LEEM, a French professional association for drug companies, the global market for biomarkers is expected to soon exceed $45 billion.

Many promises are being made in this context, such as: optimizing medical treatment, decreasing treatment side-effects, and generating significant economic benefits.

Progress made in genetics, proteomics, medical imaging, diagnostics, and therapeutics, accompanied by consideration for related societal aspects, will accelerate this method for treating patients over the next few years. In the long-term, all patients could be concerned by 6P Medicine.

Biomarkers are highly likely to play a determining role in future progress in this space. However, even though many biomarkers have already been identified and validated clinically, very few actually reach the market.

What strengths in the field?

Surveys were conducted in 2015 regarding the BioHealth Department in Montpellier and Nîmes, with the participation of about one hundred academic research teams involved with biology, health, and chemistry, along with about thirty hospitals. The goal was to identify strengths and needs in the fields of biomarkers and targeted therapies. A similar survey on industry companies was carried out in parallel by the Eurobiomed competitiveness cluster.

An analysis of these two surveys showed that nearly all the academic laboratories were working directly or indirectly on biomarkers, with a primary focus on oncology, neurology, hematology, and infectiology. In addition to generating a clear overview and large database of biomarkers in the area, these surveys also made it possible to identify needs regarding the equipment for validating biomarkers. As a result, a State-Region Plan Contract (CPER-IBDLR 2015-2020) was obtained to acquire cutting-edge equipment totaling €6.4 million, thus helping to reinforce attractiveness, accessibility, and excellence for the technology offering on essential platforms for validating biomarkers.

Survey data was updated recently by a market study funded by Occitanie regional authorities as part of the Prime@Muse project. Detailed results from the study are provided on page 21.

"Biomarkers and 6P Medicine"

This topic unites and mobilizes a large number of health stakeholders in the Montpellier and Nîmes area, and integrates several regional programs. Biomarkers and 6P medicine could end up becoming a regional, national, and international showcase for biology and health sciences, boosting momentum in the field along with territorial marketing efforts focused on attracting investors.

EXISTING RESOURCES AT THE MONTPELLIER-NÎMES SITE

The Montpellier-Nîmes site is recognized for its world leading biohealth research work and very high-level treatment offering, combined with an extremely dynamic community of biomedical companies, enhanced by particularly well developed and renowned educational possibilities.

University of excellence context

A university with a multidisciplinary health approach, University of Montpellier is the only university in the Occitanie region that has earned the I-SITE label (Initiatives-Sciences-Innovation-Territory-Economy) in France's Investments in the Future Program, with its MUSE - Montpellier University of Excellence project focusing on three key societal challenges: Feed - Care - Protect. The university is particularly active with health-related research in partnership with all the research organizations present in the area, notably CNRS, Inserm, and IRD.

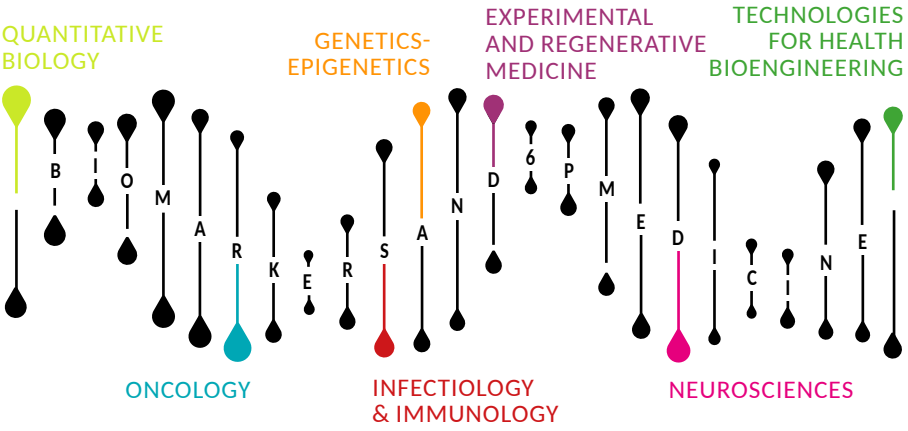
University of Montpellier (UM) is ranked #2 in the Reuters classification of French universities. UM is part of a very select group of research-intensive universities, and was ranked #1 worldwide in Ecology (Shanghai ranking) in 2018 and again in 2019, ahead of Oxford University (UK), UC Davis (USA), and Wageningen (NL).

University of Montpellier is one of 16 French establishments involved with Europe's 17 leading universities awarded the call-for-pilots launched in October 2018.

The educational offering at University of Montpellier is of world-class quality in the health and biological science fields, with 6 Master's degrees, 28 programs, and 4 doctoral schools: CBS2 (Chemical and Biological Sciences for Health), SMH (Human Movement Sciences), I2S (Information, Structures, and Systems Sciences), and GAIA (Biodiversity, Agriculture, Food, Environment, Soil, Water).

RESEARCH

Research comprises over 1,100 researchers and research-professors working in 26 institutes and laboratories as part of the BioHealth Department, organized into 7 thematic directions for research, teaching, and coordination.



Biomarkers and 6P medicine, a cross-functional focus

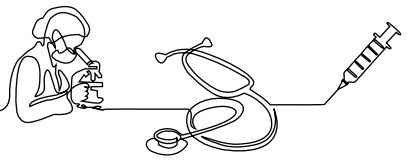
The BioHealth Department is based on a foundation of excellence, leveraging many ATIP-Avenir teams (20 teams present in Montpellier in 2018 among the 51 selected by CNRS and Inserm), ERC funding (20 projects, one of the highest levels in France), and a specialization index in fundamental biology that is 1.5 times higher than the national index, with scientific publications representing 6.9% of national production.

We also benefit from efficient research infrastructure: 5 University Hospital Federations, 3 of which are certified by Aviesan; 2 Montpellier University of Excellence Laboratories and 3 national LabEx; 1 Montpellier Cancer SIRIC; 2 Aviesan approved Excellence Centers, and 5 national research infrastructures.

The department leverages high-level technical means that are mainly grouped within Joint Service Laboratories offering class-leading technical platforms.

"Biomarkers & Therapy", a dedicated MUSE Key Initiative

Led by Prof. Sylvain Lehmann, this initiative seeks to reinforce community organization around translational research in relation to the socio-economic world. The key initiative provides support to help new projects emerge in the field of biomarkers and targeted therapy, notably via: assistance and certification; the implementation of a new management platform for retrospective and prospective clinical-biological data, including a focus on standardization and interoperability across three health establishments to facilitate access; participation in teaching efforts dedicated to biomarkers and targeted therapy, with funding for internal Master's and internal Research year grants for translational projects; and organization of events that bring together researchers-clinical practitioners-industry players essential for building collaboration as well as promoting the sector.



High-performance unifying structures

Hospital-University Federations

Evocan (Aviesan certified): Heteroclonality and personalized treatment in oncology.

RegenHab (AVIESAN certified): Regeneration and rehabilitation to restore mobility in diseases with muscular-skeletal tissue dysfunction.

InCh (Aviesan certified): Infections and chronicity. Chronic infections: from pathogenesis to care strategies.

Neuroclin: Neurosciences, from lab to clinic.

ICT4care: Information and communication technologies for health care.

The goal of these federations is to unite researchers, professors, and hospital staff around a unifying, priority, and novel theme for treating patients.

Excellence laboratories

Two **Montpellier University of Excellence Laboratories** (Lab-MUSE) are spinoffs of LabEx units with the same name:

EpiGenMed: focuses on epigenetics in relation to cell determinism, metabolism, and immune defense.

CheMISyst: focuses on the chemistry of molecular and interfacial systems.

Three national LabEx in which Montpellier teams are strongly represented:

MabImprove: Antibodies for therapeutic use.

NUMEV: Digital and hardware solutions; environmental and organic life modeling.

ICST: Ionic channels of therapeutic interest.

Excellence centers

The Excellence Center for Neurodegenerative Diseases (CoEN-Montpellier) is one of seven centers in France that are certified by Aviesan. Their overall goal is to build collaboration-based research in France and abroad by focusing on critical mass and excellence.

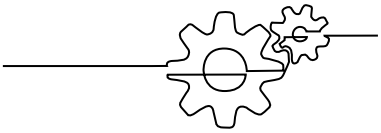
The Excellence Center for Autism (CeAND) is one of three excellence centers in France for teaching, clinical practice, and research on autism.

Integrated research sites

The Montpellier Integrated Cancer Research Site (SIRIC) is certified by INCa, DGOS, and Aviesan. There are eight SIRICs in France, each with a triple mission focused on integrating, structuring, and promoting cancer research.

National research infrastructure FranceBioImaging-FRISBI-France Génomique-ECELLFRANCE, INGESTEM.

Technological research platforms.



UMS BioCampus Montpellier

This Joint Service Laboratory benefits from a unique structure in France, with 54 technical platforms grouped in 13 technological facilities, half of which are IBISA certified, and 20 of which are ISO 9001 certified.

The **GenAc platform**
Production of human antibodies.

UMS CEMIPAI

The Center for Research on Infectious Diseases and Anti-infectious Pharmacology is a platform equipped with a Class 3 confinement laboratory. Its role is to study and handle highly pathogenic agents and develop new therapeutic molecules, including using cellular screening methods.

The **CyTOF platform**
Mass Cytometry and Imaging

The **Synbio 3 platform**
(Synthesis of Biomolecules for Biology and Biotechnology). This “chemistry” focused platform is particularly valuable for synthesizing polymers used in biomarker detection technologies. It includes two technical platforms: *Peptide* and *Polymer*.

The **SMART platform**
Mass spectrometry of nucleic acids and their modifications.

Service companies

Horiba, Histalim, Acobiom…

CLINICS

Montpellier CHU

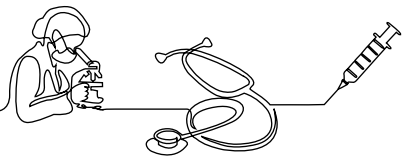
The third largest employer in the Occitanie region, with a staff of nearly 11,000 people, the Montpellier University Hospital Center (CHU) handles 570,000 appointments per year, 40,200 surgical interventions, and 3,900 births. The CHU is ranked as the 6th leading establishment in France for its research activity. Every year, its departments enroll nearly 7,000 patients for interventional academic protocols, producing over 1,500 scientific publications – half of which are in high impact factor journals. Research activities carried out at the site are supported by the Institute for Regenerative Medicine and Biotherapies (IRMB), 14 research platforms, and the Biological Resource Center (CRB).

Nîmes CHU

The Nîmes University Hospital Center (CHU) is the fourth largest employer in the Occitanie region, with a staff of nearly 6,500 people, plus over one thousand employees as part of a major joint territorial department, linked with a geriatric network. The CHU represents annual activity of 390,000 appointments, 22,500 surgical interventions, and 2,300 births. It engages in significant institutional promotion activity, funding over 30 new research projects per year. Its departments enroll nearly 4,000 patients for interventional academic protocols every year, producing over 500 scientific publications – nearly half of which are in A- and B-ranked journals – with a portfolio of 20 patents. The Nîmes CHU also includes an Institute for Medical Device Evaluation (IDIL) and a certified Center for Biological Resources.

Montpellier Cancer Institute

ICM is one of the 20 Centers entirely devoted to fighting cancer comprising the UNICANCER Federation. It welcomes an average of over 30,000 patients per year and carries out world-class translational research in cooperation with the Montpellier Cancer Research Institute (IRCM). The Montpellier area's potential in cancer research was recently confirmed by the renewal of prestigious SIRIC certification (Integrated Cancer Research Site), established by the French National Cancer Institute to develop structure and boost cancer research in France. Montpellier thus became the only Metropolis in the Occitanie and PACA region with this certification.



Clinical research platforms

The **Clinical Proteomics Platform** (PPC) at Montpellier CHU focuses on leveraging the latest technical developments in proteomics to discover, validate, and use biomarkers in many different types of pathologies.

The **LCCRH-Infectiology platform** is dedicated to research on rare infectious cells and viral reservoirs.

The **Exposition Biomarker platform** concentrates on risks and control of diseases transmitted by mosquitoes; currently under development at the MIVEGEC laboratory.

The **MicroPet Imaging platform** works on preclinical imaging for Montpellier Cancer Research Institute (IRCM).

Biological Resource Centers (CRB)

The role of these structures is to support research. With the goal of helping medical and scientific research move forward, they handle the reception, preparation, packing, and preservation of human biological sample collections, with patient consent, respecting quality and security standards and regulations governing biobanks. The LR Occitanie Biobank Network (BB-LRO) is an original collaboration initiative involving the CRB units of three establishments – Montpellier CHU, Nîmes CHU, and ICM – designated to offer public and private users easier access to collections via a single point of contact.

Translational research laboratory (URT)

Founded in December 2013, this multidisciplinary operational organization provides continuity in expertise by working in close collaboration with the ICM Biological Resource Center (CRB-ICM). Located at the Montpellier Cancer Research Institute (ICRM) on the ICM campus, the URT benefits from a dynamic research environment that is conducive to interactions between clinical practitioners and researchers.

The Montpellier Early Phase Clinical Trials Center (CLIPP),

(INCa certification renewed for 2019-2024).

Clinical Investigation Centers (CIC)

CICs are Inserm and CHU centers that offer researchers and clinical practitioners the resources they need to carry out tests based on fundamental research with patients and healthy volunteers.

The Institute for Medical Device Evaluation (IDIL)

at Nîmes CHU

This institute's goal is to assist companies needing clinical evaluation.

Shared innovation platform: KYomed INNOV

This company was initially funded by the Investments in the Future program, leveraging technical platforms (living lab, biomarkers, informatics) to make it easier to set up innovative R&D projects at the crossroads of diagnostics, therapy, and e-health.

PARTNERS

Occitanie Economic Development Agency (AD'OCC)

Ad'OCC is the agency in charge of several economic development missions, such as supporting investment, assisting innovation, and adapting human resources. Every year, it works with over 1,500 regional companies and coordinates an annual program featuring more than 400 actions in 23 countries to help boost international growth.

Montpellier France Health Hub

The Montpellier France Health Hub project leads and assists structural projects involved with health projects in the greater Montpellier area to benefit both residents and the economy. These projects are opportunities for companies to set up their operations, partnerships, and business activities.

Business Innovation Centre (BIC)

Ranked #2 in the UBI Index of the world's Top 10 startup incubators, the Montpellier Méditerranée Métropole BIC helps innovative companies get started faster and supports their growth.

Eurobiomed Cluster: driving regional development

With over 380 members, 300 of which are companies, the Eurobiomed competitiveness cluster unites all players in the Southern France health sector. For over 13 years, Eurobiomed has been supporting business innovation through R&D, from identifying academic and industry partners to following up on projects after funding.
Public and private stakeholders in the medical diagnostics sector within Eurobiomed's scope are grouped within Eurobiomed Diagnostics. Now representing the most extensive French network of innovative players in medical diagnostics, Eurobiomed Diagnostics brings together over 60 companies and 2,500 jobs, most of which are in the Montpellier and Nîmes area. The entire value chain is covered, from people discovering biomarkers for a preventive, diagnostic, prognostic approach or for making optimal therapeutic decisions, to manufacturers of kits and automated tools for developing proof-of-concept, rapid diagnostic-oriented, and multiplexing tests.

ANNUAL EVENTS

BIOMARKER DAYS

As part of the Regional Innovation Strategy – the MUSE I-SITE's "Biomarkers and Therapy" Key Initiative – the Ad'OCC Regional Economic Development Agency and the Eurobiomed Competitiveness Cluster organize two days of meetings every year focusing on specific themes related to biomarkers. In 2017: Neurosciences, 2018: Infectiology, 2019: Oncology (co-organized with the Montpellier Cancer SIRIC).

The goal of these events is to foster new collaborations between academic, clinical, and industry researchers. They are held in the new Montpellier Faculty of Medicine in mid-June, and are considered as being among the leading regional and national representations in the field. Guest speakers become the foremost ambassadors for the quality of fundamental and clinical research in the region, as well as the wealth of its companies.

Biomarker Days is an event not to be missed for:

- Learning about the latest advances and prospects for biomarkers in specific areas
- Discovering innovative technological solutions related to biomarker development
- Establishing new collaborations

Thematic focus

MEANS AND PROSPECTS

QUANTITATIVE BIOLOGY

ONCOLOGY

GENETICS-EPIGENETICS

INFECTIOLOGY & IMMUNOLOGY

EXPERIMENTAL AND REGENERATIVE MEDICINE

NEUROSCIENCES

TECHNOLOGIES FOR HEALTH - BIOENGINEERING

RESEARCH AND DEVELOPMENT

QUANTITATIVE BIOLOGY

The goal of Quantitative Biology is to understand the underlying principles of complex biological behaviors in terms of physical and mathematical parameters. It is therefore an approach that encompasses all fields in biology, levering technological expertise such as:

- Structural biology
- Biophysics and microscopy, from single molecule to tissue
- Bioinformatics (structural, genomic…) and biostatistics
- System biology
- Multi-scale molecular modeling

This community comprises 16 research teams operating in 9 laboratories (CBS, CRBM, IRMB, LBN, Sys2Diag, IGF, IBMM, LPHI, and L2C).

With teams supported through funding from prestigious sources (ERC, ATIP-Avenir, Bettencourt-Schueller…), the Quantitative Biology community coordinates and/or participates in 5 certified "Investments for the Future" projects, namely: the Institute of Computational Biology (IBC), the Bip-Bip integrative structural biology project, and 3 national infrastructure programs in the field of optical imaging (France Bio-Imaging-FBI), structural biology (French Integrated Structural Biology Infrastructure - FRISBI), and chemical-informatics (ChemBioFrance). In addition, several teams working in this field are major stakeholders in prestigious international networks, notably Physics of Living Systems and LifeTime.

Actions in the Quantitative Biology field regarding biomarkers and personalized medicine involve both modeling approaches and structural characterization at atomic and multi-cellular levels.
Mathematical models are thus developed to identify aspects and parameters related to the main molecular networks specific to certain pathologies. This data is notably used to adapt cancer treatment to the clonal and spatial heterogeneity of tumors. In addition, machine learning methods are used to identify genetic aspects that could be deregulated due to certain pathologies.

Structural biology also makes it possible to characterize some biomarkers at a cellular level. Those biomarkers, as well as the complex biological systems with which they are associated, can also be observed at the cellular level thanks to the development and use of innovative microscope techniques, such as super-resolution, light-sheet microscopy, and high-throughput microscopy combined with microfluidics.

Prospects

Moving forward, this community wishes to organize itself in terms of common methodological and biological themes.

Computational aspects: bioinformatics, systems biology, biostatistics, machine learning, artificial intelligence, big data, and modeling.

Genomics, using individuals' genomic information for their clinical treatment in order to improve diagnostics, prognostics, theranostic follow-up, and therapeutic strategies.

Structural, functional, and pharmacological characterization of protein targets such as G-protein coupled receptors and associated biomarkers, particularly in neurology, infectiology, and oncology.

ONCOLOGY

The large research community in the Montpellier area focusing on cancer (60 teams and about 600 research staff members) is involved with efforts to understand fundamental cancer mechanisms, with the goal of improving treatment. Its teams operate with various Montpellier institutes (IRCM, CBS, CRBM, IGMM, IGF, IGH, INM, IRIM, and LBN) and treatment centers (CHUs and ICM).

The community's excellence is well recognized for the quality of its research, as well as for the certifications it has earned, such as SIRIC (Integrated Cancer Research Site) certification in 2013 with the "Montpellier Cancer SIRIC" project (INCa, DGOS, Aviesan) as well as Aviesan certification in 2017 of the EvoCan Hospital-University Federation (FHU).

The Montpellier Cancer SIRIC is one of eight centers in France. It is based on the "Comprehensive Cancer Center" model used in the United States, with a single site uniting all the medical services, multidisciplinary research teams, and high technology resources and platforms to offer the best possible global care for patients. Certification was renewed in 2018 to establish a structure based on three main axes: colorectal cancer, radiation therapy, and genome integrity/ resistance to treatment.

In a complementary and coordinated effort, the FHU focuses on themes related to heterogeneity and tumor heteroclonality, a major challenge to be met with respect to therapeutics and diagnostics.

Research teams study different aspects of cancer using a wide variety of models (colon, lung, breast, ovary, glioma, blood cancers, etc.), cutting-edge approaches (notably the various "omics" technologies, such as transcriptomics, genomics, proteomics, modifomics, metabolomics, etc.), and significant bioinformatic modeling for research on new biomarkers of clinical interest.

Biomarker projects in the cancer community are often elaborated in close cooperation with the:

- Genetics-epigenetics community
- Chemistry community, whose expertise plays a growing role in characterizing and analyzing biological entities (chemical)
- MIPS community (Mathematics, Informatics, Physics, and Systems), for processing massive amounts of data
- SHS community (Human and Social Sciences), expanding the notion of biomarkers beyond molecular entities to include social and behavioral biomarkers associated with cancer

Prospects

Significant progress has been made by the cancer community in the Montpellier area on biomarkers and 6P medicine over the past few years. Nonetheless, the community must continue to evolve in order to remain competitive and be able to face new challenges in the fight against cancer, in particular represented by the development of personalized approaches for treatment, identification of new biomarkers, and producing companion tests of clinical interest (diagnostics, prognostics, and theranostics for adapting and following up on treatments as well as detecting relapses).

While continuing to develop our traditional areas of expertise (such as cell signaling, cellular biology, molecular biology, genomics-epigenomics, metabolism, tumor biology and microenvironments, preclinical models, liquid biopsies, technology platforms, and clinical services), we feel that it is important to reinforce the following points to stimulate research on biomarkers for oncology:

Develop complex statistical analyses and disease modeling, in particular by leveraging approaches based on artificial intelligence and deep learning.

Develop "single cell" and "topological/three-dimensional" type analyses, which are essential for properly understanding tumor heterogeneity, concepts of cancerous stem cells, and the complexity of interactions between cancer cells and their environment.

Understand the metabolic deregulation of cancer cells.
Pursue research on immunotherapy and related companion/biomarker tests.

Develop research regarding environmental impact on carcinogenesis.

Support efforts to develop, organize, standardize, and use tumor sample banks

GENETICS-EPIGENETICS

The Montpellier area genetics-epigenetics community represents 28 teams operating in 11 research organizations (IGH, IGF, IRCM, INM, TransVIHMI, MIVEGEC, IGMM, CRBM, LPHI, PhyMedExp, and LGMR).

In 2010, as part of France's Investments for the Future program, research excellence in this field was recognized with the creation of the EpiGenMed Excellence Laboratory (LabEx). The goal of this LabEx was to promote clinical and fundamental research by setting up interdisciplinary projects to "move forward from the genome and epigenome towards the molecular medicine of tomorrow." The EpiGenMed LabEx brought together 49 excellence research teams studying the implications of genetic and epigenetics in cell differentiation and proliferation, normal development, neurobiology, infectiology, and cancer. EpiGenMed encountered remarkable success, with major discoveries made by its teams, who have earned awards as well as both national and international recognition. Following recommendations expressed during its evaluation by an international jury, the EpiGenMed LabEx will evolve into a Montpellier University of Excellence Laboratory (Lab-MUSE) as part of the I-SITE project.

Genetics and epigenetics are both fields in biology that study genes and mechanisms that modify gene expression in an adaptable, transmissible, and reversible manner, with potential impact in the four following biomedical axes: oncology, neurology, infectiology, experimental and regenerative medicine.

Genetics-epigenetics covers a range of highly diverse themes, such as:

- Genetic and epigenetic analysis of cellular physiopathology, including the study of gene expression, DNA replication and repair, and recombination.
- Epigenetics in cell differentiation, stem cell biology, and cellular reprogramming and development.
- Nuclear organization and its role in gene expression, the role of coding and non-coding RNA in the living world.
- Medical genetics and epigenetics.

Clinical research also represents a significant portion of the activity in this area, notably seeking to:

- Identify new genes responsible for genetic diseases.
- Study the role of genetic and epigenetic factors in cancer and disease expression.
- Understand the role of small non-coding RNA and the alteration of mRNA splicing in genetic diseases.
- Explore therapeutic options through industry partnerships and creating innovative companies.

Prospects

The Genetics-Epigenetics pillar is preparing to launch a major action for research and health in Europe. The "**LifeTime**" project will leverage momentum generated by new imaging techniques and technologies referred to as "multi-omic", able to carry out multiple measurements at a genomic level (RNA, genomic DNA methylation) on thousands of unique cells.

This project intends to take advantage of new potential to map the state of healthy and diseased cells, and then analyze the data using computational learning and artificial intelligence technologies to identify biomarkers and develop therapeutic strategies with a 6P medicine approach of unprecedented strength. LifeTime's goals are to:

Describe and understand the spatial heterogeneity of cells.

Capture cellular changes over time.

Establish computational strategies to understand the causes and progression of pathologies.

Develop experimental systems that enable researchers to manipulate cell genomes and reconstruct tissue and organs containing manipulated cells.

Lab-MUSE EpiGenMed (2020-2024) is now taking shape, limiting itself to teams that are highly focused on epigenetics. Its calls-for-projects will be open to the area's entire BioHealth community with three main directions: cellular determinism, metabolism, and immune defense as related to epigenetics.

IMMUNOLOGY, INFECTIOLOGY

The Infectiology and Immunology community is organized as a continuum based on fundamental research, clinical research, and health research on populations. It is coordinated and led by a Hospital-University Federation (FHU) "Infection and Chronicity" (InCh) comprising seven hospital services and departments at the Montpellier and Nîmes CHU university hospitals; 10 research laboratories (TransVIHMI, PCCI, IRIM, MIVEGEC, IGH, CBS, IGMM, LPHI, MMDN, and VBMI), and a hospital platform (LECRII). Benefiting from strong international presence with several l²boratories operating in Africa, Asia, South America, and more, this community is heavily involved with many international projects relating to HIV, Ebola, and Arbovirus infections in coordination with countries in the southern hemisphere and research organizations operating there, notably IRD and Cirad.

In addition to the exceptional technical platforms at the BioCampus Montpellier joint service unit, which are available to all BioHealth researchers, the community also benefits from other more specific platforms, such as those at the CEMIPAI (Research Center for Infectious Diseases and Anti-infectious Pharmacology) joint research unit and infrastructures for housing, breeding, and experimental-experimentation preparation in A2/A3 animal facilities and I2/I3 insect facilities.

Lastly, a major partnership was established with large industry groups and solid SMEs/VSEs, namely: Horiba, SANOFI-Aventis, Biorad, Abivax, Metafora, Deinove, Nosopharm, and Azilead.

Local infectiology specificities and strengths in Montpellier include:

- Research on emerging and re-emerging infections and their vectors (HIV, Ebola, Zika, Chikungunya)
- Mycobacterium tuberculosis (MTB) and HIV co-infection
- Study of anti-infectious resistance
- Development of diagnostics, prevention, and treatment methods for chronic and emerging infections
- Design of new therapeutic targets at the crossroads of chemistry and biology
- Evaluation of new molecules and antiretroviral strategies

Effort with respect to biomarkers is primarily focused on intensive research on biomarkers for diagnostics and follow-up on diseases transmitted by mosquitoes, and on biomarkers related to susceptibility as well as vaccine side-effects, epitranscriptome imprinting after emerging viral infections, representing a new asset for predicting and tracking chronic afflictions due to emerging viral infections.

Prospects

We are seeking to take on new challenges in the field of infectious diseases, including:

Setting up an "exposure biomarker" platform that would become an international reference laboratory, welcoming projects focused on evaluating risks related to vector-borne diseases and the efficacy of vector control strategies, such as new tools and methods for vector control and programs for monitoring arbovirus risks.

Creation of a diagnostics platform using a combination of molecular, immune, biochemical, and even hematological biomarkers to resolve infectiology diagnostics challenges in cases of fever due to unknown causes, unfamiliar clinical symptoms, and travel to tropical areas.

Research on biomarkers for predicting unfavorable progression (plasma leaking as a sign of severe dengue fever) and the appearance of co-morbidity for crippling and chronic pathologies following arboviral infection (particularly chronic joint afflictions, CHICV, and ZIKV neurological deficiencies) or retroviral infections (co-morbidity related to immune activation).

In the field of human and animal vaccination, qualifying and quantifying immune response induced by vaccine, in order to differentiate individuals who have had contact with pathogens naturally from those individuals who have been vaccinated as the result of vaccine biomarkers.

Validating a proof-of-concept study to evaluate the use of human monoclonal antibodies to neutralize HIV (bNAbs) to prevent HIV transmission from mother to child during breastfeeding.

EXPERIMENTAL AND REGENERATIVE MEDICINE

Experimental and regenerative medicine is the study of the mechanistic foundations of pathologies and the development of new therapies based on tissue regeneration, cell therapy, and pharmacology. With that goal, teams involved with this field have developed unique models for target human pathologies, as well as patient cohorts, for testing innovative therapies. Teams in the community are mainly present in six laboratories: IRMB, PhyMedExp, IGF, DMEM, BC2M, and CafeDiVa.

Excellence in the experimental and regenerative medicine community is recognized by National BioHealth Infrastructure certification for E-Cell France, which provides services covering all phases of cell therapy projects. In addition, the RegenHab Hospital-University Federation (FHU) is certified by Aviesan.

RegenHab FHU is a clinical, biology, and technology consortium that comprises stem cell biologists, physiologists, roboticists, complex movement imaging specialists, and clinical practitioners in rheumatology, muscular diseases, anesthesia-reanimation, and rehabilitation. The consortium develops new therapeutic approaches to help restore movement for patients suffering from diseases in which musculoskeletal tissue function is altered.

Local specificities include the particularly strong involvement of researchers in:

- Physiology and cardiac and muscular pathophysiology
- Inflammation and osteoarticular diseases
- Diabetes
- Regenerative and translational medicine

Emphasis is placed on establishing extensive clinical and biological databases on patients with osteoarthritis, heart failure, and muscular disorders.

It is also essential to identify diagnostic, prognostic, and predictive biomarkers with therapeutic efficacy in regenerative medicine, and to study changes in biomarker expression in musculoskeletal and chronic inflammatory diseases.

Identifying markers of therapeutic cell efficacy (including mesenchymal stem cells) currently undergoing validation in clinical trials is an important research focus for developing prognostic tests on the efficacy of those cells and to improve patient care.

Prospects

One of the major goals of this clinical research axis is to set up a continuous care path for treating patients, notably relating to chronic joint diseases. This involves integrating several different factors within a given treatment program: implementing innovative regenerative medicine treatments; defining a patient's RMD profile via imaging and functional examination (algorithms and biomarkers or imaging and integrated functions of biological biomarkers); ensuring personalized rehabilitation for patients, including in-home care using connected tools.

A future goal also includes setting up a CARTIGEN Regional Research and Innovation Platform (PRRI) to integrate clinical and biological (biomarker) data with anatomic data (imaging biomarkers under load and in movement) and mobility data (movement biomarkers).

The goal in regenerative medicine and biotherapies is to better identify cells of interest, such as progenitor cells, drug cells, target cells, and more. New technologies that include multi-omic approaches and generate quantitative "omics" data and qualitative cellular data will make it possible to create models for modifications associated with physiological and physiopathological processes and identify new markers to be validated functionally.

A major objective for the community is to develop software tools to support the prescription of targeted therapies in the field of rare diseases, in particular muscular dystrophies and chronic diseases.

NEUROSCIENCES

The Montpellier Neuroscience Community comprises over 300 researchers, research-professors, and clinical practitioners working at Montpellier and Nîmes CHUs and eight research institutes. Some specialize in neuroscience (INM, MMDN, and U1061), others cover a broader range of topics (IGF, CRBM, IGMM, IGH, and IRMB).

The community includes two Aviesan certified Excellence Centers. The Montpellier Excellence Center for Neurodegenerative Diseases – "CoEN" – focuses on promoting biomarkers and personalized medicine. The center's goal is to foster the emergence of multidisciplinary projects that bring fundamental, preclinical, clinical, and epidemiological research together with social sciences covering diseases representing major public health issues such as Alzheimer's and Parkinson's diseases, as well as multiple sclerosis and ALS. The other entity is the Excellence Center for Autism – "CeAND" – whose goal is to boost translational research on Autism Spectrum Disorder (ASD) and the discovery of biomarkers for a common pathology for which clinical diagnosis is sometimes difficult to establish.

The neuroscience community also benefits from the FHU NEUROCLIN Hospital-University Federation, whose goal is to provide structure for neuroscience research in fields where regional expertise is strong (sensor-motor pathologies, neurodegeneration, cognition, psychiatry), leading up to clinical trials and the creation of companies to develop new drugs and technological devices.
These excellence centers also leverage their synergy, particularly by sharing multicentric cohorts, certified biobanks, and cutting-edge technology approaches such as next-generation sequencing (NGS), quantitative mass spectrometry, and ultrasensitive multiplex immunodetection.

Local specificities include the particularly strong involvement of researchers in:

- Molecular approaches seeking to define signaling pathways, receptors, ionic channels involved in physiology, and pathologies of the central and peripheral nervous system.
- Mechanisms that are common to different pathologies (protein aggregation phenomena, neurodevelopmental alteration, immune system deregulation…).
- Development of innovative models (iPSC), with cell and gene therapy approaches combined with omic techniques and using biological collections available locally, to identify new biomarkers that are the subject of intense clinical research. Their goals are to (1) facilitate and improve detection and diagnosis of neuro-psychiatric diseases, (2) determine their prognosis and choose the best possible therapeutic treatment, and (3) enable patient stratification for clinical trials.

Prospects

The neuroscience field in Montpellier is already widely recognized regarding both fundamental and clinical molecular aspects. In order to pursue and reinforce excellence acquired in the biomarker and 6P medicine fields, it seems important to take actions that facilitate translational research and the use of latest-generation tool:

Optimize care systems by fully integrating translational and innovative considerations: standardized protocol, harmonization of clinical-biological data gathering, collection of multi-sample and longitudinal biological resources, and access to new treatments.

Develop a trans-pathology perspective in neuroscience (neurological and psychiatric diseases) to create synergy for using and validating new biomarkers.

Build integrative vision regarding neuroscience, from development to environmental impact.

Dedicate significant investment for new technologies (omics, imaging…), bioinformatics, and artificial intelligence to improve diagnostic performance and help understand physiopathological mechanisms.

Facilitate company creation to develop new drugs and diagnostic devices (multi-mode biomarkers, medical devices…).

TECHNOLOGIES FOR HEALTH - BIOENGINEERING

This technology-oriented axis covers four main topics, ranging from synthetic biology to information and telecommunication technologies (ICTs) for health, surgery, and imaging.

Bioengineering includes all *in vitro* diagnostics and/or analysis technologies, their implantation in living organisms, and biomaterials aspects.

Synthetic biology is a recent discipline that combines biology and engineering to design new living biological systems for diagnostic and therapeutic applications. The teams involved with this field include the clinical teams at Montpellier CHU (endocrinology-diabetes, psychiatric emergencies and post-emergencies, wounds, and scarring) and fundamental research teams at six laboratories: CBS, IGF, Sys2Diag, IBMM, CRBM, and INM.

ICTs are increasingly used to help patients with chronic diseases, as well as elderly people. They make it possible to collect and track the biomarkers needed for treating patients, adapting their treatments, and patient rehabilitation.

The main teams involved in this area are at Montpellier CHU (Nutrition Department, Clinical Physiology Department) and research teams such as: PhyMedExp, LBN, Epsylon, and EA MRM, as well as Institut des Mines d'Alès. Extending beyond clinical services and research laboratories, these activities are also carried out within two FHUs, ICT4CARE and RegenHab.

An e-Health chair was established in this field within the University of Montpellier Entrepreneurship Foundation.

In addition to surgical technologies that include remote operations, materials, and related equipment, the Surgery theme also covers implantable devices, functional assistance/replacement devices, and prostheses.

The Imaging theme includes all the anatomical and functional technologies used for imaging, both *in vitro* and *in vivo*.

The main actions carried out in diabetology for diagnostics and follow-up (blood sugar, hemoglobin A1C, microalbuminuria) have helped with:

- Identification of new biomarkers for diabetic nephropathy risks.
- Development of the first synthetic biology approaches for diagnostic purposes (glucosuria detection).

Follow-up on chronic diseases using digital solutions has led to:

- Implementation of remote oral-dental consultation in retirement homes.
- Development of a telemedicine network for wounds and scarring.
- Development of a connected bandage that integrates infection biomarkers.

Prospects

>>>>>>>>>>>>>>>>>>>>>>>>

Progress on this axis will require reinforcement of synergy between multiple scientific fields, namely bio-health, chemistry, physics, computer science, bioinformatics, health engineering sciences, and human and social sciences, notably with respect to ethical and legal issues, and management of information systems for health and health marketing.

The development of synthetic biology is expected to help achieve major progress by creating new experimental models, such as "organoids", which also help reduce the need to use animal models.

A strong "Digital Health" axis that combines the expertise operating at our site will make it possible to accompany chronic diseases using digital solutions, reorganizing treatment options via telemedicine, and developing e-health and artificial intelligence for health.

We have real potential to create a "Digital Health" axis that combines the expertise operating at our site for accompanying chronic diseases using digital solutions, reorganizing treatment options via telemedicine, and developing e-health and artificial intelligence for health.

RESEARCH & DEVELOPMENT

Funded by Occitanie regional authorities as part of the Prime@Muse project, In Extenso performed a market study in early 2019 on biomarkers, one of the five high-potential pillars identified for partnership development with the industry.

The goal of study was to assess the current situation in the field by analyzing trends on market volume and collaborations, and by establishing a map of related companies. Interviews with industry players were also conducted as part of the study, to learn their needs, expectations, and feeling regarding existing collaborations with public and academic laboratories in the region.

According to the study, nearly all academic laboratories work more or less closely on the topic of biomarkers, with 106 University of Montpellier research teams involved with biomarkers. Oncology and neuroscience play an important role in France's Occitanie region, as these two therapeutic domains alone represent nearly half of all internal expertise in the field of biomarkers. It is worth pointing out that, even if the difference in market share held by oncology with respect to neurosciences is relatively low in Occitanie (25% vs. 19%), the difference is greater worldwide (57% vs. 10%).

The Occitanie region thus harbors a strong level of skills in neuroscience biomarkers that will be important to promote. The study also shows that the region also holds a high level of biomarker expertise in niche therapeutic domains such as infectiology (11%), metabolism and immunology (9%), and cardiovascular (3%) with respect to the global market, which shows a consistent level of 8% for all fields excluding oncology, cardiology, and neurology.

On the entrepreneurial side, the study showed 31 companies specializing in biomarkers in the Occitanie region. The companies with particular skills in infectiology and immunology are mainly VSEs and SMEs. Those companies focus on *in vitro* diagnostics (12/31), R&D services (8/31), and the others are pharmaceutical companies (7/31).

There is most certainly room for progress in terms of collaboration, as only 27% of the research teams have already established collaborations with industry partners (29 teams out of 106) and 65% of the collaborations in place are with partners located in the region.

With respect to patents on a national scale in France, biomarker patents are mainly filed by academic organizations (73%). Remarkably, University of Montpellier is the second leading entity in France for filing patents related to biomarkers.

The study also revealed interesting information regarding strengths and weaknesses with respect to companies. Our main strengths are our scientific expertise, unique assistance structures, and geographical proximity that facilitates exchanges. Points for us to improve include our responsiveness in terms of setting up collaborations, generating exposure for our skills, considering global industry constraints, and implementing contractual arrangements.
The study thus demonstrates the presence of expertise and a considerable focus on biomarkers in the Occitanie region, on the research side, but industry aspects need to be developed on the entrepreneurial side. Only 31 companies are specialized in biomarkers, compared to 90 companies specialized in the therapeutic field.

Directions to prioritize include biomarker research in oncology and infectiology for application in personalized medicine and molecular diagnostics. It would also be a good idea to expand the scope of collaborations outside the Occitanie region.

Furthermore, the study also highlighted the needs and expectations of industry players, which need to be matched in an operational phase with the skills available within MUSE to foster the development of new collaborations.

Success stories

FUNDAMENTAL BIOLOGY DISCOVERIES

Key role played by membrane metabolite transporters in the survival and proliferation of tumor cells

Marc Sitbon's team at IGMM showed that retrovirus surface glycoproteins primarily selected membrane transporters for metabolites expressed on the cell surface as viral receptors. This enabled the team to use genetic engineering to develop a set of tools for specifically recognizing these transporters (which is referred to overall as cell surface "transportome"), for which levels, combinations, and relative proportions enable predicting the metabolic state of the cells expressing it. There are many applications for these tools in the cancer field, as tumor cells and other cells in their environment display a deregulated metabolism. Work on this topic led to the creation, in 2012, of the startup Metafora, which recently brought its first diagnostic kit to market.

New approaches for fighting HIV (viral reservoirs and antisense transcription)

The world of HIV research has recently seen the emergence of promising new possibilities concerning viral reservoirs as well as antisense transcription: (1) characterization of CD32a as a biomarker of the viral reservoir. This finding has triggered the emergence of many research programs internationally on the topic of this reservoir biomarker; and (2) demonstration that a tenth gene appeared at the same time as the emergence of the HIV pandemic, encoding the ASP protein (antisense protein) on the antisense strand of the proviral genome. This achievement is the result of 15 years of leadership in the field of antisense transcription among retroviruses (Antoine Gross, IRIM). Although these discoveries have not yet led to direct applications at the patient's bedside, they do nonetheless open up fundamental and clinical prospects of the highest importance and have strongly stimulated applied research programs, particularly for biomarkers.

New biomarkers for early diagnosis of dry eye syndrome

Dry eye syndrome affects as much as 34% of the elderly population. Faulty tear film induces progressive corneal disease and eventually leads to blindness. There are no early detection markers or definitive cures at this time. Frédéric Michon's team at INM concentrates on discovering the factors that are altered as dry eye syndrome sets in. The discovery of early biomarkers in the tear film (such as GDF5 or IGF1) would help in the early use of supplemented eye drops for affected patients. Early diagnosis is the key to reducing corneal impact and long-term effects on vision.

Demonstrating the strong correlation between Amyotrophic Lateral Sclerosis severity and Vitamin D deficiency

Cédric Raoul's research team at INM and William Camus' Neurology Department have highlighted a link between Vitamin D deficiency and neurodegenerative diseases, including Amyotrophic Lateral Sclerosis.

Neurofilaments involved as potential biomarkers for neurodegenerative diseases

Within the context of Neurofilaments (NFs) as biomarkers for neurodegenerative diseases, it is essential to work both on developing new methodologies to quantify NFs in patients' biological fluids, and on better understanding the basis for NF secretion outside cells along with the proteolytic processes for which NFs are targeted in these fluids. In that framework, Pascale Bomont's team at INM is in a strong position to study NF proteolysis. The team has indeed identified Gigaxonin as being the only E3 ubiquitin ligase that has the capacity to control degradation of intermediate filaments, of which NFs are the neuronal constituents. Their expertise on the degradation of NFs in neurodegenerative diseases is thus a major asset that will make it possible for the team, using the biological tools being developed by the laboratory to define the constitution of NFs in fluids, to understand their formation and progression during pathological processes.

Identifying a biomarker signature for multiple sclerosis diagnosis and prognosis

Eric Thouvenot's Neurology Department at the Nîmes CHU university hospital, along with Philippe Marin's research team at IGF and the Montpellier proteomic platform (PPM), have identified a combination of diagnostic and prognostic biomarkers for multiple sclerosis, including during the preclinical stage (EP18305630.8, 2018). They performed quantitative proteomic analysis on cerebrospinal fluid from patients at different stages of the disease – preclinical stage, after a first neurological incident suggesting multiple sclerosis, remitting and progressive forms – and from control patients with inflammatory and non-inflammatory diseases of the central nervous system and peripheral nervous system.

Creating cultures and characterizing circulating tumor cells (CTCs) to reveal critical data for understanding this cell sub-population that causes relapse in cancer patients

The LCCRH laboratory headed by Catherine Alix-Panabières recently demonstrated the clinical position of CTCs in breast cancer (STIC METABREAST). Leveraging EPISPOT/EPIDROPT techniques and CTC cell culture, the laboratory's expertise enables the team to study CTCs that are responsible for initiating metastases in order to identify and target activated signaling pathways in those cells and to eradicate the tumor cell sub-populations that cause clinical relapses in patients.

Success stories

INNOVATIVE TECHNOLOGIES

Developing a minimally invasive, cost-effective, and rapid method for detecting tumor cell mutations based on a blood sample.

Alain Thierry's team at IRCM was a pioneer when it developed a reliable and sensitive multi-parameter test (IntPlex) for detecting oncogenic KRAS and BRAF mutations in patients with metastatic colorectal cancer and for early detection of mutation and clonal heterogeneity emergence following targeted therapy. Their effort validated the prognostic potential of circulating DNA. Several clinical studies are currently in progress and the team is coordinating or co-coordinating 10 clinical trials in France. This work enabled the creation of an IRCM spin-off: DiaDx SARL.

Creating the first human model of retinal choroideremia obtained from patient iPS cells

Choroideremia is an X-linked chorioretinal dystrophy in which the choroid, the retinal pigment epithelium, gradually degenerates. Dr. Vasiliki Kalatzis, a researcher at the Montpellier Institute of Neurosciences (INM), created the first human model of retinal choroideremia from patients' induced pluripotent stem cells (iPS). She is currently using the model to test pharmacological and genetic therapies. Her research is the foundation for creating a start-up company (Horama) to carry out the first clinical trials in 2019.

Developing a computer application to monitor chronic joint diseases

Working with Christian Jorgensen at IRMB, Bodysens has developed an application to monitor chronic joint diseases, integrating demographic, environmental, mobility, and prehension (grip) strength data. These factors can be used to predict the response to biotherapies and provide personalized in-home follow-up for patients with rheumatoid arthritis in the Occitanie region.

Developing a computer application to help personalize and adapt anti-oxidant nutritional supplements for patients with FSHD

The application was developed by Dalila Laoudj (PhyMedExp) with support from SATT AxLR following studies showing that nutritional antioxidant supplementation has a positive effect on muscle function in patients with facio-scapulohumeral dystrophy (FSHD).

Developing a computer application to improve mobile rehabilitation in chronic diseases

Maurice Hayot's team at PhyMedExp, in collaboration with the Epsylon-MRM-EMA laboratories and 5Santé, has developed a digital solution comprising a patient application, website, and physician website offering personalized programs accessible via smartphone. The solution combines physical activity, therapeutic education, and nutritional behavior modification or supplements. The team's first digital solution, tested with cases of obesity, has proven its effectiveness and highlighted many issues relating to the use of digital technology to coordinate remote care.

Building modified bacteria for use as biosensors in diabetes

A collaborative effort by the teams of Jérôme Bonnet, Franck Molina, and Eric Renard has led to the development of modified bacteria that can be used as biosensors in treating diabetes. This translational research has enabled the development of other acellular systems currently being designed for the simple, rapid, and adaptable detection of various molecules of interest. These new diagnostic procedures could be applied *in vitro* and, in the more distant future, potentially *in vivo*, in combination with therapeutic action.

Using induced pluripotent stem cells (iPS) to develop precision medicine for patients with inherited heart disease

Sylvain Richard's team at the PhyMedExp laboratory has acquired expertise in functional diagnostics, at both molecular and cellular levels, for genetically induced heart rhythm disorders. Research undertaken in collaboration with clinical practitioners in Lyon (cardiologists, geneticists) has helped establish proof-of-concept regarding the rationale, feasibility, and relevance of this approach for understanding the impact of genetic variations identified upstream. This work established a foundation for creating a startup company, Diag'nCell, whose innovative goal is to develop precision medicine for patients suffering from hereditary heart disease.

Success stories

NEW DIAGNOSTICS TESTS AND PRESCRIPTION ASSISTANCE

A blood test that identifies patients at risk of developing side effects from radiation therapy

50% of cancer patients undergo radiation therapy as part of their treatment. About 5% to 10% of those patients develop severe and late side effects resulting in pain, hypersensitivity, oedema, and inflammatory reactions that significantly affect their quality of life. The teams of Mahmut Ozsahin and David Azria first developed a lymphocyte apoptosis test (RILA, radio-induced lymphocyte apoptosis) to predict the intrinsic radiation sensitivity of cancer patients based on radiation-induced T cell apoptosis rates. Prospective large-scale validation was conducted in multicenter Phase 3 trials with over 500 patients. Lastly, this test was combined with predictive analysis – nomogram – to improve overall performance. The new combined test is now marketed under the name NovaGray Breast® following the creation of NovaGray, a spin-off at the ICM campus.

A syndrome-based approach for diagnosing several infectious diseases simultaneously with a single test

These simple and rapid approaches, which take from 1 to 4 hours, meet key objectives in the field of infectious diseases to combat multi-resistant bacteria and reduce patient mortality, as they: (1) cover the major syndromes encountered in infectious diseases: meningitis, encephalitis, sepsis, respiratory infections, digestive infections, and osteoarticular infections; (2) reduce the time required for analysis and results; (3) help clinicians choose appropriate antibiotic therapy from an early stage; (4) contribute to the proper use of antibiotics, and; (5) reduce the length of hospital stays. In this context, Chantal Fournier-Wirth works at Philippe Van de Perre's PCCI UMR in collaboration with Horiba to coordinate the ArboMag project for the differential diagnosis of arboviruses and determination of infection age.

A rapid test - epidemiological indicator - to detect biomarkers for exposure to Aedes and Anopheles mosquito bites (under development)

For the past 15 years, biomarkers used to assess exposure to Aedes and Anopheles mosquito bites (salivary antipeptide antibodies) have been validated as epidemiological indicators to (1) identify the risks of transmission of arboviruses and malaria, and (2) evaluate the effectiveness of vector control on human-vector contact. Work to develop these biomarkers in the form of a quick "point-of-care" test (self-reactive test strip) is currently being carried out with ACOBIOM in Montpellier, as a collaboration with the MIVEGEC laboratory.

Adapting conventional blood sampling methods to fingertip sampling to detect or predict neurological pathologies

The team led by Sylvain Lehmann and Christophe Hirtz at IRMB, in collaboration with the neurology departments of the Montpellier CHU university hospital (Pierre Labauge, Audrey Gabelle, William Camu) and Nîmes CHU university hospital (Eric Thouvenot), has demonstrated that determining neurofilament light subunits (NF-L) using an ultra-sensitive SIMOA assay can detect or predict Alzheimer's disease, multiple sclerosis, amyotrophic lateral sclerosis, brain metastases, and concussions resulting from sports. Adjustment of these dosages on fingertip samples is currently being carried out in collaboration with the start-up Spot-To-Lab.

Creating computer and bioinformatics infrastructure to support diagnosis based on next-generation sequencing data, with applications in oncology and human genetics

The infrastructure relates to the CORTECT maturation project, which led to the creation of the startup SeqOne. The company offers bioinformatics services for biomedical needs, based on using open source tools and creating an innovative platform architecture. The SeqOne platform is now operational and employs 9 people. Analysis software developed by SeqOne is used by eight hospitals in France, including the Montpellier CHU university hospital. The market targeted by SeqOne is comprised of "about thirty university hospitals and approximately 500 public and private institutions in France, with the European market estimated at 13 billion euros."

Success stories

INNOVATIVE AND TARGETED THERAPIES

Stratification of multiple myeloma (MM) patients based on identifying epigenetic modification biomarkers

Multiple myeloma is a neoplasia in which tumor plasma cells accumulate in bone marrow. It is genetically and clinically heterogeneous. Epigenetic changes are involved in MM pathophysiology as well as in treatment resistance mechanisms. Those changes can be targeted by inhibitors already used for treating MM or currently under clinical development. Jérôme Moreaux and Bernard Klein's group developed a biomarker based on the gene expression profiles of patients' tumor cells to predict response to HDAC (Histone Deacetylase) inhibitors. This work led to a clinical trial conducted at Montpellier and Poitiers CHU university hospitals. The same group also worked in collaboration with Guillaume Cartron and Giacomo Cavalli at IGH to develop a biomarker that could identify a subgroup of MM patients who might benefit from treatment with EZH2 inhibitors. In 2015, these developments served as the foundation for creating Diag2Tec, a company specializing in biomarkers and precision medicine for hematological cancers.

Antiviral and anti-inflammatory therapies based on molecules regulating RNA splicing and metabolism

Fundamental research carried out by Jamal Tazi's team at IGMM has demonstrated that molecules interfering with the alternative splicing of messenger RNA can interfere with viral infection such as HIV. The first discoveries in this area led to the filing of several patents and the founding of a startup called "Splicos" in 2008. In 2009, company creation was followed by the launch of a joint CNRS/University of Montpellier/Splicos laboratory. In 2014, Splicos merged with two other SMEs, forming Abivax, which continues to develop antiviral therapies based on a second generation of molecules that regulate RNA splicing and metabolism, notably RNA biogenesis. The strategy blocks viral replication and can be applied to a wide range of viruses. By shedding light on these molecules' mechanism of action regarding cellular RNA biogenesis, Jamal Tazi's laboratory uncovered a new mechanism to effectively fight inflammatory diseases.

Improving FSHD patient performance by including antioxidant supplements in their diet

Many studies agree on the prominent role of oxidative stress in facioscapulohumeral muscular dystrophy (FSHD). In 2015, a randomized double-blind, placebo-controlled clinical study based on using antioxidants on 54 patients with FSHD demonstrated the supplement's beneficial effects on physical performance, muscle volume, and muscle quality in the quadriceps. Results were correlated with a decrease in oxidative stress and an increase in antioxidant defenses in FSHD patients. This study led to (1) the implementation of specialized and personalized check-ups to analyze the long-term effects (over 3 years) of antioxidant intake adjusted to each patient's own muscle function analyses, and (2) the European Commission's adoption of the term "Orphan Medicinal Products" including antioxidant supplementation.

Treating tinnitus with NMDA receptor antagonists

Tinnitus research at the Institute for Neurosciences of Montpellier (INM) has shown the efficacy of transtympanic injections of NMDA receptor antagonists. A multicenter Phase 3 clinical study is currently being carried out under the supervision of Auris Medical, an INM spinoff. Another INM company is conducting a Phase 1 trial (SENS111) on vertigo.

Treating drowsiness and hypersomnia with reverse histaminergic receptor antagonists

Research conducted in the Sleep Department at the Montpellier CHU university hospital, coordinated by Yves Dauvilliers, has highlighted the role of histamine in drowsiness and hypersomnia, which could lead to treatment using a reverse agonist for histaminergic H3 receptors. The research was carried out in partnership with Bioproject. Initiated 8 years ago in the Narcolepsy Reference Center, this work made it possible to obtain European marketing authorization in 2016 for a narcolepsy therapy.

Treating Type 1 Diabetes with closed-loop insulin therapy

The endocrinology-diabetes team at the Montpellier CHU university hospital/Functional Genomics Institute worked in collaboration with University of Virginia (USA) and University of Padoue (Italy) to develop closed-loop insulin therapy for treating Type 1 diabetes (“artificial pancreas”). This is a good example of successful personalized medicine, implementing continuous blood sugar monitoring using subcutaneous sensors and automated adjustment algorithms for subcutaneous or intraperitoneal insulin infusion via portable or implantable pumps. These devices are being marketed for the routine treatment of Type 1 diabetes.

NEEDS AND ACTIONS IN ACADEMIC/CLINICAL RESEARCH

Big data modeling and analysis

Develop complex statistical analyses and disease modeling, in particular by leveraging approaches based on artificial intelligence and deep learning.

Integrate research on systems biology and bioinformatics directly at CHUs to combine a clinical approach with powerful analytical methods applied to disease diagnosis and treatment.

Cellular engineering and unique cells

Develop “single cell” and “topological/ three-dimensional” type analyses, which are essential for properly understanding tumor heterogeneity, concepts of cancerous stem cells, and the complexity of interactions between cancer cells and their environment.

Acquire equipment and increase our expertise to perform “omics” analyses at the single cell level (single-cell omics).

Apply for “Cell Center” certification, either alone or in conjunction with the Curie Institute, whose role is to serve as a distribution center for biological materials, technological development, and training for involved researchers and clinical practitioners.

Metabolism and metabolome

Unify and reinforce expertise in the field of cell metabolism analysis, in particular by investing collectively in dedicated equipment.

Set up a platform for analyzing metabolites and metabolic pathways.

Biobanks, patient phenotyping, and cohorts

Organize and standardize biobanks, and make it easier to access them by:

- Implementing computing infrastructure (data) along with several types of biobanks: multi-domain (oncology, neurology, infectiology, regeneration, rehabilitation, and digital health), multi-sample (blood, nucleic acids, other liquids), longitudinal (regular sampling using the same patients), and related to cohorts (monitoring a large number of people).
- Increase the impact of Biological Resource Center (CRB) capacities by focusing on acquiring software able to integrate data, with interoperability across clinical and biological databases.
- Establish a framework agreement for transferring biological samples and data.
- Set up common phenotyping and a shared biological collection (DNA, serum, LCR, urine…) to exchange ideas, compare, and develop synergy for biomarker research in target domains.

Actions to promote interdisciplinary and translational research

Identify pilot pathologies for which the community has strengths.
Support initiatives and means for developing interdisciplinary research (i.e. MUSE Key Initiatives)

Create dedicated spaces for translational research at CHU university hospitals
Foster the creation of startups involving therapeutics and diagnostics.
Make it easier for clinical practitioners to access omic platforms.

Organize scientific events to promote an interdisciplinary approach (such as Annual FHU Days, Inter-FHU Days, Multidisciplinary Meetings, common events with the Institute of Advanced Knowledge).

This white paper was written as a joint effort involving the entire BioHealth community in the Montpellier-Nîmes area in France. Its goal is to highlight the unifying nature of the “Biomarkers and 6P Medicine” domain, which represents a major strategic and economic issue for our region.

This collective work enables us to highlight the site’s undeniable strengths in terms of fundamental and clinical research, as well as the strong potential for developing partnerships with companies in the business world. Describing some of the fundamental discoveries made locally, along with innovative therapies being developed and new diagnostics tests and support for prescription, success stories further encourage us to pursue our efforts along this path with full support from our governing bodies and institutions.
The needs and actions to carry out for academic and clinical research all represent opportunities to leverage and develop within our community, whether for big data analysis, cellular engineering, metabolism, organizing biobanks, or developing interdisciplinary and translational activities.

This strong synergetic momentum driving a common topic will help make the Montpellier-Nîmes site a nationally and internationally recognized reference for biomarkers and 6P medicine.

IN PARTNERSHIP WITH