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NExT I-Site Scientific Roadmap

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Nantes Université

NExT HEALTH AND ENGINEERING

Editorial

“Defining new priorities and ambitions for the NExT I-Site”

Frédéric Jacquemin, Vice President Innovation and Partnerships, I-site

The definitive awarding of the I-Site label in March 2022 enabled Nantes Université, its member establishments, and its partners to strengthen and enduringly pursue the project’s strategy around two scientific focuses of excellence: Industry of the Future, and Health of the Future. Since then, the NExT I-Site has continued to develop and consolidate this dynamic by initiating new structural projects and partnerships, and by actively supporting the scientific community in conducting research activities.

The NExT I-Site is a project that is also open to and toward the world. In a society that is constantly transforming and changing, it became necessary to reflect on how to redefine the project’s scientific orientations in light of emerging issues, and in keeping with the national strategy advanced by the France 2030 plan.

Over the last few months, a collective consultation and reflection effort was pursued with the broader Nantes scientific community, as well as territorial actors, to define the NExT I-Site’s new priorities and ambitions for the coming years. This pathway will position our institution—and the entire Nantes area—as a major actor in the necessary transformation of society.

Our co-created scientific roadmap serves as a reference document guiding the strategy, choices, and future investments of an internationally recognized university in connection with two focuses of excellence, both rooted in its territory, as well as steadfastly open and sustainable.

I would like to thank all contributors, members, and partners of Nantes Université for their active participation in this collective undertaking. We can count on our strengths in research, training, and innovation to meet the challenges of today, and to prepare the world of tomorrow.

Sommaire

1 Introduction

The NExT I-Site's scientific roadmap outlines the trajectory of research activities for the years ahead. This roadmap connects long-term objectives, and identifies priority areas of development. It reflects the I-Site's commitment to promoting scientific excellence, innovation, and societal impact by offering a clear and ambitious vision.

This roadmap was developed using a two-stage methodology:

- Conducting an assessment of Nantes Université
- Co-creating the roadmap's content with the communities involved (I-Site members and partners)

1.1 Site assessment

Several indicators and rankings selected during the planning phase were analyzed for all Nantes Université members[1]; this effort included all scientific disciplines present, with no consideration given to the scientific scope of NExT or the previous roadmap. The goal of this assessment was to provide an overview of present strengths, with a view to establishing NExT I-Site's new 10-year roadmap.

The indicators selected and validated by all members provided a clear picture of scientific excellence—in order to identify driving forces—as well as emerging disciplines and their positioning within the innovation spectrum. This assessment yielded a comprehensive, 360-degree view.

The following data and sources were used:

Research

- **Individual recognitions**
  - Stanford ranking (career and single year)
  - Distinctions, prizes, and scholarships
- **Collective recognition**
  - International rankings (Shanghai, Leiden, THE)
  - European projects
  - National projects

Innovation

- Patents
- CIFRE theses
- Associated research laboratories (not exclusively LabComs)
- Chairs
- Start-ups (including those not selected by the I-Lab or the EIC)

- Information sources:
  - Metrics for which Erdyn gathered source information: Stanford, Shanghai, Leiden, THE, Institut Universitaire de France (IUF), European Research Council (ERC), EURATOM (Treaty of the European Atomic Energy Community) projects, and PCRD (Research and Development Framework-Agreement) projects (via the Community Research and Development Information Service or CORDIS), national projects (via ScanR), patents (via Questel Orbit). This data (for the last ten years) was gathered while producing the assessment's first draft in April 2023.
  - Metrics for which the source information was provided by I-Site partners: CIFRE, chairs, associated research laboratories, start-ups. Data for the last five years.

[1] Nantes Université, Centrale Nantes, Nantes CHU, INSERM, Beaux-arts Nantes Saint-Nazaire, School of Architecture, IRT Jules Verne

- Bibliometric analysis conducted by Nantes Université in the field of health, with inclusion of results

For certain analyses (Stanford ranking and European projects), we calculated specialization indices (using the same model as the French Science and Technology Observatory or OST[2]) in order to identify distinguishing features aside from areas of strength determined by the number of projects or researchers.

Finally, K-Means clustering was used to establish a typology of disciplines based on the results from these various metrics. It encompasses four classes, three of which include the site's fields of excellence and distinguishing features.

- Three variables were used to determine scientific excellence, and four to determine innovation:
  - Research: Stanford specialization indices for single year and career ranking, individual prizes and distinctions.
  - Innovation: Chairs, Industrial Agreements for Training Through Research (CIFRE), associated research laboratories, start-ups.
- For Stanford, we drew on specialization indices in order to identify distinctive disciplines in Nantes with respect to global trends.
- Results from the bibliometric analysis were not included in the K-Means clustering, due to the extensive correlation with the Stanford ranking.

Disciplines that distinguish themselves very strongly for individual distinctions, and strongly for CIFRE	Disciplines that distinguish themselves very strongly for the Stanford ranking's specialization indices (career and single year), and strongly for associated research laboratories	Disciplines that distinguish themselves very strongly across all innovation metrics and individual distinctions
Business & Management Cardiovascular System & Hematology (classification du Stanford) Law Endocrinology & Metabolism Energy Fluids & Plasmas Genetics & Heredity Information Systems Solid mechanics Clinical research Engineering sciences Sociology, demography	Acoustics Biomedical Engineering Civil Engineering Dermatology & Venereal Diseases Design Practice & Management Emergency & Critical Care Medicine Industrial Engineering & Automation Information & Library Sciences Ocean Engineering and Marine Resources	General & Internal Medicine Process engineering Immunology Oncology & Carcinogenesis

These analyses confirmed the site's excellence in the two research focuses of NExT I-Site: Health and Industry. They also revealed a strong distinguishing feature for Nantes in biomedical engineering, a potential bridge between NExT's two major research focuses, and one that calls for developing transversal

[2] Indicators and methods | Hcéres (hceres.fr)

approaches. In compliance with specifications, the applied methodology also revealed—beyond the historic strengths of Nantes (oncology, civil engineering, ocean engineering, etc.)—a remarkable emerging presence in gastroenterology, management science, the social sciences more generally, traumatology, and emergency medicine, among others.

On the basis of these various analyses, two thematic research focuses were identified, serving as an initial basis for refinement with the various actors involved.

1.2 Co-creating the roadmap

NExT I-Site's scientific roadmap was developed according to a participatory methodology that involved the broader Nantes scientific community in its creation. This approach complemented the site assessment with the "insider's" view—and ecosystem knowledge—of Nantes stakeholders, thereby ensuring the community's involvement in its implementation.

The methodology for creating this scientific roadmap drew inspiration from other technological roadmaps, with a view to helping build a sustainable future. The reflections touched on six primary issues listed below:

Where do things stand ?
Scientific state of the art
Description of the current functioning of value chains, regulations.
Difficulties and curbs

Why ?
Major trends
Industrial bottlenecks to be overcome
Future regulatory changes

What ?
Scientific objectives
Expected research results

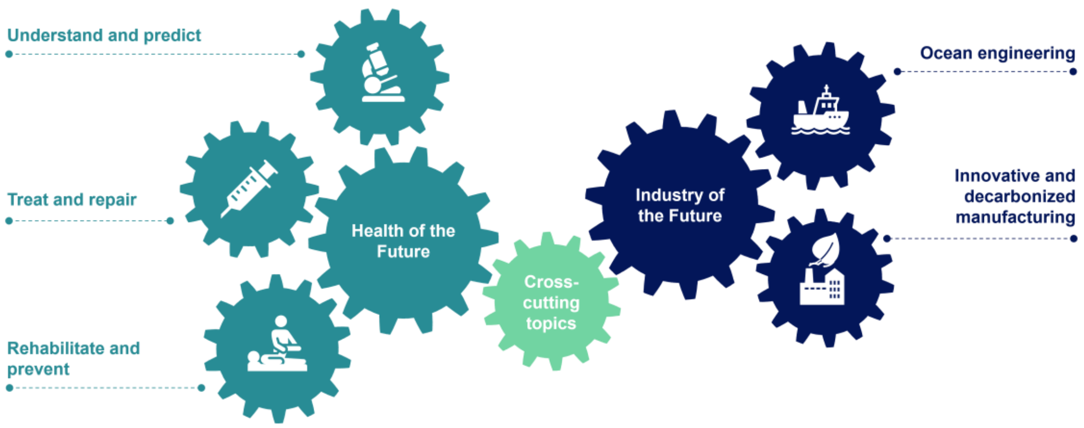
How ?
Means and resources : platforms, tools, HR, funding

Where do we want to go ?
Forward vision in keeping with ambition

When ?
Major stages and milestones from today to reflections on the future

The co-creation effort, which began in September 2023, involved the broader industry and health communities of I-Site members and partners, and lasted until March 2024. The composition of workshops is presented in the appendix (see 5.2). The effort was organized around the I-Site's two focuses of excellence—Health of the Future and Industry of the Future—as well as reflections on transversal topics to identify any potential intersections between the I-Site's two fields of excellence, with some subjects leading to cross-cutting approaches fostering synergy among the site's strengths.

1.3 Structuring the roadmap



2 Industry of the Future research focus

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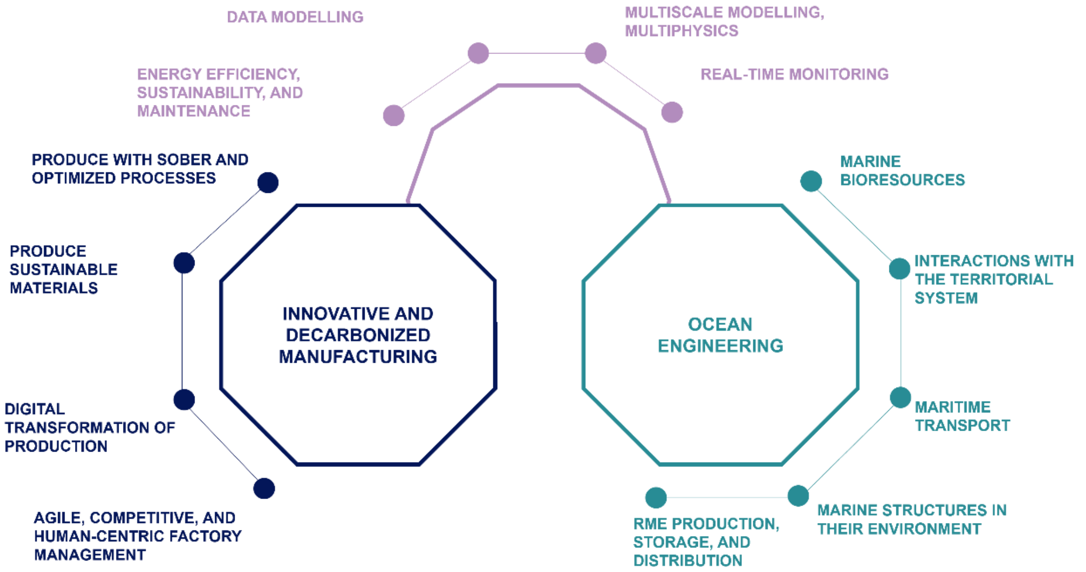
In an established tradition of collaboration between academic research and industry — and on the basis of scientific excellence in process engineering and materials characterization, mechanical engineering, industrial engineering, civil engineering, ocean engineering and hydrodynamics, energy, robotics, digital modelling, simulation, and optimization — NExT is pursuing the following two research focuses:

- Ocean engineering
- Innovative and decarbonized manufacturing



2.1 Ocean engineering

2.1.1 Socioeconomic context and issues

Ocean engineering is in keeping with the global and long-term development of the "blue economy," a driver of key issues and challenges that raises questions that require multidisciplinary and decompartmentalized approaches on the part of the scientific community.

The blue economy, which seeks to sustainably and responsibly use the seas, oceans, and marine resources while promoting economic growth, job creation, and environmental protection, refers to all economic activities connected to the oceans, seas, or coasts. The blue economy represents approximately 1.5% of French GDP, provides 525,000 or 1.8% of the nation's jobs[3], and encompasses a range of sectors such as marine products (including the extraction of marine materials), maritime transport, naval construction, marine energy production, coastal tourism, and any other uses of the coastal system. As such, the blue economy is considered an important lever for sustainable development and efforts to combat climate disruption.

Despite the immensity of oceans, this growing interest for the blue economy among socioeconomic actors has led to a growing number of use conflicts connected to the maritime space. While uses have developed (fishing, aquaculture, offshore wind or photovoltaic power, the exploitation of mineral and biological resources, tourism), the growing number of protected marine areas has limited possibilities. Greater sobriety in the use of maritime space is therefore essential, as part of a democratic dynamic and public debate. Our knowledge regarding these uses and their impact (notably articulating various impacts) must

[3] French General Secretariat for the Sea, 2022. "The blue economy in France"

be gathered, with the data being usable by all (metadata, monitoring over time).

Among these uses, the maritime space near coasts can be used for renewable marine energy production (RME[4]), doing so in perfect synergy with various uses of the sea, all while controlling environmental impact. RME technologies are a major factor in the energy transition: the key is to reduce the cost of these technologies, thereby guiding them toward maturity, and ultimately increasing their installed capacity. For industry, RME technologies represent a potential source of sustainable and high added value jobs, and have also raised hopes of becoming an export sector.

Marine bioresources raise major environmental and economic considerations. While the decarbonization of surface transport (land, sea) has proceeded via electrification and hydrogen use, due to technical constraints and technology maturity, aviation (long haul in particular) must continue using—for decades to come—petroleum-based kerosene as its primary fuel, which will gradually be supplemented and then replaced by biokerosene. With this in mind, marine bioresources potentially represent an economic advantage for coastal territories, just as petroleum did during the 20th century for countries with abundant underground deposits. Like petroleum, marine bioresources can be valorized well beyond energy, including molecules of interest (chemistry, pharmaceuticals, food), in addition to the creation of virtuous cycles (circular economy).

Representing nearly 3% of global greenhouse gas emissions, maritime transport must also contend with its decarbonization, and reduce its environmental footprint in general. According to the International Maritime Organization (IMO), the energy transition for maritime transport can be achieved via two primary levers: energy efficiency and energy conversion. New technologies will contribute to this effort (eco-design, sober technologies, more effective energy mix, low-carbon fuel), with fleet doctrine and optimized operations also representing future solutions.

The common technical factor within the blue economy is commonly referred to as “marine structures,” whether this involves ships, offshore structures for energy production and conversion, dykes, structures for aquaculture or marine bioresource production, along with beacons, lighthouses, and lights. These structures play a crucial role in the blue economy; their sustainability, cost, and environmental impact are therefore key considerations.

- The roadmap’s common thread for ocean engineering includes the Nantes scientific community’s contributions to understanding and sustainably developing the blue economy

2.1.2 Ambitions of the Nantes scientific community

Leveraging its advantages (see assessment), the NExT I-Site’s ocean engineering community formulated clear and realistic ambitions firmly rooted in today’s reality. These seek to amplify intrinsic dynamics as well as those enabled by the NExT I-Site, with a view to making the Nantes – Saint Nazaire academic and metropolitan site a global reference across the research spectrum, ranging from initial, continuing, and international education to innovation and entrepreneurship in ocean engineering. These ambitions include:

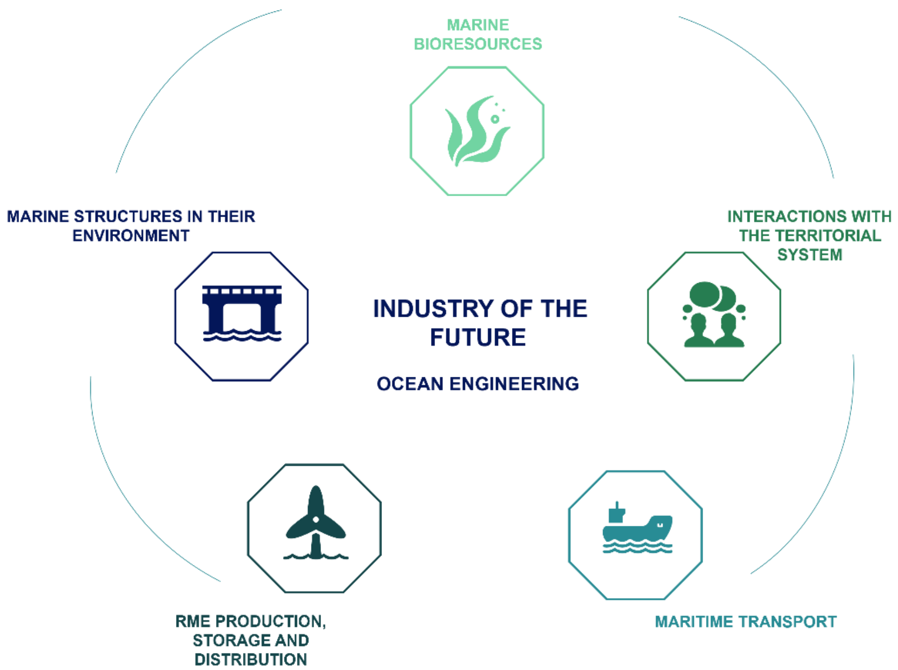
- Maintaining and increasing the site’s recent Shanghai ranking in “Marine/ocean engineering” (October 2023)
- Consolidating the site’s current position as French leader — and pushing to become a global reference — for three fields central to ocean engineering: marine wind power, RME, and the decarbonization of maritime transport

[4] We are extending the usual understanding of RME to encompass offshore wind

- Emerging as a global reference in microalgae by significantly raising TRL (especially in the 2-6 segment) from basic and applied science up through demonstrators and new procedures, products, and uses. Positioning the site as a leader in microalgae research, especially for the production of 3rd generation biofuels, and positioning AlgoSolis as a global reference (via its inclusion in rankings such as Leiden and Stanford)
- Successfully integrating HSS in ocean engineering and marine biotechnology (social acceptability, economic models, law and regulations, use conflicts)
- Developing interdisciplinarity and collaboration
  - "Short-distance" interdisciplinarity in engineering science
  - "Long-distance" interdisciplinarity (taking advantage of site dynamics) between engineering and health (the I-Site's second major focus), in order to position the site as a pioneer in microalgae use for human and animal health (including food)
  - Establishing enhanced strategic collaboration with global universities, research centers, and experts in ocean engineering
- Solidifying territorial integration and links with regional priorities (microalgae, RME, etc.)

2.1.3 Scope of *Ocean engineering* research focus

The scope of Ocean engineering encompasses five structural research subjects :



2.1.3.1 Marine structures in their environment

Complementary and varied research activities are an integral part of "marine structures in their (hydro- and aerodynamic) environment." Characterizing the resource at its production site, at the beginning of its life cycle, promotes good technical and installation choices.

The ability to model structures in their environment—their hydro and aero-elastic response while operating, and their ability to survive extreme events—are crucial to designing these structures. Optimized moorings are also key to improving sizing-related factors, and hence their cost and environmental footprint (raw materials, manufacturing, installation, dismantling).

Optimizing the functioning of structures via command/control and using massive measurement data are important topics due to their capacity to produce and operate. Modelling and optimizing marine operations is also the subject of high-level research, notably involving underwater robotics. To increase the durability of marine structures, tools must be developed to monitor them while in service.

In a context of evolving coastlines, research is being conducted to monitor and prevent the erosion of coastal dykes, as well as to pursue their characterization and the valorization of sediment.

2.1.3.2 Marine bioresources

Valorization processes for marine bioresources promote its sustainable exploitation, minimizing societal and environmental impact all while addressing the constraints of the targeted applications.

Research in physiology and the metabolism of microalgae—in addition to microalgae cultivation processes and valorization—is central to the scientific project. These advances will lead to continuous progress, as well as to the integration of knowledge within multi-scale modelling from the cell up through the process level.

The scientific community will drive progress in eco-design, the sustainable exploitation of marine and agricultural bioresources, and biodiversity preservation, in addition to new applications for industry, human health, animal health, food, biofuels, biosourced products, and green chemistry.

Developing the biorefinery concept will optimize the exploitation of biomass while minimizing environmental impact, especially via monitoring and advanced bioprocess control.

The biological valorization of industrial waste (CO2, wastewater treatment) is also central to the bioeconomy, and involves the scientific disciplines working on marine bioresources.

2.1.3.3 Production, storage, and distribution of renewable marine energy

Electrical engineering is central to this topic, as are the scientific fields connected to energy storage and transport: multiphysics modelling of batteries, underground energy storage, and energy cables.

It also spans command and control, production optimization, and the network connection (smart grids) of RME production sources, which are intermittent by nature. Marine energy storage is also studied, as is conversion, for instance in connection with marine electrolyzers, whose durability is a key bottleneck.

2.1.3.4 Maritime transport

Decarbonizing maritime transport is at the heart of the research conducted by the Nantes scientific community on this topic, including wind propulsion and new fuels with adapted port infrastructure to accommodate them (GNL, hydrogen). Optimized consumption, retrofitted ships, and durable marine fuel cells and batteries are also explored in research on decarbonization.

In a more digital vein, high-level research is driven by instrumentation ships producing massive data (whose analysis via adapted AI-based tools will help improve, optimize, predict, and even move toward a digital twin), autonomous ships (and even fleets), and ship collisions.

Contributions from HSS (economics, geography, etc.) explore subjects such as the technical and economic optimization of decarbonized fleet strategies, demassification, sobriety, hinterland reconfiguration, and the adaptation of port structures.

2.1.3.5 Interactions with the territorial system

The links between the four preceding subjects (marine structures, bioresources, renewable marine energy, and maritime transport) and territorial actors (local content) represents an interesting field for interdisciplinary research.

The dynamism of human maritime activities (data, law) will be analyzed, mobilizing the human and social sciences. The methods by which the maritime space will be shared in situations of co-use and multi-use (acceptance, planning, conflicts, law, climate change, etc.) will also be studied. Impacts will be assessed, especially cumulative ones. This will lead to the development of new environmental monitoring tools (methods, issues).

2.1.4 10 year targeted research results

The scientific issues presented above will translate into significant research results within 5-10 years. Below is a non-exhaustive list of expected results, broken down into 3 categories:

- Upstream knowledge
- New tools and methods
- Technological and use-related breakthroughs

For increased readability, the targeted results are connected to one of the roadmap's 5 subjects, although many of them have interdisciplinary potential for multiple subjects (modelling swell behavior and marine operations).

2.1.4.1 Upstream knowledge

- Marine structures in their environment
  - Improved modelling for marine structure behavior using artificial intelligence
- Marine bioresources
  - Generic radiative transfer models that can predict light transfer in complex biological environments (dense environments, non-spheric cell morphologies, structures in colonies)
  - Understand the influence of radiative transfer on the growth and natural synthesis of hydrocarbons among Botryococcus colonial microalgae in view of solar production
  - Identify potential marine bioresources for formulating biomaterials and biosourced materials compatible with human health
  - Knowledge models that can predict the metabolic response and physiological adaptation of microalgae under varying conditions of solar stress
  - Hybrid AI-mechanistic models for real-time optimization of intensified solar photobioreactors
- Maritime transport
  - Identify different CO2 capture and valorization technologies
- Interactions with the coastal system
  - Study emerging forms of co- and multi-use
  - Groundwork for an integrated approach of cumulative effects
  - Emergence of new research issues at the intersection of the Maritime Chair (HSS) and ocean engineering
  - Understanding key issues relating to acceptance or conflict in connection with industrial marine projects, understanding avenues for blockage and reconciliation for marine spatial planning approaches

2.1.4.2 New tools and methods

There is a need for new multiscale and multiphysics methods, which entails strengthening and combining theoretical, digital, and experimental approaches, in addition to those from engineering science and the life sciences. The goal is to link different deterministic and statistical digital models, and to conduct prototype tests in the laboratory or experimental basins, as well as actual marine systems.

The primary results expected in 5-10 years are presented below (non-exhaustive list).

- Marine structures in their environment
  - Experimental site for studying sea dyke behavior
  - Experimental basin prediction of behavior tests for floating structures in their environment (swell-wind) over characteristic statistical periods
  - Experimental representation of atmosphere and aerodynamics on a marine structure using

Software-In-the-Loop

- High-fidelity digital modelling of interactions between a floating body subject to multidirectional aerodynamic efforts and swell
- Behavior models including the combination of data from digital / experimental simulations on models / measured on operational marine structures
- Develop the capacity to test optimal structural design/maintenance choices using a database generated from tests in an experimental basin and during marine operations

- Marine bioresources
  - Next-generation metabolic sensors for the advanced monitoring of optimized molecule-of-interest production based on marine bioresources
  - Software sensors for the online monitoring of microalgae metabolic markers in production conditions, including solar
  - Forecasting models for local weather over short time periods (1 hour to 2 days) in order to control solar bioprocesses
  - Predictive metabolic control models for production in photobioreactors
  - Digital twins for the controlled production of microalgae in photobioreactors
  - Digital twins for integrated marine bioresource value chains
  - Integrated medium-throughput screening system for identifying industrial strains of interest
  - Advanced tools for the optimal operational management of solar photobioreactors in the presence of climatic variations (optimized solar conversion, heat management for cultivation systems)
  - Decision assistance tool based on predictive models for optimized wastewater treatment (industrial wastewater, bio-concrete from urine) via microalgae.
- RME production, storage, and distribution
  - Test benches to reproduce usage conditions for marine electrolyzers with respect to seawater composition, mechanical and thermal constraints
  - High-fidelity multi-mechanistic modelling (atmo-aero-hydro-elastic + moorings) for offshore wind power
  - Digital models and test benches for thermodynamic energy storage systems and their development, culminating in the creation of a physical demonstrator
  - Digital twin of a complete floating offshore wind farm that can simulate behavior in realistic environmental conditions (swell, wind, current) across 50 km2 for a duration of 3h: wind turbine movements, optimized turbine control to minimize overall production cost, interaction with the electrical network and storage system.
- Maritime transport
  - Experimental resources for testing marine operations (dynamic positioning, mechanized hoisting solutions)
  - Instrumentation and monitoring for materials, ship parts, floaters
  - Optimize, via test bench and digital modelling, a marine motor using an innovative biofuel
  - Integrated technical and economic model for maritime transport
  - Predictive model for ship consumption and behavior, including new decarbonized motorization, wind assistance, short-term environmental prediction (swell, wind, current) using on-board instrumentation (data assimilation), and environmental data in real time
  - Optimized emulators (command and control) for wind propulsion for tests in experimental basins and on digital twins

- Eco-driving model in route and in ports, including hydro-aero-motor optimization
- Capacity to test optimal design/maintenance choices using test benches in experimental basins and marine operational data
- Routing model with hybrid propulsion and validation on an instrumented fleet

- Interactions with the coastal system
  - Fully functional monitoring platform for the dynamics of human marine activities, based on the principles of open science
  - Assessment method for cumulative effects

2.1.4.3 Technological and use-related breakthroughs

- Marine structures in their environment
  - Qualification of low-carbon, economical, and sustainable solutions for floaters
  - Floaters with reduced carbon impact
- RME production, storage, and distribution
  - Multi-mechanistic high-fidelity modelling (atmo-aeero-hydro-elastic + moorings) for offshore wind turbines
  - Single-cell electrolyzer operational in a marine environment
  - High-performance (stack) offshore operational system
  - Optimized RME production systems for increasingly hostile environmental conditions
  - New concept for RME production systems that are both environment-aware (prediction/monitoring for wind, waves, current, wakes, avian fauna, other uses of space) and resilient. These new technologies will, for example, lead to the implementation of POC / demonstrator for an autonomous floating wind turbine (dynamic positioning, storage)
- Marine bioresources
  - AlgoFilm intensified solar photobioreactor technology for the large-scale production of microalgae biomass with low environmental impact
  - Decision assistance tool for optimal management of intensified photobioreactors in the presence of climatic variations (real-time optimization of solar conversion, heat management of cultivation system)
  - Biorefinery processes for optimized conversion of microalgae biomass into liquid biofuels (biodiesel, bioethanol, biokerosene)
  - New technologies for Good Manufacturing Practice (GMP) photo-bioproduction of biological polymers with viscous behavior
  - Innovative methods for purifying and polishing metabolic fractions extracted from microalgae
  - First pilot-scale demonstrator for microalgae-based health compounds
  - Demonstrator of Botryococcus microalgae’s potential for simultaneous production in intensified hydrocarbon and synthon photobioreactors for energy and green chemistry
  - New photobioreactor technology for the industrial production of microalgae-based therapeutic compounds (cGMP)
- Maritime transport
  - Full-scale carbon capture of a marine motor and associated digital modelling
  - Demonstrator and digital modelling of innovative e-fuel storage
- Interactions with the coastal system
  - Support for innovative and bottom-up forms of co-use and multi-use

2.1.5 Required resources

2.1.5.1 Technological resources

Technological resources that match ambitions will be essential to achieving the targeted research results. Some of these resources, exceptional due to their functionality or impact, will serve as distinctive "emblems" for the broader Nantes scientific community.

The experimental basins of LHEEA should be adapted to model marine operations with multiple structures (cost of a few hundred k€). Adaptation of LHEEA's engine test bench will be used to test biofuels (approximately 200 k€). There are plans to develop (engineers and postdoctoral fellows) an experimental/digital integrative tool for marine structure behavior in their environment (digital-experimental methodology, shared configurations, data merger, database, AI).

A structural technical resource—a microalgae production platform dedicated to health (production of active compounds in GrMP environment for clinical trials)—will be created thanks to the extension of the HEALTH-PHASE demonstrator (estimated total budget of 4 M€). The AlgoSolis platform will be supplemented with instrumented solar photobioreactors (advanced metrology, metabolic sensors) with weather forecasting command, and their associated digital twins will also be created (approximately 200 k€), supplemented by computing capacity for Monte Carlo type modelling tools for micro-location weather forecasting.

Research on renewable marine energy requires technical resources that are representative of real conditions at affordable cost (investment, functioning). A platform near the coast (low access cost) for testing technological building blocks such as robots, sensors, instrumented components (100-120 k€ for installation + 20-25 k€/year). A reduced-scale thermomechanical characterization test bench for energy cables (~100 k€), test bench equipment adapted to seawater electrolysis (20 k€), and test bench equipment for generating marine air will also be required.

Research on wind-assisted propulsion requires substantial testing and qualification resources, especially a full-scale land-based test site for the assessment of wind-assisted propulsion systems, whose investment cost is on the order of several M€. LHEEA's experimental test basins (model scale) must be adapted (200 k€) to test ships with wind-assisted propulsion (Subsea Intervention Lubricator or SIL). These resources will be supplemented by a digital tool, a complete behavioral model of the ship including hydrodynamics, aerodynamics, wind-assisted propulsion, and motorization (new fuels), along with techno-economic modelling to optimize the choice of ship fleet in preparation for decarbonization (new fuels, route optimization).

The platform for monitoring the dynamics of human marine activities—described above as a targeted 10-year research result—will become a key infrastructure for the broader Nantes scientific community. Other technical resources supporting the "Interactions with the territorial system" research topic will essentially consist of digital tools for accessing information and analysis: a digital platform providing access to data, and even models for reducing access time and detecting gaps (database for energy cost over ten years supplemented by a forecasting model, database for subaqueous soil, an environmental monitoring platform).

2.1.5.2 Partnerships and collaboration

We distinguish between two key types of collaboration and partnership: those between stakeholders within the broader Nantes scientific community, and those with actors beyond the site. While some collaboration methods have been tried and tested, others offer innovative approaches that are adapted to the identified issues.

2.1.5.2.1 Collaboration internal to the Nantes scientific community

Collaborations will be reinforced:

- LHEEA/GeM/LS2N in connection with the hydro/aeero/structural digital twin (including moorings) and command and control for RME structures

- IMN/ LTEN Auvity team and/or CEA Tech (and/or a yet-to-be identified team)

Collaborative tools (interdisciplinary and inter-institutional) will be maintained and developed, notably in connection with the Maritime Chair[5], which should be consolidated and extended to other HSS fields, and collaborative projects open in their form towards emerging topics, such as "Engineering-Health Call for expression of interest" (thesis, technical reinforcement, depending on the needs). The research spectrum (led by Nantes Université) will also be promoted and strengthened, as will collaboration (led by the NU foundation) and valorization (led by Capacités, Centrale Innovation, the site's incubators and Ouest-Valorisation). Measures could include incentivizing laboratory-enterprise projects with subsidies and industrial co-investment (coordinating post-doc + leveraged support).

While of course not specific to ocean engineering, funding for platform-based R&D programs will generate inter-laboratory synergies, with a typical duration of 2-4 years, and targeted for clearly identified bottlenecks, such as advanced metrology for bioreactors. Each of these projects could be funded in the amount of approximately 100 k€/year.

On the same order of ideas, the challenges requiring longer timeframes could be addressed via interdisciplinary projects typically lasting 6 years, with a mid-point milestone, and conditional funding for the second phase.

The collaborative ecosystem is structured by a key tool: The West Atlantic Marine Energy Community (WEAMEC), which is made up of thirty institutions and laboratories including Centrale Nantes, Nantes Université, IRT Jules Verne, CEA Tech, and l'Université Gustave Eiffel.

2.1.5.2.2 International collaboration

This firstly entails consolidating the involvement of Nantes-based researchers in existing academic networks (such as the Marine Spatial Planning Research Network or MSPRN). Targeted international collaborative projects such as International Research Projects or IRPs (theses with long stays abroad), of a duration compatible with a graduate degree (5-7 years), will be initiated. Finally, these instruments should be developed in order to host global experts under good conditions and over long durations (six months to two years), or for the secondment abroad of researchers from the site.

International collaborations could take the form of a structured and expansive program for a generic topic such as marine bioresources, including engineering, health, and HSS, in addition to a research component (theses), coordination, and international impact (organizing conferences, etc.).

2.1.5.3 Human resources, organization, management

Human resources are presented below depending on their purpose, direct involvement in research activities, implementation of technical platforms and resources, and procedural coordination:

- Human resources directly involved in research activities: Master's internships, PhD theses and postdoctoral fellowships, tenured researchers. Special attention will be given to:
  - Signposting internships, theses, and postdoctoral fellowships in inter-laboratory Graduate programs focusing on topics identified over multiple years, for results in ten years.
  - Theses focusing on "methodological tools" shared by one or more I-Site partners (i.e., radiative transfer models, micro-location weather forecasting)
  - Co-supervised theses (such as the Laboratoire de Thermique et Énergie de Nantes or LTeN, CEA Tech) with time recovery for 5-year research programs
  - HSS theses focusing on transversal topics
  - ...

[5] https://chairemaritime.univ-nantes.fr/

- Support staff: research engineers, study engineers. In keeping with the description of technical resources above, the roadmap's implementation will be conditional on mobilizing adequate personnel for:
  - Instrumentation and in-service monitoring of materials and structures (including floaters)
  - Support for platforms (such as AlgoSolis)
  - Installation of the full-scale land-based test site for wind-assisted propulsion
  - The long-term viability/capitalization of software tools developed in laboratories
  - Support for the human marine activity monitoring database
  - ...
- Personnel for procedural coordination
  - Research engineer or postdoctoral fellow for platform-based collaborative public-private R&D on biofuels
  - Research engineer or postdoctoral fellow to coordinate a Health-Engineering-Microalgae topic
  - ...

2.2 Innovative and decarbonized manufacturing

2.2.1 Socioeconomic context and issues

The transition toward a sustainable economy has become imperative globally in light of the pressing challenges of climate change. Central to this transformation is the need to rethink industrial production methods to make them innovative, attractive, and decarbonized.

Industry is responsible for 20% of GHG emissions in France, which it aims to divide by 5 by 2050[6]6. Sixty-nine percent of energy consumption in industry is for heat processes. By developing new methods for process electrification and waste heat recovery, and creating new optimized energy management tools, we can achieve the goal of decarbonization.

Industrial productivity is another key issue, which can be addressed via scientific and technological advances. Additive manufacturing, automation, integration of artificial intelligence, and the digitalization of production in general have been identified as essential levers for increasing the efficiency of production processes, all while reducing their environmental impact.

A third issue involves the attractiveness of industrial jobs for employees. Numerous industrial jobs are under strain, with industrial careers no longer attracting candidates, who prefer jobs in the service sector. Working conditions, and well-being at work in general, are key to restoring attractiveness, unless we agree to be dependent on manufactured products imported from countries with low labor costs, where fundamental human rights are not always respected.

- The roadmap's "common thread" for this issue is the Nantes scientific community's efforts to develop new knowledge, tools and structural equipment, with a view to providing industry with the highest level of excellence, sobriety, and sustainability

[6] Source : https://www.usinenouvelle.com/article/dossier-production-decarboner-s-impose.N2099161

2.2.2 The ambitions of the Nantes scientific community

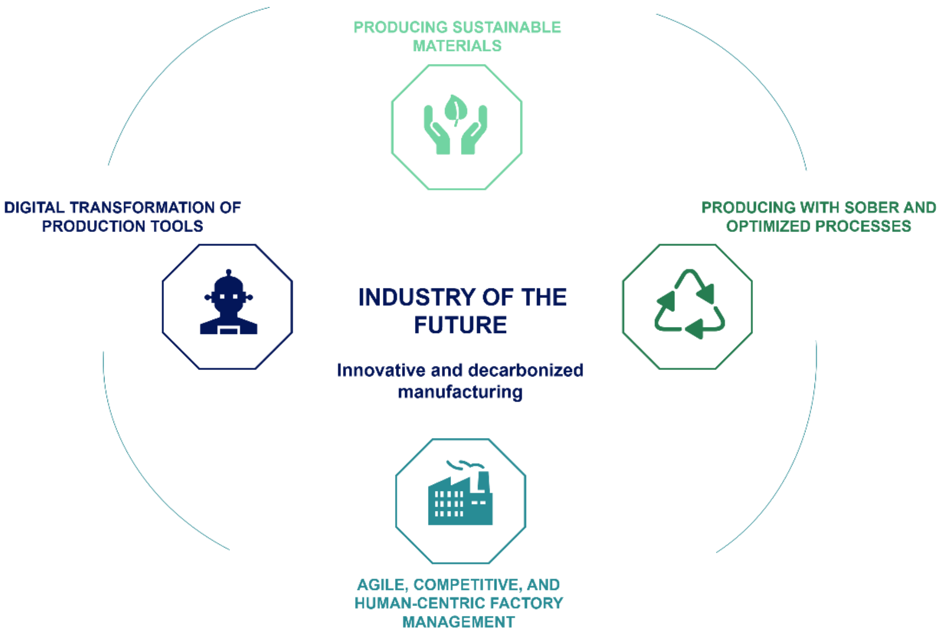
The Nantes research community's ambition is to become a reference in this field of research.

- Become a **European leader** in a specific area such as manufacturing, industrial engineering, energy control for manufacturing processes, multifunction materials and their applications, and high-temperature heat storage technologies for industry.
- Develop the Nantes scientific community's **visibility** and **collaborations** both within and beyond the site
  - Create a network of collaborations relating to "Composite materials and processes" and their applications
  - Ensure inclusion in a European roadmap for research infrastructure
  - Develop industrial collaborations
  - Create a group including HSS (spatial planning, design) on the topic of "compromise and systems"

Develop emblematic facilities and recognized cutting-edge technologies. Actions will be based on a network of existing technological platforms, supplemented by new equipment that can address key domains in the Industry of the Future.

2.2.3 Scope of the Innovative and decarbonized manufacturing research topic

Four major research subjects structure and outline the scope of *Innovative and decarbonized manufacturing:*



2.2.3.1 Producing sustainable materials

Producing sustainable materials with a light environmental footprint, promoting judicious resource management, and addressing the issues faced by the industrial world are all central to research on this topic.

The production of biosourced materials is a key subject for the broader Nantes scientific community. This notably translates into research on biogenic carbon (fixed by the plant following photosynthesis) and its use in biosourced materials production, in keeping with an effort to reconsider material sourcing. The assessment and availability of deposits, whether new or not, will be an influential factor for this topic. Research on sustainable materials also encompasses the production of materials that are hybrid, multifunctional, and agile, in addition to their integration within advanced subsystems (sensors, actuators), notably driving innovation to adapt and respond to industrial decarbonization issues.

The economic dimension (impact on product cost, cost-quality relationship) in a context of climate transition, as well as efficiency (service continuity in severe environmental conditions), are two essential and integrated aspects that are actively explored in research.

The valorization of recycled materials is a key element bringing together all of the disciplines under the Innovative and decarbonized manufacturing topic, serving as a driver for alternative materials to cut GHG emissions (for instance construction materials such as cement, whose production generates very high GHG emissions).

2.2.3.2 Producing with sober and optimized processes

Research on "sober and optimized processes" is varied and complementary. Teams have especially worked on developing and optimizing different processes such as additive manufacturing (for the development of new products), composite materials, material removal, continuous flow synthesis, the synthesis and formulation of organic composite materials from green processes, bioprinting, and recycling. The performance variability of the process and its flexibility (low tech, mobility, adaptation) are two research subjects in which the Nantes scientific community is also active.

New manufacturing processes also mobilize research in developing adapted production components, such as industrial robotics, simulation tools (high performance computing multiphysics), and embedded systems.

Finally, to help respond to environmental challenges, research has focused on improved energy efficiency of processes, waste heat and energy storage management in particular.

2.2.3.3 Agile, competitive, and human-centric factory management

The transformation of factories and production, in a context of environmental crisis, is central to the Innovative and decarbonized manufacturing topic.

This encompasses the environmental impact of industrial production, which is why the Nantes scientific community identified it as a key bottleneck in its research. Special attention will be given to the territorial impact of factories (regenerative design with a territorial dimension benefitting both humans and nature), LCA (life cycle assessment) and ecological design, sustainability assessment, energy management (approach ranging from elementary components to devices and networks/systems), and sorting processes, all within a context of evolving standards and regulations.

The knowledge management, the articulation of human-robot collaboration, and information system agility will optimize human-centric factory management, especially in enhancing attractiveness for employees.

2.2.3.4 Digital transformation of production tools

The digital transformation of production tools is central to industry's trajectory of change. The Nantes scientific community's research on sensors and communication networks is central to its efforts in this area (manufacturing sensors made of electroactive materials, sensor networks, antenna-sensors, cooperative communications, propagation in complex environments, IoT, electronics and embedded systems, and safe, reliable, and low-consumption architectures). These tools for optimizing and improving visualization in operations have garnered considerable research attention for a number of years, with the development of digital twins for production systems ultimately being envisioned.

Research also focuses on artificial intelligence (embedded AI, connected AI) and its implications, enabling simple, fast, and sustainable data gathering and production optimization. AI is also connected to research conducted by the scientific community on augmented reality, deep learning, monitoring, and information systems.

2.2.4 5-10 year targeted research results

The scientific issues presented above should yield significant research results within 5-10 years. Below is a non-exhaustive list of some expected results.

- Upstream knowledge
- New tools and methods
- Technological and use-related breakthroughs

For enhanced legibility, the targeted results are connected to one of the roadmap's four subjects, although many of them have interdisciplinary connections with multiple subjects.

2.2.4.1 Upstream knowledge

- Producing with sustainable materials
  - Characterization and modelling of multiphysics and multiscale couplings under manufacturing conditions
  - Instrumentation and inverse methods for identifying properties
  - Eco-processes for implementing biosourced materials
- Producing with sober and optimized processes
  - Multiphysics models for resources and inputs (materials, fluids, energies, human resources) for industrial processes
- Agile, competitive, and human-centric factory management
  - New methodologies for human-robot integration/interaction
- Digital transformation of production
  - Emergence of new integrated approaches (engineering sciences, human and social sciences) for modelling production
  - Digital transformation of factories: understanding possibilities and acceptability

2.2.4.2 New tools and methods

- Produce with sustainable materials
  - Digital twins describing material behavior
  - Artificial intelligence to predict the impact of transitions (including climate-related ones) on the quality and quantity of territorial raw material deposits, with a view to optimizing processes and functionalities, and digitizing production and preventive medicine
  - Integrated resource screening system to identify the best compromises between environmental and economic costs
- Produce with sober and optimized processes
  - Analytic and digital prediction models for materials
  - Development of tools and methodologies for eco-efficient industrial management
- Agile, competitive, and human-centric factory management
  - Development of assessment tools for the impact of industrial organizations on regional planning
- Digital transformation of production
  - AI-based production optimization using experimental data obtained from a range of sensors (T, vision, rheology) via wireless communication systems
  - Digital twin of production to provide a real-time view and anticipate events

2.2.4.3 Technological and use-related breakthroughs

- Produce with sustainable materials
  - Demonstrator for a plastic recycling line that can manage variability
  - Proof of concept for recyclable and/or hybrid biosourced materials
  - Microalgae-based technical plastics
  - Sustainable biosourced electronics processes
- Produce with sober and optimized processes
  - Additive manufacturing processes for controlling architecture and microstructure, and for achieving functionalities not possible through 2D processes (miniaturization, etc.)
  - Energy-optimized production tools combined with storage/energy valorization elements within a high-temperature context (metal/composite processes)
- Agile, competitive, and human-centric factory management
  - Robotized systems, sensors, and communicating systems for production that are adapted to changing environments
  - Innovative industrial robots, including demonstrators for environment-aware industrial robots
- Digital transformation of production
  - Demonstrator for communicating environments representative of a digitally transformed factory
  - Material-process-product multiphysics digital tools integrating resource variability

2.2.5 Required resources

2.2.5.1 Technical resources

To achieve the research results detailed above, the Nantes scientific community must be equipped with technical resources matching its ambitions.

This firstly entails acquiring equipment for shaping and characterizing materials—and conducting electronic functional tests on them—and for robotics (industrial databases, connected data systems, TIRREX) and the assessment of future communications in complex environments (production lines, centers for storage, sorting, and recycling). Research on sustainable material production also needs a production line for each type of material, thereby enabling optimized production. Site characterization equipment is another need, with a view to developing additive manufacturing processes that control material architecture and microstructure. The scientific community will also need new demonstrators (funding POC to test Factories of the Future or FoF for actual cases of industrial use).

In general, the Nantes scientific community needs enhanced experimental platforms. A structural technical resource for the site will be deployed: a micro-factory / laboratory factory type demonstrator that can accommodate a variety of sober and optimized experimental solutions (energy optimization in particular) for sensor production (especially wireless) and production digitization, in addition to communication networks suitable for the specific environments of the factories of the future.

- This “research factory” could become one of the scientific emblems for the Nantes academic community. One option for this factory is to expand and reinforce the existing MAPE (Materials, Processes, and Energy) platform.

2.2.5.2 Partnerships and collaborations

To successfully complete its research projects, the Nantes scientific community will also need support in developing and submitting projects (for instance equipment calls for proposals), as well as in project monitoring, especially for large-scale collaborative projects.

2.2.5.2.1 Collaboration internal to the Nantes scientific community

The creation and development of collaborative tools such as chairs should be strengthened through longer instruments (5 years) and co-funding, in order to facilitate industrial involvement.

These internal collaborations will also include the development of bridge laboratories in chemistry; new interdisciplinary collaboration between materials, electronics, and computer science for the digital transformation of production; and the creation of new MSC doctoral student networks, or new collaborations with Ecoles Universitaires de Recherche (EUR/Graduate schools) and doctoral schools.

To achieve the desired research results, the community's researchers will need to rely on NExT clusters (Faistos, Mad4AM, Delphi), and could also participate in Priority Research Programs and Equipments or PEPRs (TOTEM, 5G, IA, TASE)

2.2.5.2.2 International collaborations

The research community for this field must develop its international network and collaborations, along the following lines:

- Creation of joint international cotutelle agreements
- Hosting high-level international researchers for long-term stays (6 months to 1 year)
- Developing long-term outbound mobility (beyond 6 months)

2.2.5.3 Human resources

The human resources listed below are divided into two categories, those directly involved in research activities, and those providing support.

- Human resources directly involved in research activities:
  - Funding for theses
  - Expand permanent staff
  - Permanent research engineering positions to enhance attractiveness
  - Creation of "short theses" (1 year, see EUR)
  - Interdisciplinary teams (geographers, data scientists, geologists) shared between multiple laboratories working on the topic
- Support staff
  - Dedicated staff for platforms (training, operation, management, maintenance)
  - Personnel de communication (dédié aux laboratoires et plateformes)
  - Department tasked with the administrative component of European projects

- Governance: establish a Strategic Committee

3 Health of the Future research focus

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3.1 Socioeconomic context and issues

3.1.1 Context: translational research as a signature of the Health research focus

For a number of years, Nantes has built expertise in translational research by applying basic research discoveries from laboratories in clinics, with a view to improving human health and promoting concrete changes in medical practice. This notably led to the creation of multiple research institutes in the early 2000s, such as the Institute of Transplantation Urology-Nephrology (ITUN), the Thorax Institute (for the treatment of cardiovascular, metabolic, and respiratory diseases), the Institute of Digestive Diseases (IMAD), and the securing of two LabEx labels (IRON and IGO), one EquipEx label (ArronaxPlus), and more recently two SIRIC labels (Integrated Cancer Research Site) on the part of ILIAD (Imaging and Longitudinal Investigations to Ameliorate Decision-making). These integrated research structures enable close collaboration between researchers from research units, clinicians and clinical research staff from Clinical Investigation Centers (CIC), and industrial partnerships to develop innovative therapeutic solutions. The ultimate goal of this structuring is to accelerate each step of the process for developing and implementing new medical interventions for improved disease prevention, diagnosis, and treatment, along with patient rehabilitation. As is the case with Nantes-based institutes, the structuring of the NExT I-Site, whose founding members include the primary actors in health research—Nantes Université (NU), Inserm, and the Nantes University Hospital (CHUN)—is a major advantage for conducting translational research of excellence. This is especially true considering that NExT's health research projects can also count on support from partners such as the CNRS, INRAE, the Nantes-Atlantic National College of Veterinary Medicine, Food Science and Engineering (Oniris VetAgroBio), and the Cancer Institute of the West (ICO). The creation of the NExT I-Site will also strengthen existing collaborations between the Health of the Future research focus and structures from the Industry of the Future, such as Centrale Nantes and IMT Atlantique (see the transversal research topic section).

3.1.2 Key issues: inventing and implementing the medicine of the future

Public health issues are varied, and subject to major changes, notably with regard to population aging and the rising prevalence of disabilities. In France, one in five people is over the age of 65 (21.3%), with this proportion increasing continually over the last 30 years. This situation translates into the constantly rising impact of chronic diseases (including cancers) in the healthcare system: by 2030, chronic diseases will be the cause for 70% of total deaths, and 56% of diseases throughout the world. There are also difficulties relating to medical demography, with substantial disparities in terms of access to care, in addition to changing lifestyles (nutrition, sedentariness, exposure to pollutants, urbanization) that promote the development of these chronic diseases (metabolic diseases, inflammatory diseases, cancer, allergies, infertility). At the same time, the continuous development of research has led to considerable innovation in the treatment and care for diseases and disabilities, such as cell and gene therapy, biomaterials, robotics, digital technology, big data processing (including "omics" data), and artificial intelligence.

The primary challenge for our societies is to build the patient-centered medicine of the future, one that to generates fundamental discoveries and technological innovations to create personalized health care pathways for prevention and care, including improved risk characterization, and care for refractory diseases resisting conventional treatment.

Societal acceptance of this medicine of the future should also be explored, notably with respect to precision medicine and personalized risk prevention strategies. An interdisciplinary approach is indispensable to addressing these challenges, with NExT including interactions with the human and social sciences (socioeconomic determinants of health, epistemology, philosophy, ethics, law, transformation and acceptance of medical practices) and the Industry of the Future (mathematics, physics, chemistry, digital health, materials, additive manufacturing, robotics, process engineering). The creation of cross-cutting Health-Industry research topics is specifically aligned with this dynamic.

3.1.3 Overall research structuring for the Health of the Future research focus

Nantes has established topics of excellence in health revolving around internationally recognized teams that will serve as demonstrators for new approaches developed in connection with this roadmap. These medical topics notably include:

- Oncology and hematology
- Nuclear medicine
- Immunology and chronic inflammatory diseases
- Cardiovascular, metabolic, and nutritional diseases
- 4R Medicine (Repair, Replace, Regenerate, Reprogram)
- Biotherapies

Beyond strengthening these topics of excellence, the roadmap's goal is to enhance synergies between research teams as part of an integrated approach to the physiopathological mechanisms shared by the various medical fields (such as immunology and oncology, immunology and metabolism, inflammation and cardiovascular diseases), and technology sharing connected to the development and implementation of 5P medicine (preventive, personalized, predictive, participatory, and proof-based medicine).

This interdisciplinary structuring between research teams from the Health focus also consolidates topics under development, such as: infectiology (with a strong link to immunology), the link between food-health as part of a One Health approach, and fostering the emergence of new topics, such as developmental biology, the study of human movement, and epidemiology.

Most of these topics are part of translational and clinical research conducted by the Nantes CHU, including: i) Inflammation, Transplantation, Infections for immunology, chronic inflammatory diseases (neuro-digestive in particular) and 4R Medicine; ii) Thorax, Neurovascular for cardio-neurovascular and metabolic diseases; iii) Hematology, Cancerology, Nuclear Medicine for oncology, hematology, and nuclear medicine; and iv) Populations, Territories, Vulnerability for emerging topics relating to epidemiology, psychiatry, patient-centered participatory medicine, and health care pathways.

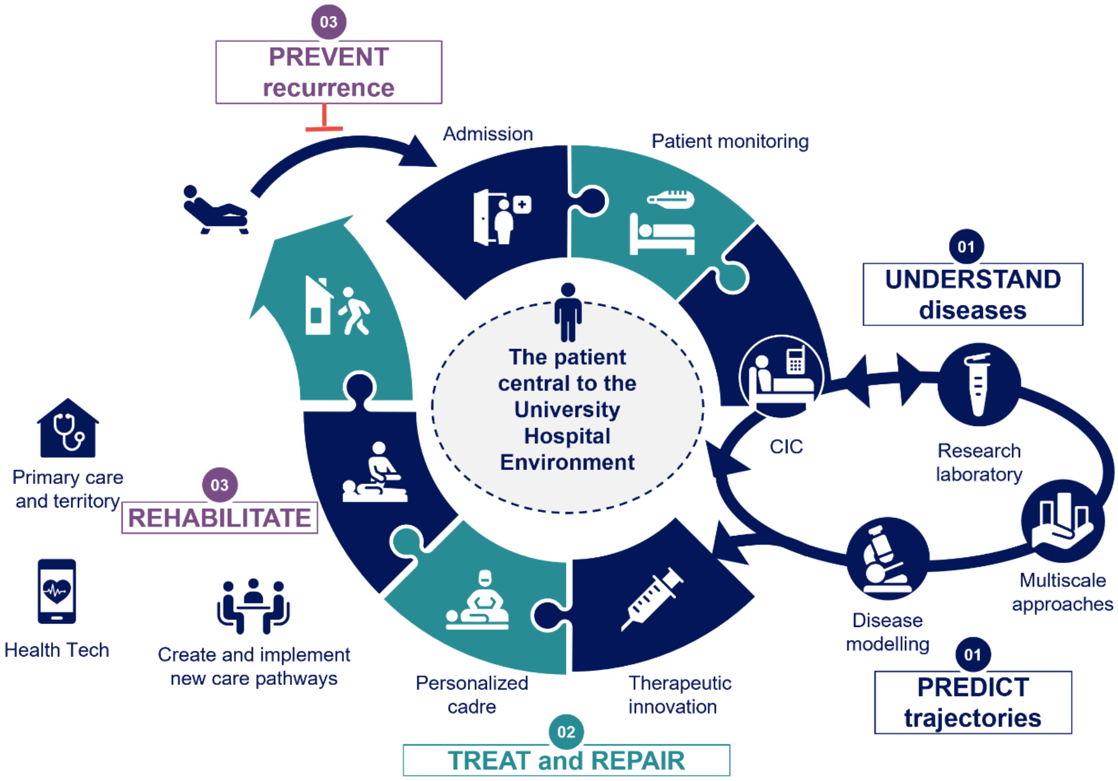
In terms of training and attractiveness, most of these research topics can rely on the graduate programs within the EUR/ Graduate School Health Sciences and Technologies. This is true for graduate programs (CMD I, Immunology and Immuno-Intervention)3, OHNU (Oncology, Hematology and Nuclear Medicine), InnoCARE (Innovation for Cardiovascular, Metabolic and Respiratory diseases), M4R (Repair, Replace, Regenerate, and Reprogram), and MICAS (Microbiota, Intestine, Brain, Food, Health). The goal of these GPs is to provide international training for and through research, in close collaboration with the site's research units.

The implementation and development of this cross-cutting and integrated approach between medical topics will require a consolidated relationship between basic and clinical research (work on samples, access to patient data). The roadmap includes rigorous guidance for partnerships between NExT's founding health institutions (CHUN), its partners (ICO), and Public Scientific and Technical Research Establishment (EPSTs, such as Inserm, CNRS, INRAE), in connection with Nantes Université.

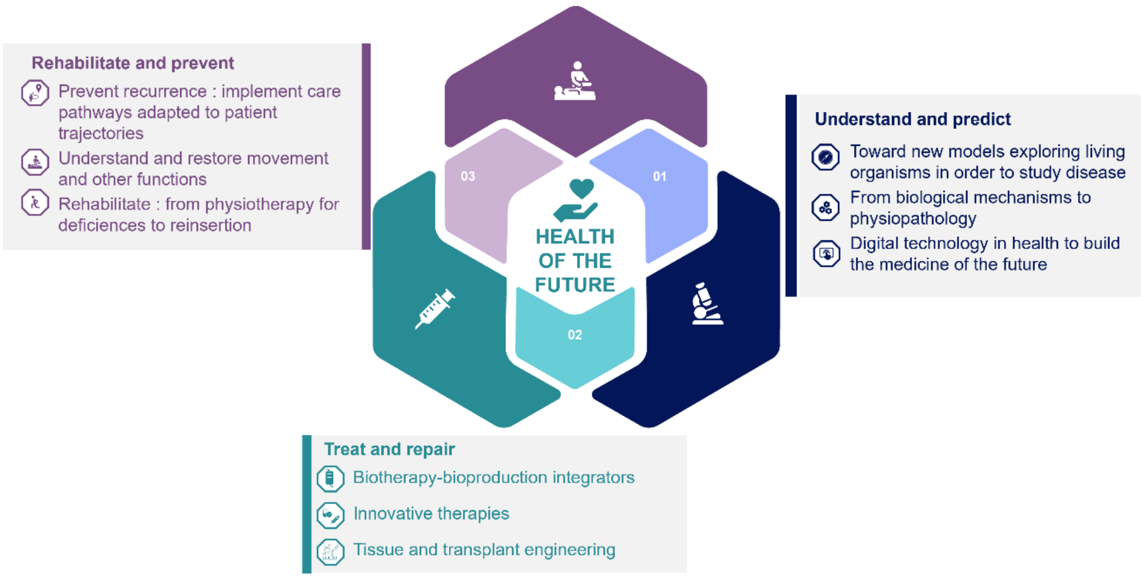
To better address the challenges of the medicine of the future, and in view of structuring the health-related strengths of Nantes, the Health of the Future focus will be organized around 3 synergistic research topics, which have the advantage of applying to all medical pathologies

1. *Understand and predict*
2. *Treat and repair*
3. *Rehabilitate and prevent*

The diagram below summarizes each topic's positioning with respect to patient treatment.



The figure below provides an overview for the various topics:



3.2 Understand and predict

We believe it is strategic for the site to strengthen interdisciplinary basic research in order to identify new physiopathological mechanisms behind diseases, as well as new mechanisms for treatment resistance.

The objective of this research topic is an in-depth understanding of biological mechanisms that can decipher the molecular, cellular, and tissular processes underpinning disease development and treatment response, and hence patient outcomes (notion of disease trajectory). This basic research approach improves disease classification, and paves the way for therapeutic innovation. A firmer grasp of the physiopathology and molecular heterogeneity of diseases, including treatment resistance mechanisms, is a prerequisite for developing precision medicine that can predict individual health trajectories as well as personalize treatment and patient monitoring, with ambitions of 5P Medicine. This predictive approach requires integrating data from various sources, such as electronic health records; massive health data (French National Healthcare Data System or SNDS); data from genomic approaches, transcriptomics, proteomics, metabolomics, and fluxomics; imaging and radiomics data; and other clinical-biological information in order to establish a holistic view of an individual’s health and disease trajectory.

3.2.1 Ambitions of the Nantes I-Site

We aim to promote innovation in basic research by identifying the new physiopathological mechanisms—cell-autonomous or intercellular—behind diseases and their resistance to current treatments.

To this end, and to promote interdisciplinary collaboration, we plan to reinforce methodological developments via researcher clusters and cutting-edge technological platforms. This will especially involve human organoids and other ex vivo models, innovative animal models, bio-imaging techniques, single-cell analysis techniques, spatial biology, and extracellular vesicles (EVs).

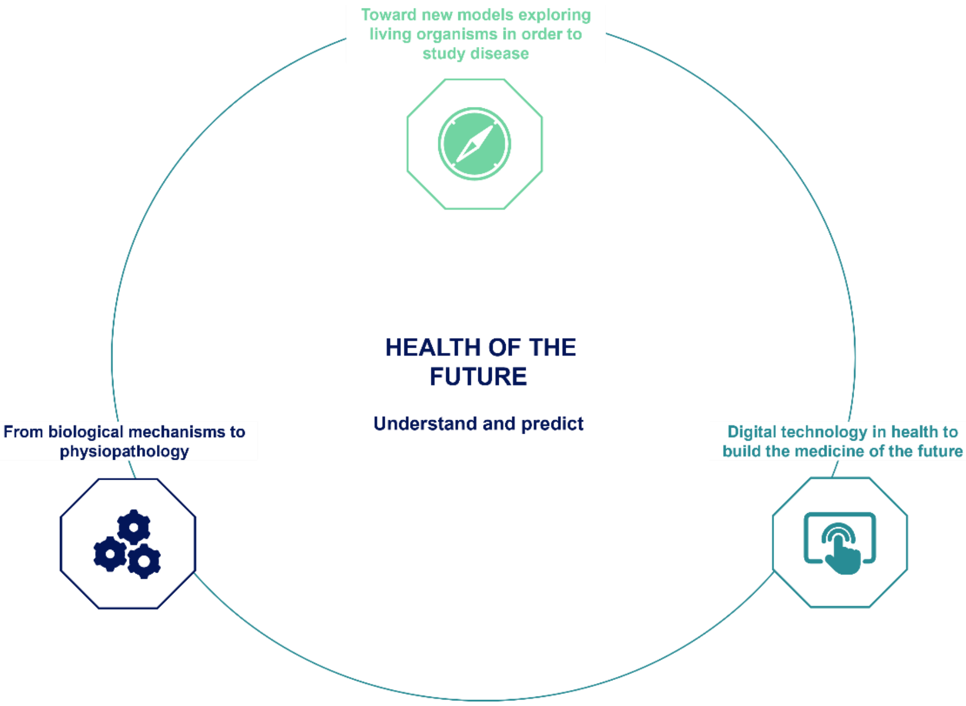
In view of implementing 5P Medicine, our goal is to make Nantes a national leader and international reference in digital health. Beyond collaborations with researchers from the Industry of the Future research focus, this will require: i) developing and sharing hospital health data warehouses from I-Site NExT partners (CHUN and ICO), especially for outpatient monitoring; ii) data quality monitoring and digital infrastructure interoperability (GLICID, GALAC, DACAS); iii) dedicated and sufficient computing resources adapted to the site’s needs; and iv) the ability to use sovereign cloud solutions to comply with the ethical framework for data protection, in concert with patient associations.

To confirm this ambition, models for digital twins will be developed to help predict and prevent the risk of disease relapse, and will be implemented in new care pathways in connection with Prevent research topics. Our 10-year goal is to develop and validate five digital twins that can improve treatment for disease, including cancer, cardio-neurovascular and metabolic diseases, and inflammatory and infectious diseases.

A corollary goal is to make Nantes a reference in training for new jobs in digital health (industry-health interface, dual diploma).

3.2.2 Scope of the Understand and predict research topic: from physiopathological bases to 5P Medicine.

The scope of this topic is represented in the diagram below:



3.2.2.1 From biological mechanisms to physiopathology: Understanding to predict

Identifying new physiopathological mechanisms is a vital step in better understanding diseases, identifying their trajectories, and improved treatment targeting.

This topic brings together researchers and clinicians from all research units in the Nantes scientific community, each contributing their expertise in a specific field to understand the biological mechanisms of living organisms. As emphasized above, the creation of interdisciplinary researcher clusters will help overcome bottlenecks for the following topics:

- Developmental biology: mechanisms of differentiation and cell plasticity during development, modulating developmental trajectories with environmental factors through the DOHAD concept (the Developmental Origins of Health and Disease)
- Genetics and multi-omics approaches, from cells and organs to patients
- Immunology, infectiology, and inflammation
- Metabolism and aging
- Intercellular and interorgan communication, EVs
- Resistance mechanisms: antitumor (survival and spread of abnormal cells during tumor progression, metastases, treatment, and evasion of innate and adaptative immune monitoring), antimicrobial
- Host-pathogen interaction, microbiota
- Radiobiological and immunological mechanisms in response to ionizing radiation, radiolysis

3.2.2.2 New models exploring life to study disease: Modelling to understand and predict

Modelling diseases is key to better accounting for their heterogeneity, and to predicting their trajectories and treatment response. To address this challenge, we plan to develop new study models to overcome certain technological bottlenecks, and to then implement them within platforms, making them available to all site members.

Our 5-10 year goals will concentrate on developing:

- Single cell analysis techniques, notably to study the pathologies associated with somatic alterations (cancer, genetic diseases). These techniques include multi-omics analyses (genetics, epigenetics, transcriptomics, metabolomics, and proteomics), combined with spatial biology techniques (multiplexing: multiscale data analysis, unsupervised molecular characterization) that give access to the spatial information of molecular and cellular events. The interest of this approach is that it applies well to both cancers (tumoral heterogeneity, intra- and intercellular communication) and chronic diseases (cardiovascular, metabolic, inflammatory, and neurodegenerative diseases).
- Human organoids that serve as relevant study models for analyzing pathological organs or tumors (tumoroids) acting like pseudo-organs. Organoids can also test responses to treatment from a 5P Medicine perspective. Such approaches require expanding knowledge and tools in developmental biology (in connection with the iPS cell platform)
- Additive manufacturing, biomanufacturing with organ-on-a-chip, microphysiological systems (microfluidics), and bioprinting for complex tissues
- Innovative animal models that can perform whole-body analysis for physiopathological mechanisms: zebrafish (currently being installed at the site); rodents (mice, rats), including transgene and "humanized" models; large animals (domestic carnivores, primates, pigs, mini pigs) by developing the "animal patient" concept, for which the expertise of the Nantes-Atlantic College of Veterinary Medicine, Food Science and Engineering (ONIRIS) and the Large Animals Laboratory (LGA) is an advantage for the site
- Multimodal imaging to produce innovative radionuclides and to manufacture new radiopharmaceuticals exploring various molecular processes
- Functional high-throughput phenotyping in humans with platforms for multi-omics analyses (genomics, metagenomics, transcriptomics, proteomics, lipidomics, metabolomics, and fluxomics), immunophenotyping, in vivo kinetics (kinetics of lipoproteins, hyperinsulinemic clamps), automated patch clamp.

3.2.2.3 Digital technology in health to build the 5P Medicine of the future

To predict disease trajectory, substantial clinical, biological, imaging and even socioeconomic data must be collected longitudinally. The primary bottleneck in this 5P Medicine approach is the massification of health data, and the ability to analyze it with suitable mathematical and statistical models. We can take advantage of the on-site relationship with LS2N teams to overcome these obstacles.

- **Multimodal approaches**

With respect to multimodal approaches, we can collect the following types of data:

- Phenomic data from patient cohorts monitored at CHUN and ICO: longitudinal studies for certain diseases, biocollections, health data warehouses (Electronic Health Records or EHR, natural language processing or NLP); psychometric data with quality of life questionnaires (Patient-Reported Outcomes or PRO)
- Exploitation of multiscale longitudinal real world data from population-based cohorts (CONSTANCES cohort, UK-BioBank) or the SNDS.
- Imaging data: theranostic and radiomic approaches
- Gathering and exploiting environmental contamination data by pollutants of anthropic origin: exposome

To integrate and interpret this multiscale data, we must: (1) create dedicated digital warehouses; (2) develop data management methods and standards; and (3) propose adequate algorithms, models, and informatics strategies to integrate and interpret data in a holistic and non-biased manner.

- **Data interoperability, security, and confidentiality**

Managing sensitive health data while ensuring interoperability with research data reference sources is vital to predicting patient trajectories based on artificial intelligence (AI). To this end, we will develop: (1) new adapted solutions for accessing and using health data and/or sensitive data for research; (2) systematic annotation and indexing methods for widely distributed data sources; and (3) federated learning approaches for distributed data analysis (multisite and multicloud). Our goal is to create and deploy a FAIR (Findable, Accessible, Interoperable, Reusable) data infrastructure combining clinical and research data sets, ensuring the confidentiality of patient/subject data, and promoting science that is more open and reproducible.

- **Mining databases; Natural language processing (NLP)**

Considerable methodological and technological work remains to be done to extract exploitable/reusable information from electronic health records (EHR). Since 2020, we have developed data extraction methods — notably via NLP approaches for the automated extraction of clinical information from EHR with a view to implementing a complete "data circuit" with Nantes CHU's Data Clinic (C2D). Our goal is to improve decision making by enhancing risk prediction scores with data extracted from EHR.

- **Medical image analysis/Statistical signal and image processing/machine learning**

New automated image and signal processing approaches at different stages of the disease cycle can predict disease trajectory. Our goal is to develop longitudinal and multimodal data analysis through systematic exploitation of medical signals or images.

- **Integration of multiscale data/Modelling biological systems**

Data integration, computational disease modelling, and result prediction require new approaches based on mathematical models — as well as AI— for treating ever-increasing quantities of available data. We will develop (1) graph-based approaches for the statistical integration of heterogeneous data (multi-omics); (2) knowledge databases using graphic representation via ontologies for the semantic integration of multisource data; and (3) mechanistic modelling of biological systems based on multiscale data networks. Our specific goal is to model the patient's trajectory towards a given outcome by capturing the cascade of biological mechanisms involved in intermediary stages. Methodological bridges could be considered with multiscale modelling efforts to analyze the diffusion of pathogenic agents and host responses for an epidemiological representation of systems.

3.2.3 5-10 year targeted research results

3.2.3.1 New biological mechanisms

In-depth understanding of biological mechanisms is an opportunity to discover new therapeutic targets and disease biomarkers, which will be developed within Treat and Predict research topics respectively.

We plan to identify 3 new therapeutic targets and 5 new biomarkers that can be translated to clinics within 10 years.

3.2.3.2 New tools and methods

We aim to develop the following tools over the next 5 years

- Single-cell models
- Organoid models: self-assembled or bioprinted with biomaterial mediums, microfluidics, manufacturing processes (optimization)

- High-throughput genome editing (CRISPR/Cas9) for in vitro (organoids) and in vivo (animal models) functional genomic analyses
- New computers and servers for storing and integrating data for multiscale analysis
- Predictive multiparametric models via machine learning
- New mathematical and statistical approaches for analyzing and predicting disease trajectories
- Managing data sharing in open science to promote 5P Medicine approaches

3.2.3.3 Ruptures technologiques et d'usage

- **Organoids** as functional study models of reference for modelling diseases (alternatives to certain animal models in order to reduce animal experimentation)
- **Animal patients** and veterinary clinical research as a new ethical approach to exploring diseases and therapies in animals relevant for humans
- **Digital twins** as new tools assisting medical practice and 5P Medicine
- **Multimodal and multi-tracer imaging** for predicting therapeutic effectiveness
- **Trajectory medicine** with longitudinal monitoring of patients via conversational agents and/or telehealth tools for real-life data gathering

3.2.4 Moyens nécessaires

3.2.4.1 Moyens techniques

- Investment initiatives for **large-scale facilities**, groundbreaking technological factors such as sequencers for genomics, microscopes for spatial biology, large field PET, PET-MRI for precision imaging, and ultra-high-field and high-resolution MRI
- Acquire **imaging devices dedicated to clinical research** for multimodal patient-based approaches, in order to solve the problem of machine access during care
- Acquire dedicated **clinical exploration platforms** at the CIC within the new university hospital complex (QHU) for phenomic approaches
- Acquire **dedicated spaces for digital technology in health within the QHU,** with the possibility of collaboration between researchers, clinicians, engineers, and data managers, allowing smooth and interoperable access between research and health data

3.2.4.2 Partenariats et collaboration

- Be selected for University hospital research (**RHU)** and University Hospital Institute (IHU) calls for proposals, which are effective in obtaining funding and in attracting industrial actors for the site's flagship topics
- Secure European projects that position teams on the European and international scene
- Bolster participation in national priority research programs and equipment (**PEPR)** (current participation in the Digital Health PEPR)
- Develop **research partnerships with industrial actors,** on the model of the NExT Chair with Siemens for imaging, the NIKON center of excellence for bio-imaging, and the MEDITWIN I-Demo with Dassault Systèmes for digital twins in health

3.2.4.3 Moyens humains, organisation, management

- Develop and perpetuate **HR in bioinformatics and bioanalyses,** with recruitment at the sites and within the teams requiring it

3.3 Treat and repair

The goal of this topic is to develop innovative and personalized therapeutic solutions, notably in biotherapy (immunotherapy, gene and cell therapy, EVs), new radiopharmaceuticals/radiotherapeutics (vectorized internal radiotherapy and theranostic approaches) or host-pathogen interactions (microbiota).

With respect to regenerative medicine, this entails approaches based on tissue engineering that associate cells with synthetic extracellular matrices (in close connection with biotherapy), structural biomaterials (bioprostheses, implants, artificial hearts), as well as additive manufacturing and biomanufacturing technologies.

At the same time, we aim to develop bioproduction processes that can manufacture these biotherapies on a large scale, as well as innovative analytical methods that can characterize these new and complex therapeutic products, in preparation for their transfer to patients and the medical market of the future.

Topic 2 Treat and repair will proceed in complete synergy with Topic 1 Understand and predict, especially with respect to:

- Identifying and assessing new therapeutic targets through a better grasp of physiopathological mechanisms
- Testing these new therapeutics on disease models developed within Topic 1 (organoids and tumoroids in particular)
- Assessing their clinical effectiveness via predictive models developed in Topic 1

Research on Topic 2 Treat and repair could use approaches developed in Topic 3 Rehabilitate and prevent, notably to assess the synergy of therapeutic approaches based on rehabilitating movement and biotherapies, for instance in connection with neuromuscular and osteoarticular diseases that are the subject of developments in laboratories from Topic 2.

The Treat and repair topic will also take advantage of the multidisciplinary approach in Nantes (digital technology, chemistry, robotics, process engineering) and collaboration with the Industry of the Future.

This research topic includes multiple Nantes research units, each with its distinguishing features and expertise in a specific field such as:

- Genetics and multi-omics approaches, from cell and organs to patients
- Gene therapy and viral vectors, gene editing
- Cell therapy
- Innovative immunotherapy and CAR T-cells
- EVs and exosomes
- Biomaterials and tissue engineering
- Organ transplants, bioprostheses
- Biotherapy-microbiota interaction
- Preclinical studies, assessing the effectiveness and immunogenicity of biotherapies developed
- Development of bioprocesses and large-scale production
- Development of analytic methods for characterizing biotherapies, identification of specifications to secure approval for patient use

3.3.1 Ambitions of the Nantes scientific community

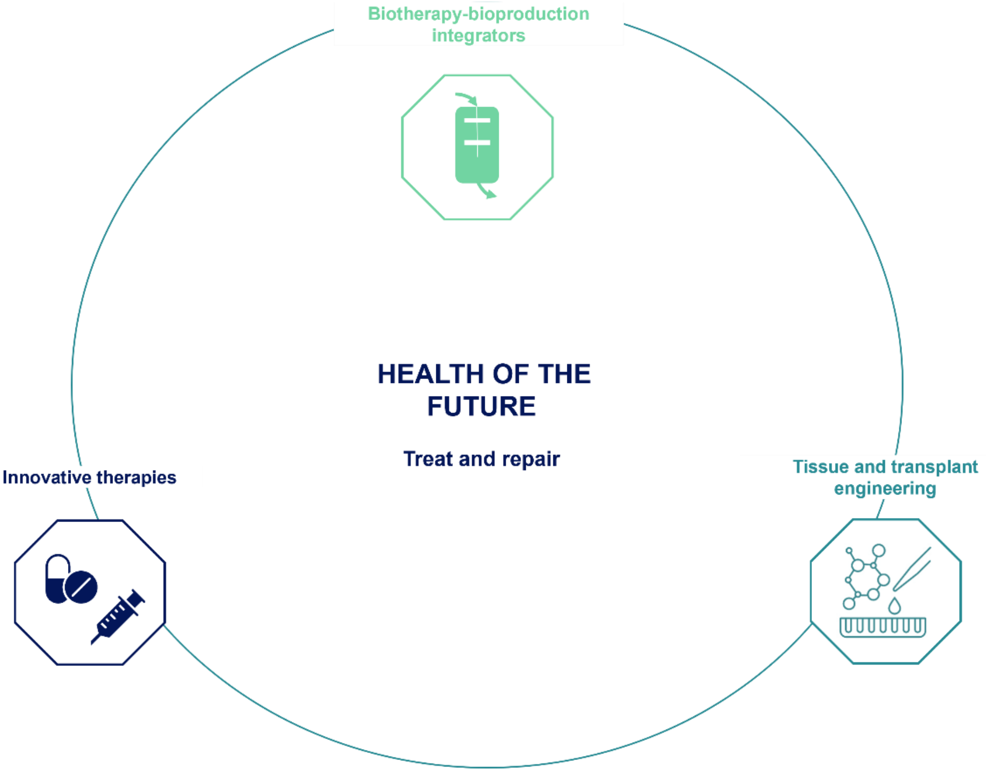
The Nantes scientific community aims to occupy, within 5-10 years, a prominent place on the national and international scene in biotherapies, bioproduction, and 4R Medicine, especially by driving research and development, and implementing innovative medical solutions.

We specifically aim to:

- Become a reference in **immunotherapy** by bringing 5 candidate drugs to market within 10 years
- Acquire **innovative proprietary generic vectors** for gene therapy and gene editing
- Develop a **proprietary production cell line** for viral vectors on a large-scale within 5 years
- Develop large-scale, **highly specific purification processes** for viral vectors within 5-10 years
- Develop new gene therapy/gene editing products for **retinal diseases** within 10 years, up through the first clinical trials
- Develop innovative biotherapy characterization methods
- Develop new **approaches for preventing graft rejection** in transplanted kidneys and lungs, up through the market phase
- Successfully implant a new and **totally artificial heart** within 5-10 years
- Secure new indications for **vectorized internal radiotherapy (VIR),** with new tracers in multiple cancers or malignant hemopathies. This is especially true for alpha therapy, with the goal of conducting the first clinical trials using **astatine**
- **Target microbiomes** with biotic approaches in treatment for infections (pneumonia in particular), antibiotic resistance, chronic diseases, and their response to treatment (effectiveness vs. toxicity)
- Develop new therapeutic approaches based on **EVs**

3.3.2 Scope of the *Treat and repair* research topic

The scope of the topic is represented in the diagram below :



3.3.2.1 Biotherapy and bioproduction integrators

A key issue in rolling out innovative therapies among patients, gene therapy in particular, is their large-scale production. The viral vectors used for gene transfer are actually complex biological therapeutics whose production presents a number of scientific and technological challenges: (i) change of scale and compliance with best practices for pharmaceutical manufacturing; (ii) quality and homogeneity of viral vectors produced, which requires the development of integrative characterization methods; (iii) the cost and environmental impact of bioprocesses; and (iv) the absence of intellectual property in France for production cells in particular.

It is within this context that the TaRGeT Laboratory's Vector Production Centre (CPV) pursues its scientific strategy. It was one of the 6 industrial integrators awarded the great national challenge label in bioproduction for 2019-2022, and recognized once again as one of the 8 national integrators for France 2030's biotherapy acceleration strategy. This integrator pursues an interdisciplinary strategy for developing more effective and less costly bioprocesses, doing so on a large scale (with ties to multiple laboratories from the Industry of the Future focus, such as CEISAM, GEPEA, the GEM entitled Robotization: new manufacturing processes, LS2N). The integrator also works with multiple industrial actors and biotechs from the field to optimize the necessary solutions and equipment (such as Sartorius for upstream processes, Pall for downstream processes), and to prepare the transfer of large-scale processes towards industrial bioproduction structures, such as CDMO (Contract Development Manufacturing Organizations) producing commercial lots for the pharmaceutical market.

3.3.2.2 Innovative therapy

Therapeutic innovation within the Health of the Future focus will encompass various fields, in keeping with the development of complementary approaches and tools offering clinicians the therapeutic options best suited for each patient.

On peut citer notamment :

- **Viral vectors** and "viral-like particles" for ex vivo and in vivo gene therapy and gene editing
- **Immunotherapy**: oncology, hematology, immuno-infections (pneumonia), chronic inflammatory diseases (CID, osteoarticular), prevention, and treatment rejection
- Vectorized internal radiotherapy (VIR) and **theranostic approaches:** new vectors and radiotherapeutics, innovative radionuclides and alpha therapy, astatine-based in particular (SIRIC ILIAD, RHU OPERANDI, LabEx IRON), new indications (leukemia, refractory solid tumors), available facilities: ARRONAX 70MeV, IK18, CIMA, IMRAM, BeaQuant and alpha camera for alpha dosimetry
- **Nanomedicine** with the development of new tools for the local and prolonged release of therapeutic agents
- **Cell therapy** (CAR-T cells, stem cells) and acellular therapy (**EVs**) for homeopathy and cancer; osteoarticular, immuno-inflammatory, neurodegenerative, and metabolic diseases
- Identification of new drug candidates by targeting **protein-protein interactions** via rational approaches based on molecular modelling (PIRAMID regional project led by CEISAM)
- **Photopharmacology** that involves chemically modified high-throughput ligands screening to make them photosensitive. These approaches have led to developments, notably in modulating cardiac electrical activity by implanting light sources in areas of interest
- **Microbiota** manipulation using biotic therapy (prebiotic/probiotic/fecal transplant) in chronic diseases, inflammatory in particular

To conduct translational research of excellence, Topic 2 has the support and expertise of: i) the cell and gene therapy unit (UTCG) for producing clinical lots in compliance with good manufacturing practice (GMP), thereby ensuring their quality (ISO 9001 certified since 2003), security, and traceability. UTCG possesses know-how applied to multiple cell types: lymphocytes, dendritic cells, keratinocytes, fibroblasts, chondrocytes, myoblasts, embryonic cells, iPS and fetal cells, along with the production of CAR vectors. It is one of only two hospital organizations for cell therapy bioproduction authorized to produce experimental advanced therapy medicinal products (ATMP), making the site highly attractive among industrial partners; ii) from the Biotherapy Clinical Investigation Centre (CBT 0503), which brings together researchers, clinicians, and industrial actors around clinical research protocols for biotherapies, and possesses administrative and regulatory authorizations to conduct such clinical trials; and iii) the Boisbonne (Oniris) Centre, which is internationally recognized for Gene and Cell Therapy on animal models for human diseases.

It is also equipped with the ILIAD CLIP2 center led by the GCS IréCAN (Nantes CHU, ICO, Angers CHU), which was awarded the early-phase label by INCa in 2019. CLIP2s are investigative centers specializing in early clinical trials (phase I, phase I-II) for new pharmaceutical drugs. ILIAD CLIP2 is one of 16 CLIP2s awarded the label up through 2024, and is among the 7 with the dual label for its activity in adult and pediatric cancerology, a field especially neglected in early trials.

3.3.2.3 Tissue and transplant engineering

To address the shortage of transplantable organs, tissue engineering has gradually emerged as a clinically relevant alternative. It is situated at the intersection of engineering science and the biological and medical sciences, and requires biomaterials, diverse biological factors, and/or cells to reconstruct unhealthy or damaged tissues or organs. The last decade saw important progress in our knowledge of biological/material interface environments, enabling the development of 3D printing techniques for the "personalized" manufacture of bioartificial organs for implant, or for use as in vitro disease modelling tools to screen therapeutic agents. At the same time as these developments in engineering science, our knowledge in stem cell biology, especially for therapeutic purposes, has led to their use in numerous applications, notably including:

- **Bioprinting** for biomaterials and (bio)artificial organs (organoids), with the development of microfluidics approaches
- **Biomaterials** that are implantable/injectable/organic/inorganic, especially for inflammatory bone diseases
- Improved **biocompatibilit**y with the use of personalized biomaterials, for instance to reconstruct lost facial tissue (cleft lip, palate, and mandible)
- Development of **connected biomedical devices** for data analysis, monitoring, surveillance, and treatment
- New graft conservation methods
- New valvular bioprostheses minimizing the rejection mechanisms that lead to functional degeneration
- Study of fluid-structure interaction (rheology) for the development of new **intravascular stents** and **valvular bioprostheses** (LHEEA collaboration)

3.3.3 5-10 year targeted research results

3.3.3.1 New tools and methods

- **AI** and machine learning as tools for accelerating **new vector design** (choice of ligands, targeted cellular receptors, residues to modify)
- **Biotherapy characterization** using a multiscale approach: genomic via high-throughput sequencing methods, proteomics (secretome), metabolomics
- Contribution of spatial biology in tissue engineering for the analysis of reconstructed or genetically modified organs, via in vivo administration of viral vectors using high-resolution imaging devices
- Material **patterning methods** (lithography, two photons), control of the physicochemical properties of materials

3.3.3.2 Technological and use-related breakthroughs

- Multiscale approaches and **digital twins** i) in 4R Medicine for disease modelling and treatment; and ii) in bioproduction for in-line monitoring and quality control of large-scale bioproduction processes

- Better integrate and control immuno-inflammatory mechanisms to improve **biocompatibility** in regenerative medicine strategies using biomaterials
- Use **RNA-based therapy** for regenerative medicine
- New cellular and acellular bioproduction systems for safer and less costly innovative therapies (DNA synthesis and plasmid manufacturing, plant cells)

3.3.4 Required resources

3.3.4.1 Technical resources

- Develop a bioproduction platform for allogenic cell banks
- Develop a large-scale, semi-roboticized and proprietary AAV bioproduction platform (proprietary production cells and purification columns)
- Expand the bioproduction sector for biological molecules (CPV national integrator, CGTU, and ONIRIS)
- Create a multimodal (multi-omics) platform for the site, coupled with a bioinformatics platform (in connection with the *Understand and predict* topic)
- Create an additive manufacturing platform for the entire Nantes academic scientific community in connection with the Industry of the Future (Centrale Nantes)
- Acquisition of a new dedicated cyclotron for astatine production

3.3.4.2 Partnerships and collaboration

Industrial partnerships are key to this topic, notably for the clinical development of new therapeutic targets and/or bioproduction processes. This also concerns the start-ups developed by Nantes researchers, who continue to collaborate with research teams. It is important to achieving the site's goal of continuing, strengthening, and developing these partnerships.

Examples include:

- For **gene therapy**: Sanofi (WiDGeT project funded by the biotherapy acceleration strategy), Pfizer (for Duchenne myopathy), Pfizer UCB and BioMérieux (Duchenne myopathy and the new ERDERA European network to create a European rare disease alliance), Sartorius and PALL for bioproduction, Clean cells (CDMO) and the Coave Therapeutics start-up (formerly HORAMA) for genetic eye diseases
- For **biomaterials** and **tissue engineering** with HTL Biotechnology (polymer production), Biomatlante (synthetic bone grafts), and GOLIVER Therapeutics (regenerative liver medicine)
- For **VIR** and **theranostics**: Novartis, Telix Pharmaceuticals, Bayer, Curium, Atonco
- For the **artificial heart** project: Procope Medicals
- For microbiome manipulation and **biotic approaches**: Biofortis

Joining teams working on this topic within national and European scientific networks helps reinforce research dynamics, notably via:

- Inclusion within 2 national PEPRs connected to biotherapies and bioproduction: Biotherapies and Bioproduction of Innovative Therapies (BBTI); Food Systems, Microbiome, and Health (SAMS); and the Antibiotic Resistance PEPR with PROMISE networks and Antibiodeal. The RHU OPERANDI for VIR also bears mentioning
- There is also active involvement in European networks via the HAP-2 and HOMI-LUNG projects in severe pneumonia and the respiratory microbiome; Posture, Maxibone, Orthounion, Respine, Ipspine, NanoImplant in the field of 4R Medicine for bone tissue; and UPGRADE and ERDERA in gene therapy and gene editing
- 4R Medicine has been structured at Nantes since 2016 via RFI Bioregate

3.3.4.3 *Human resources, organization, management*

- Create a **biomedical engineering university department** (see foreign universities) for training and research in engineering applied to health (biotherapy, bioproduction, materials, additive manufacturing)
- Integrate Master's track pathways (biotherapies and drugs for innovative therapy, health product quality control, health bioproduction) with bioproduction resources for clinical use
- Integrate platforms within national (IBISA) and European infrastructure (French Ministry of Higher Education, Research, and Innovation or MESRI roadmap)
- Strengthen human resources in bioinformatics and multiscale data processing (in connection with Topic 1 *Understand and predict*)
- Reinforce human resources in bioprocesses engineering

3.4 Rehabilitate and prevent

The goal of this research topic, which continues to emerge on the site, is to develop a global patient-centered approach enabling the transition from health care pathway to life course. This approach includes the full spectrum of treatment, from acute phases (such as intensive care) to the chronic phase (return home, return to activities and work, disability management). The goal of patient rehabilitation integrates care and research, with each treatment period promoting the emergence of new knowledge, innovative care strategies, and sectors.

As part of a 5P Medicine approach, we also develop preventive medicine by seeking to prevent relapses for chronic diseases (secondary and tertiary prevention) via improved identification of risk trajectories (in connection with Topic 1: Understand and predict). We later plan to leverage this structural foundation to broaden primary prevention approaches, notably in keeping with primary care actors, as well as pediatrics in connection with DOHAD (first 1,000 days).

One of the greatest challenges for 5P Medicine is translating scientific discoveries into health care pathways. This is partly due to the range of actors in the field, which makes it difficult to coordinate care around the patient. We would like to use this roadmap to unite the actors needed to implement innovative care pathways, namely: (1) primary care physicians and actors already grouped together within the federated center for primary care; (2) dedicated paramedical staff involved in outpatient care pathways; (3) the Medical and Economic Assessment Unit of Nantes CHU; (4) public administrative establishments in charge of health, such as the Regional Health Agency (ARS) for the Pays de La Loire region, and the Primary Health Insurance Fund (CPAM); (5) research laboratories such as SPHERE (Joint Research Unit/UMR 1246), specializing in cluster-randomized trials, complex interventions, and psychometry; (6) strategic partnerships, notably with the School of Public Health (EHESP), which specializes in public health policy; and (7) patient associations in connection with participatory medicine.

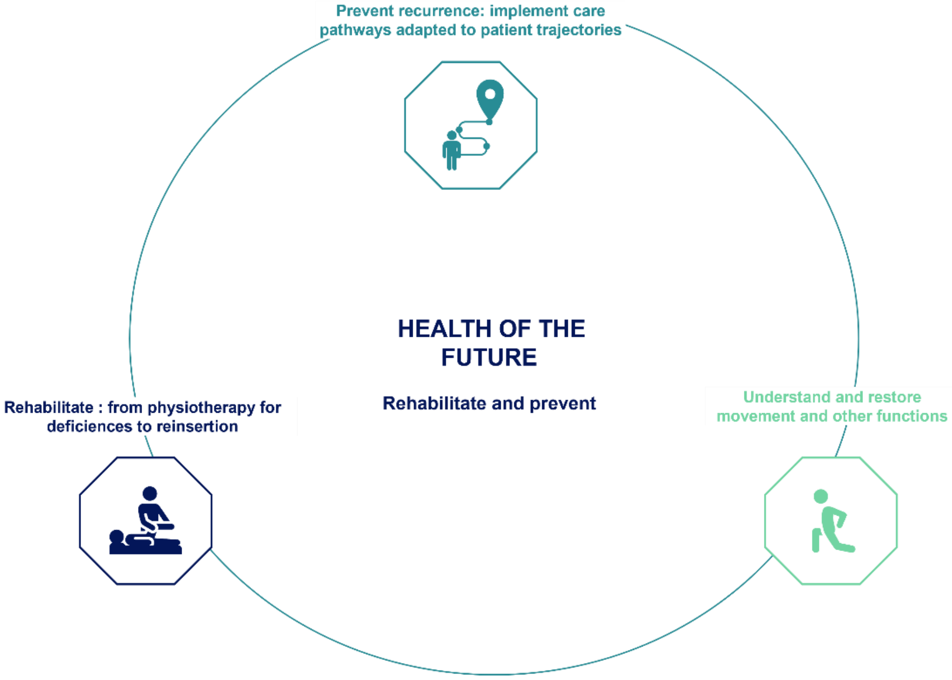
3.4.1 Ambitions of the Nantes scientific community

- **Become a leading global center for studying human movement** from the standpoint of research, care, and training (through the development of a new Graduate program) for jobs involving physiotherapy-rehabilitation, and adapted physical activity in health (in connection with STAPS). We aim to reinforce this integrated research topic, in order to promote the rehabilitation of disabilities, treatment for chronic diseases, age-related autonomy loss, and prevention of musculoskeletal disorders.
- As part of the *Predict* topic, develop a **site of excellence for digital health and 5P Medicine for the prevention of chronic diseases**, notably by relying on: (1) translational research of excellence to identify new risk markers: biomarkers and imaging, and building digital twins; (2) collaboration with the site's laboratories focusing on digital technology and the human and social sciences (HSS) to address the methodological and societal challenges of digital health; (3) Graduate dual degree programs to train for new careers in digital health; (4) actors promoting health and primary prevention (Health Hall); and (5) established industrial partnerships.

- **Structure the site's strengths in epidemiology and public health** (in interaction with clinical disciplines connected to Nantes CHU's Focus 4: *Populations, Territories, Vulnerabilities*, especially by developing implementation sciences).
- **Develop research in primary care**: collect and analyze patient data in primary care physician offices and multiprofessional health clinics via P4DP, the national platform for outpatient care **data**, in order to regionally implement pilot care pathways based on disease trajectories
- **Promote participatory research:** as part of 5P Medicine, offer new digital tools for research participants (conversational agents, portable sensors), involve patients and their families in implementing new treatments and in co-constructing ambitious research projects
- **Make the Pays de La Loire region (~ 4M people) an experimentation site for new health care pathways** that could be extended nationally during a second phase if proven effective from a medico-economic standpoint.
- Make Nantes an **industrial hub in HealthTech** by fostering the development and experimentation of digital solutions for patient monitoring and improved health care pathways
- Become a leading national center in **implementation science** to accelerate acceptance of these sector-related and technological innovations on the part of health professionals, patients, and new healthcare actors occupying a growing role in chronic diseases, such as caregivers

3.4.2 Scope of the *Rehabilitate and prevent* research topic

This research topic is structured around the three major subjects of movement, rehabilitation, and prevention.



3.4.2.1 Preventing relapses: implementing care pathways suited to patient trajectories

In a logical consequence of the Understand and predict topic, and within a 5P Medicine perspective, the development of personalized prevention strategies is a solution for improving the treatment of chronic diseases, thereby reducing their cost for society. This challenge is all the more urgent given that the continuous decrease of health professionals in the region over the next 10 years complicates the implementation of efficient health care pathways. We believe this challenge can be addressed only through effective implementation of new patient-centered health care pathways, with support from digital tools in health. The ultimate goal is to select the patients with the highest risk in order to ensure the profitable and targeted use of therapeutic innovations developed in the Treat and repair research topic.

For outpatient care, we will identify individual screening priorities to promote early diagnoses and interventions in critical care, cancerology, inflammatory diseases (such as CIBD), and cardio-neurovascular diseases.

To maximize strategy effectiveness, the perspective of users and health professionals should be integrated (in terms of resources and organization of care). The conditions in which these new health care pathways are applied, along with acceptance of digital tools, should be tested in real situations in primary care research networks. Patient perception of these new health care pathways will be analyzed from an ethical perspective. The role of implementation sciences will therefore be decisive for the success of this ambitious program.

A medico-economic assessment of the efficiency of each new health care pathway will be conducted in connection with public health administration establishments (ARS, French National Conservatory of Arts and Crafts or CNAM, Caisse Primaire d'Assurance Maladie or CPAM) and the medico-economic unit of Nantes CHU, with a view to validating the potential national roll-out of these pathways.

The Nantes scientific community can rely on a number of demonstrators in multiple pathologies of interest, such as:

- Cardio-neurovascular diseases, with a project to improve patient treatment after an acute event (heart attack, stroke, obliterative arteriopathy) using a digital tool for monitoring cardiovascular risk factors, as part of an innovative health care pathway seeking to reduce the recurrence of cardio-neurovascular events (tertiary prevention).
- Preventing the rupture of intracranial aneurysms (IA) by developing integrated digital tools for detecting IA, predicting rupture risk, and offering guidance and psychological support as part of the eCAN RHU.
- Preventing the recurrence of cancer (multiple myeloma and breast cancer in particular) thanks to theranostics approaches developed as part of the ILIAD SIRIC.
- Preventing gambling addiction by identifying at-risk "gamer" profiles using AI approaches based on data gathered via online platforms.

3.4.2.2 Understand and restore movement

The multidisciplinary study of movement (biomechanics, neurophysiology, muscle physiology, psychology) helps better understand how humans generate movement via the muscular system, as well as its command and control. It also helps analyze how it adapts to various constraints (environmental, physical, psychological), with a view to creating effective restoration and readaptation protocols for motor, nervous, and vegetative functions. A firmer grasp of the variability of patient response is crucial to eventually predicting them, thereby individualizing readaptation protocols. The study and understanding of patients' needs is consequently central to this approach. This research is conducted using the conceptual framework of the international classification for functioning and disability, applied to diseases of the nervous and locomotor systems, psychological disorders, and aging. It is also necessary to better understand interactions between physical, cognitive, and psychobehavioral physiotherapy/rehabilitation, and innovative pharmaceutics-based therapeutic interventions (link to Topic 2 Treat and repair), in order to determine if they can potentiate the effects.

In this context, the Performance, Health, Ergonomics (PEPSE) platform can provide its scientific and technical expertise in conducting mono- and multidisciplinary projects relating to human motricity in the life sciences, engineering science, and/or human sciences.

Exoskeletal and robotic approaches (neural interface, robotics) are being developed for the future, notably with teams from the Industry of the Future focus (see section on transversal research topics). This raises questions regarding augmented humans (ethics, philosophy, legislation, communication with the general public), which will be studied with HSS teams

3.4.2.3 Rehabilitate: from physiotherapy for disorders to reinsertion

The key issue of the research subject is to develop a patient-centered global approach that enables the transition from health care pathway to life course. A major issue is reinforcing the treatment spectrum from the acute phase (for example intensive care) to late phases (disability, physical medicine and rehabilitation, human movement studies). The implementation of this spectrum is based on Nantes excellence, and notably includes sectors historically specializing in neurotrauma (CoSCINus cohort in physical medicine and rehabilitation, IBIS cohort for intensive care). Lesions of the central nervous system affect not only movement and function, but all organs and systems as well. This offers a view of multisystem impairments, and represents fertile ground for applying translational research, including 3 Health of the Future topics, as well as collaborations with Industry of the Future.

In the field of neurological disorders, adapting to the consequences—whether they be neuromotor, cognitive, vegetative, functional or identity-related—requires research in all of these fields, in addition to: patient experience; adjustment processes in the face of disability (coping); adapted physical activities, ergonomics and the development of human machine interface (HMI); and 4R Medicine strategies relating to the Processes and manufacturing research topic under the Industry of the Future focus. Links with HSS aspects (socioeconomics of health, epistemology, philosophy, ethics, design) are also decisive for crafting responses to disability.

Support for changes and their evolution over time is a central subject, notably to better integrate caregivers, promote well-being, account for the multi-dimensionality of quality of life, and promote adaptation to new behaviors facilitating rehabilitation. This multidimensional approach to quality of life and disability could incorporate explorations such as implementing new sectors; nutritional approaches (microbiota, probiotics, post-biotics); functional physiotherapy and rehabilitation programs with a view to personalized adjustment and long-term prevention; and innovative approaches to affective and cognitive remediation (virtual and augmented reality, psychological and psychiatric rehabilitation). Psychiatric clinical teams have developed a research focus on recovery, or how to support patients suffering from chronic diseases to regain satisfactory quality of life and a life “full of meaning,” notably by helping them recognize their limits all while reinforcing their skills. The assessment of this recovery proceeds via qualitative studies in collaboration with researchers from the SPHERE team, who are experts in analyzing and interpreting data from self-reported questionnaires, such as PRO.

The return to work and resumption of previous activities—with the socializing nature they entail—impact personal health, quality of life, financial security, and their human environment. Multidisciplinary research on professional and social rehabilitation must be conducted, and should involve physiotherapy-rehabilitation clinicians, psychologists, and sociologists. Return-to-work after the occurrence and treatment of cancer is also explored in connection with the ILIAD SIRIC. The ReWork-QoL program includes teams of clinicians and researchers from the Angers and Nantes CHUs, the ICO, the Ester team (UMR Inserm 1085 – IRSET, Institute for Research in Health, Environment, and Work), the Loire Atlantique-Vendée cancer register, and the SPHERE Laboratory (UMR Inserm 1246). It is based on the multidisciplinary expertise of Loire-based actors in epidemiology, public health, psychology, occupational medicine, and ergonomics, all of which involve the coordination and exploitation of health data from multiple cohorts (Constances and ELCCA) and the Loire-Atlantique Vendée cancer register. The ReWork-QoL program provides new epidemiological information on the importance of social and professional context during the initial treatment of the cancer, as well as post-therapy quality of life and professional reintegration (return-to-work, remaining employed).

3.4.3 5-10 year targeted research results

3.4.3.1 New tools and methods

In close collaboration with the Understand and predict research topic, various methodological focus areas are under development, and should be operational for patient assessment within 5-10 years :

- Test conditions for real-life application of new health care pathways in primary care research networks
- Validate digital tele-monitoring tools for pilot pathologies
- Integrate socioeconomic determinants in analyses of patient trajectories and adherence to prevention strategies, including the impact of gender, social inequality, and health inequality
- Integrate the perspective of users and health professionals, as well as regional particularities (organization of health), in order to maximize the effectiveness of prevention strategies
- Combine imaging and movement analysis methods to develop new biomarkers
- Markerless movement analysis that can be used beyond movement analysis platforms
- Decode motoneuron activity using high-density electromyography to assess healthy and pathological motor coordination
- Neuromodulation, cerebral and medullar transcutaneous stimulation
- Develop non-invasive neural interfaces

3.4.3.2 Technological and use-related breakthroughs

- Develop clinical trials including innovative physiotherapy and rehabilitation interventions implemented in Nantes
- Develop patient engagement models in rehabilitation (predictive factors for engagement and therapeutic response)
- Research in ethics: consequences of predictive possibilities in decisions relating to care, prevention, and health research
- Develop implementation science. Develop new health care pathways centered on various actors (patients and caregivers in particular)
- Large-scale roboticized movement physical therapy on patient cohorts with neuromotor disability (MPR CHU technical center and the new Île de Nantes CHU technical center)
- Intra-hospital: develop instrumental measurements for movement with real-time feasibility in clinical hospital situations to understand the neurophysiological and biomechanical phenomena associated with pathological movement
- Develop large-scale actimetric measures: real-life movement (“beyond the lab”) using data from inertial measurement units, markerless movement analysis
- Integrate conversational agents in prevention strategies
- Develop interventional trials to reduce the risk of chronic disease by completing the treatment spectrum from early to chronic phases

3.4.4 Required resources

3.4.4.1 Technical resources

- Construction, within 5 years, of a new building (State-region Planning Contract or CPER funding) to house the MIP Laboratory and its technical center, with a view to studying movement.

  Station-S project for hosting, innovation support measures integrated within university innovation hub (PUI)

- offerings (such as Manufacturing innovation), and immersion of HealthTech start-ups and enterprises in the future QHU in close proximity to care.

3.4.4.2 Partnerships and collaborations

New collaborations with the laboratories involved in the Treat and repair research topic must be developed to study interactions between gene or cell therapy with physical activity or physiotherapy (laboratories such as Regenerative Medicine and Skeleton or RMeS, Translational Research in Gene Therapy or TaRGeT, Physiology of Nutritional Adaptations or PhAn, and The Enteric Nervous System in Gut and Brain Disorders or TENS). This is also the case for artificial intelligence/data management (data clinics, Nantes Laboratory of Digital Science or LS2N, Jean Leray Mathematical Institute or LMJL), psychological support, and patient involvement in physiotherapy/rehabilitation protocols (Pays de la Loire Psychology Laboratory or LPPL, Nantes Sociology Center or CENS), law (Law and Social Change Laboratory or DCS), and ethics. The following industrial collaborations bear mentioning:

- **Digital health enterprises** such as Dassault Systèmes (iDEMO MEDITWIN project with the Thorax Institute) for cardiovascular prevention approaches via digital twins in health
- **Pharmaceutical laboratories** for developing new health care pathways such as Novartis: partner for a new care pathway to improve treatment for patients after a cardio-neurovascular event
- **Industrial actors in imaging** (Siemens) for theranostic approaches
- **La Française des jeux** to identify individuals at risk of gambling addiction

It is important to strengthen the partnership with agri-business enterprises (baby food), and to define primary prevention strategies in keeping with DOHAD and the One-Health approach.

Finally, it is important to establish a partnership with Mutuelles Santé in connection with 5P Medicine and the personalized redeployment of resources according to patient trajectories.

3.4.4.3 Human resources, organization, management

- Recruit a senior profile experienced in epidemiology and implementation science
- Develop a research team in primary care in connection with the general medicine department
- Develop training for advanced practice nurses (APN) in prevention
- Promote training programs focusing on 5P Medicine in connection with the School of Advanced Studies in Public Health (EHSP) (health professionals, health institution directors)
- Implement specific training for the prevention of chronic diseases

3.5 Conclusion: Towards a new generation of translational research institutes for the Health of the Future

The scientific approach developed in the Health of the Future roadmap is integrated—spanning the patient to the laboratory—as well as transdisciplinary. We believe that specific and thematic support for team research projects falls under dedicated national (ANR or DGOS) or European funding, and that NExT's mission is to generate leverage via structural actions and funding involving multiple sites (members and partners).

To address the issues in this roadmap, and to structure the site and promote international visibility for its key topics, we propose developing a new generation of translational research institutes, doing so based on the site's success and evolution over the last 15 years. These institutes could be extended beyond health to other research teams in the Industry of the Future and HSS. This should be done in consultation with: the various regional actors involved in the topics (researchers, clinicians); the supervisory institutions of the entities in question (UMR, CIC, clinical departments, etc.); and outside assessment by an international Scientific Advisory Board for the project's relevance and feasibility. It is important for the project's feasibility and efficiency that these institutes enjoy operational and reactive governance between the relevant supervisory institutions (UMR, clinical departments), given that they naturally fall within the scope of NExT. The goal is to raise visibility on the national and international scene, to concentrate human resources and expertise, and to promote attractiveness (recruitment of international researchers).

This new generation of institutes—characterized by a critical mass of sufficient clinicians and researchers, a full spectrum spanning basic to clinical research, a substantial track record of publications and major projects, and Graduate programs—could include:

- The Thorax Institute for cardio-neurovascular and metabolic pathologies
- An Onco-hematology-Nuclear Medicine institute
- An Immunology-Infectiology institute

Other topics could be designated as "promising" and pursued further, such as:

- A topic relating to the 4Rs
- A topic pertaining to human movement and the locomotor system
- A food, diet, health topic

These institutes could rely on LabEx type structures to become leading European centers in key fields such as immunotherapy, multimodal imaging and radiotracers, bio-production for innovative therapy, genomic medicine, and digital technology in health applied to chronic diseases.

The development of health research will proceed via support for research infrastructure (including non-service infrastructure) in terms of equipment (co-funding) and HR (sharing key staff resources), in an effort to promote implementation, sharing, tool optimization, and groundbreaking methods.

To strengthen our local partnership with teams from the Industry of the Future research focus, we support the creation and coordination of thematic clusters; co-supervised theses and dual degrees; and the immersion of researchers from the Industry of the Future focus within the teams and CIC of the Health of the Future focus.

Other drivers for the roadmap's roll-out include:

- Support for creating, via dedicated calls for proposals, **new teams and/or topics** to maintain site dynamics
- Strengthening **training for and through research** via EURs and graduate programs for the site's priority scientific topics
- **Internationalization** via **strategic partnerships** with other universities, notably with 4-year international joint theses (2 years in each country), or the further internationalization of university hospitals
- The development of **strategic academic-industrial partnerships** through chairs and other measures, as well as support for mobility and international academic collaboration
- Increased research time for university hospital clinicians, and incentives for researchers to conduct translational research via funding for interface **contracts recognized by all partners, and offering protected research time**
- Simplification on the site level, especially between UMR and CHU supervisory authorities, on process alignment, Human Biological Samples (EBH), data transfers, and intellectual property sharing

The roadmap's successful implementation and monitoring will require engaged governance by NExT and its founders, ideally with management dialogue between different site actors, culminating with an objectives and resources contract re-assessed annually.

4 Cross-cutting topics

4.1 Context and issues

4.1.1 Context

Research in health and industry are the two pillars of Nantes Université and the NExT I-Site. The two scientific communities have successfully cultivated their excellence, gradually earning national and international recognition. Sections 2 and 3 of this document develop these respective roadmaps. They are ambitious, and their implementation will have a very positive impact on the broader Nantes scientific community.

Major societal challenges have driven the scientific explorations at the intersection of these two pillars. These transversal topics can emerge from an issue in one of the communities for which the other community already possesses a body of knowledge, methodological tools, or technical resources whose redevelopment would not be advisable, but whose adaptation to specific problematics would make sense. It could also entail shared and concurrent issues. This situation is one of "symmetry," with the same scientific issues and bottlenecks simultaneously arising within both communities, which decide to join forces and work in concert to address them. These issues are an opportunity for interdisciplinary and decompartmentalized dialogue, in addition to innovative methods for conducting research and dispensing higher education. The association of multiple HSS disciplines should also be developed, with the ones appearing the most relevant mentioned below in accordance with the subject.

> The "common thread" of this roadmap for transversal health-industry topics is an integrated biomedical engineering approach in the broad sense

4.1.2 Issues

- Aiming for frugality in all activities, which could assume the following forms in particular:
  - In the industrial field, sobriety in the use of energy and natural or recycled resources
  - With respect to health, transition towards de-prescription, precision preventive medicine that optimizes health offerings by targeting the right patient, personalization of medicine, and optimization of the health system and processes (such as low-dose imaging). Some of these evolutions could fruitfully mobilize researchers in management, through the changes they generate with respect to medical staff and care pathways.
- Improve the environmental and societal footprint
  - Use biomaterials and replace petrochemical products
  - Intensify (bio)production processes for pharmaceutical drugs (reduction of inputs)
  - Recycling
  - Reduce the impact of disease (return to work), patient's role in society
  - Ultimate fate and ecosystem impact (biodegradation, toxicity, specific toxicity, endocrine disruptor effects)

- Personalize and specialize
  - Find and produce the molecule
  - Pursue a multicriteria vision (theranostics approach)
  - Optimize complex systems (systems biology, multiparametric approaches including biology, demographics, imaging, multi-task)
  - Develop personalized medicine using cell therapy, gene therapy, and drug-design on new biological targets
- Develop innovative technological solutions at the chemistry-biology and physical-biology interfaces, such as:
  - High-sensitivity, multimodal imaging (large field of view PET), dual-tracer and dynamic approach
  - Tracers for monitoring (bio)materials, cells, injected therapies (radioactive tracers, radiotherapeutics, MRI contrast agent)
  - New (bio)production technologies
  - Theranostics solutions based on nano-vectors enabling restricted action in the treatment or imaging area
  - New tools in chemobiology and bioconjugation

4.2 Ambitions of the Nantes scientific community

In light of its advantages (see assessment), the Nantes scientific community formulated clear and realistic ambitions;

- Become a leader in biomedical engineering (BME)
  - Establish a BME Department, notably including engineering schools, the university, and the CHU
  - Position the site nationally for training in biomedical engineering
- Solidify transverse dynamics
  - Develop the sharing of high-level expertise
  - Develop joint inter/multidisciplinary approaches and collaborations
  - Develop interdisciplinary culture and integrate interdisciplinary approaches in training
  - Increase the number of co-publications
  - Develop shared and enduring frameworks for interaction (clusters, Labex, Master's)
- Consolidate the recognition of excellence in identified topics via PEPR, SIRIC, RHU, Labex, European projects
  - Digital technology and health
  - Biotherapy and bioproduction
  - Food-Health
- Perpetuate and reinforce the attractiveness of the Nantes scientific community
  - Broaden the use of infrastructures / platforms of excellence in health and industry, reinforce their interconnection, and include them within national and European roadmaps
  - Transpose the "laboratory-factory" concept, an emblem of research in *Innovative and decarbonized manufacturing* (Industry research focus): conduct real-life research in the laboratory, integrate engineers in the hospital. Conversely, healthcare staff also has its place in the laboratory-factory (chairs in health engineering)

4.3 Scope of transversal Health – Industry topics

Horizontal transversal topics represent intersections between the I-Site's two focuses of excellence, Health and Industry, that could lead to interdisciplinary approaches generating synergies between the site's strengths.

In keeping with these complementary dynamics, the following transversal topics were identified as opportunities for interdisciplinary collaboration, to which the strengths of the Nantes Industry and Health communities could contribute effectively:

- Data, artificial intelligence, digital tools Production
- and production process
- Mechanical engineering
- Innovative models and therapy
- Non-digital data gathering, cartography, articulation with HSS

4.3.1 Data, artificial intelligence, and digital tools

These tools are present in many uses, as well as in support of numerous scientific advances.

Bioinformatics

- Creation of neuro-symbolic approaches (combining logical and statistical learning) to construct personalized dynamic pathology models
- Concept of "digital twins" (models configuring in real time for improved reasoning capacity), multiscale and multimodal modelling
- Creation of analysis tools for dynamic properties (complex attractors, dynamic properties expressing observed or desired behaviors) on logical models / pathology hybrids / patients

Artificial intelligence (AI)

- AI for multiscale analysis in anatomical pathology
- Image, signal, text, genomics
  - Deep image / text
  - Automated processing of writing
  - Bayesian networks
  - Knowledge graphs
  - Meta-heuristics
  - ...
- Longitudinal trajectory modelling (applicable to both patient pathways and coastlines)

Multi-scale approaches, digital twin

For research in industry, this entails integrating multiphysics models, from the molecule to the complete system. In parallel, multiscale approaches in health extend from the subcellular level to the entire body. Patient data from multiple sources: clinic, imaging, multi-omics…

The patient's digital twin raises certain issues that are shared with the digital twin of an industrial system or facility. Examples include a complete organ such as the heart and vascular system, or industrial turbine pumps and a hydraulic network.

The digital twin of complex machines such as accelerators is an interesting tool for training staff in associated risks, for preparing maintenance in keeping with the ALARA principle (as low as reasonably achievable), and for anticipating dismantling-related aspects.

Digital technology

- Questions pertaining to distributed data (patient data vs. industrial data), analyzing data without seeing it.
- Anonymization, pseudonymization, synthetic data.

These issues relating to data manipulation and use, especially in health, can also involve HSS in connection with ethical issues (philosophy), acceptability (sociology), and law.

Molecular modelling

Molecular modelling can simulate the behavior of a molecular system over time, consequently offering numerous applications in both communities. One example is the use of molecular modelling for drug discovery in silico, as well as for drug design. This approach can be used for CO2 storage, or for molecular interactions during the implementation of biomolecule purification processes.

Through its predictions of stability and mechanisms of recognition, quantum chemistry enables the rational design of chelating agents for radionuclides of interest in nuclear medicine and the nuclear fuel cycle. The data generated can feed into AI models.

Imaging and sensors

Digital tools and artificial intelligence are driven by data from sensors and imaging systems. Advances in this field are developing in the respective fields of the industry and health communities, often in partnership with imaging system manufacturers. Special research focuses for different types of imaging also bear mentioning:

- Ultrasound (non-destructive control in industry, non-invasive tests in health)
- Subcellular microscopy
- Multimodal and dynamic PET-CT, PET-MRI, and high-sensitivity large field of view PET imaging, low statistical imaging, X-ray, tomography
- Cold imagery: development of cryo-microscopic methods
- Signal analysis: EEG (neuro rehabilitation), ECG (cardio), and EMG (muscular rehabilitation)
- 3D, spherical, plenoptic, event, hyperspectral, 4D-Flow cameras

4.3.2 Production and production process

Within this topic, the transversal research subjects that often rely on industrial engineering tools include:

Production & bioproduction:

- Development of production tools: integrated bioproduction chains ranging from culture (cell culture, microalgae) to the extraction and purification of the targeted therapeutic compound, flow cell transfection processes, bioreactors (fermenters, photobioreactors). Advances in roboticization and additive manufacturing applied to industry have substantial "transversal" potential in this respect
- Multi-omics approaches and metabolic network modelling: omics data acquisition, biological metabolism modelling, advanced bioreactor management for optimized production of target metabolites
- Optimization of industrial tools: optimized (bio)synthesis processes, radiopharmaceutical agent manufacturing, overall reduction of environmental footprint while maintaining product functionality

- Constraint-based production in a context of frugality connected to both regulatory and cost constraints (notably for radiopharmaceuticals). As for any industrial process, the production of pharmaceutical drugs must reduce its environmental footprint (reduction of inputs and quantity of solvents, miniaturization of production technologies, improvement of (bio)synthesis yields)

Flow chemistry

Continuous production and intensification systems: reduced solvent use, improved synthesis yields, molecule innovation (precursor), new molecules, creation of molecule banks.

Process modelling

As with an industrial process, the patient's health care pathway in a hospital—and the hospital's functioning in general—should be analyzed and modelled to develop tools for improvement. Tools, digital ones in particular, can model and ultimately improve the "care production chain."

Management science could ultimately be mobilized to make this ambition a reality.

Circular economy

Emerging issues involving hospitals: reuse of tracers (patient urine becomes a source for product reuse in research). Expansion to all products used routinely in clinics, whose remainders can be used in research laboratories.

4.3.3 Mechanical engineering

The substantial body of knowledge and technology developed for decades by researchers in industry will enable major breakthroughs in health research, which will in turn enrich industrial approaches.

Robotics & cobotics[7] :

- Reduction of arduous tasks, ergonomics, assistance for industrial and care operators, prevention and curing of musculoskeletal disorders
- Fundamental movement, exoskeletal aids to rehabilitation; humanoids (LS2N)
- Neuronal interface for communication between patient and robot
- Robotics and computer-assisted surgery
- New sensors / detectors to support medical evolutions (Flash therapy)
- Implementation of robotics and industrial computing solutions in bioprocesses (biotherapy production; in-line quality control)

For this aspect, demography can provide predictive elements on the evolution of the working-age population. Psychology, sociology, and even anthropology could be mobilized for questions of acceptability and job transformation. The changes that these technological innovations will bring about for the organization of work could be studied from a management perspective.

Biomechanics:

- Mathematical and digital modelling of soft and hard tissue to predict mechanical response (anisotropy, viscoelasticity), growth kinetics, and interactions (especially in pediatrics, but also in regenerative medicine). Multiphysics modelling, biological systems modelling
- Crash: installations for tests, predictive digital tools
- Analysis and modelling of human movement, sensor development, material aging (degeneration of bioprostheses)
- Modelling material resistance (non-destructive)

[7] Cobotics: human-robot collaboration.

Fluid dynamics, rheology, and fluid-structure interactions. The key here is to understand and model fluid flows in the human body (especially blood) and their interaction with structures/tissues, as well as to develop or intensify new (bio)production processes for pharmaceutical compounds:

- Usage: cardiology (stents, prosthetic valves), aortic and intracranial aneurysms (flow modelling, constraint analysis)
- Creation of new industrial processes using microfluidics (improved reactivity and yields) for the frugal production of radiopharmaceuticals or medicine
- All-structure interaction (blood vessels, heart valves), behavior of biomaterials (hydrogels, viscoelastic components) and prostheses (valves).

4.3.4 Innovative models and therapy

In vitro models

- **Bioprinting**: industry has already implemented operational solutions for additive manufacturing, whose adaptation to bioprinting for health would be of great interest.
- **Organoids**: developing organoid models is an important focus area for health research. The skills of industrial actors in microfluidic chip development or the integration of (bio)sensors would be beneficial.
- **Microfluidics**: a field with multiple health uses. In addition to being central to developing organoid models, microfluidics also apply in (i) simulating vascularization, pressure, throughput, etc.; (ii) optimizing and individualizing radiomarkers, cell micro-irradiation; and (iii) creating intensified (bio)production systems (ex: design of cell flow transfection systems).

Innovative therapy

Expertise in physics and chemistry is key to pursuing innovative radionuclide therapy (nanosensors, nanoparticles, implantable materials, biotherapy), as well as manufacturing new therapeutic products in keeping with theranostics concept (radiopharmaceuticals, theranostics agents, photopharmacology, optogenetics), or from living beings (bioproduction, adeno-associated virus or AAV vectors).

Simulation, predictive and prognostic models: applied mathematics and physics are essential to developing all approaches yielding interpretable signals; improving these signals; and accounting for a series of signals to build a predictive or prognostic model. Patient modelling subsequently drives gene therapy approaches.

Marine bioresources: application of marine bioresources for nutrition and/or health

- Molecules and materials of therapeutic interest: screening of biological activities for marine bioresource extracts
- Development of new biotechnological platforms for bioproduction and vectorization (ex: microalgae, including GMOs)
- Development and health claims of nutritive supplements from marine bioresources in food-health and “supportive-care”
- New genetic models for use in health
- Characterization of microbial communities

Issues relating to law and acceptability (sociology) could be formulated for these subjects (especially biotechnology), and explored by the HSS teams concerned. Questions pertaining to the claims of nutritive supplements could involve management science (marketing)

4.3.5 Non-digital data gathering, cartography, articulation with HSS

The "interactions with territorial systems" research subject (see the Ocean engineering roadmap) involves the human and social sciences in the form of methodologies for surveying and gathering non-digital data, along with geography. The university hospital research community anticipates that some of these methodological approaches could be transposed to its specific issues (patient experience), mobilizing skills in sociology and psychology.

Conduct research on frugality, environmental footprint, and personalization, with a view to guiding health and industry researchers in their thinking for the treatment and ultimate fate of hospital wastewater, as well as its environmental impact.

The study and modelling of humans in interaction with advanced technical systems includes cognitive ergonomics and human-machine interaction. Whether the interaction relates to data visualization, process monitoring, co-action, decision making assistance, or assessment of the operator's state, the research issues are quite often transversal to fields in both health (diagnosis or prognosis assistance, assistance performing technical gestures) and industry (mixed reality, system supervision, cobotics). Psychology teams could also be mobilized.

4.4 5-10 year targeted research results

- Upstream knowledge
- New tools and methods
- Technological and use-related breakthroughs

4.4.1 Upstream knowledge

- Bioinformatics
  - Formalization and validation (theoretical) for the correction of targeted neuro-symbolic algorithms, and their implementation in software
  - Initial validation of these algorithms for previously identified target pathologies, in direct collaboration with experts (doctors, biologists)
  - Construction of models representing phenotype based on genotype (towards personalized medicine)
  - Synthesis tools for all data under a new formal abstraction (i.e. topological analysis) in order to compare patient cohorts. Integration of imaging, genetic, or metagenomic data
- Data, artificial intelligence, and digital tools
  - Analysis of activity, user modelling and human-machine cooperation
  - Deep learning applied to the analysis of images, texts, scenes. New rigorously and mathematically defined concepts and tools for multiscale configured modelling can conveniently—if well developed (generic, multi-domain, extensible, easily composable)—build evolving models from bodies of data and field-specific properties (health or industry)
  - New principles, algorithms, and reasoning systems are expected for such models to account not only for the variety of scale, data, and correlation between model parameters, but also for the quasi-natural evolution of models or systems (living or industrial)
  - For example, the evolution or artificial aging of an organism, ecosystem, or industrial system, with a view to studying potential defects and taking compensatory measures for prevention, diagnosis, and maintenance

- Digital tools for prediction and/or diagnosis, with explainability, multiscale visualization, continuous reconfiguration, and self-adaptation. In the coming years, our knowledge will yield models that are "alive," or that are at least equipped with the means to be alive, unlike current models, whose evolution remains a challenge. To this end, it is important to combine modelling, simulation, and AI tools
- Imaging
  - Production of radionuclides, chemistry and radiochemistry, radiopharmacy and nuclear medicine
  - Signal reconstruction and processing

- Mechanical engineering
  - Modelling biological materials (anisotropy, poromechanics, soft materials)
- Innovative models and therapies
  - Development of in vitro avatars (organoids)

4.4.2 New tools and methods

- Data, artificial intelligence, and digital tools
  - New multiscale algorithms (aneurysm, cancer, myeloma)
  - Systemization of the twinning process for models and systems, with the help of hybrid channels for interaction, signal exchange, data. The construction of digital twins should change scale in the years to come, shifting from empirical construction to a generative process based on data, morphology, the intrinsic properties of systems, inevitable interactions with their environment, sources of uncertainty, and difficulty in analysis. Example: engineering to simulate a digital patient under general anesthesia
  - Advanced multimodality (text, context, image, others) in frugal models, learning with little data thanks to artificial/selected data or models guided by knowledge (Physics-informed Neural Networks - PINN, Bayesian networks, knowledge graphs)
  - Use of realistic artificial data (avatar) in images, texts, and data
  - Development of systematic generation processes for digital models or digital twins, and simulation of these models. Harvesting data that was collected or generated in systems will continually impact models and their behavior. The maintenance and evolution of very large, complex, and interconnected models would indeed represent a herculean effort, requiring new methods to ensure the contextual self-adaptation of models, as well as assistance in their deconstruction/reconstruction
  - Interchangeable "kits" for the construction and methodological analysis of models to help overcome difficulties. A model or analysis component (algorithm, reasoning systems) should conveniently be composed/interchanged at different level or moments in a system, with a pre-established guarantee of coherence and functioning. This could conceivably involve a graft (biological, environmental, industrial), such as the "immediate" replacement of a component in both the system and the digital twin: transplant of organisms, organs, animal and plant species, physical components
  - New molecular modelling tools (characterization of radionuclides bonds)
  - Development of experimental and computer methods for identifying new therapeutic molecules via contributions from new technologies (AI and deep learning)
  - Imaging and sensors
    - New automatons and cyclotrons, especially to produce astatine, high-sensitivity large field of view molecular imaging system
    - Approaching a view of tumors/tissues down to the level of the single cell (cameras, AI, data processing)

- Mechanical engineering
  - Image computing (mechanical), real-time simulation
- Innovative models and therapies
  - In-depth multiscale analysis

4.4.3 Technological and use-related breakthroughs

- Data, artificial intelligence, and digital tools

Here we imagine “recycling” methods for models and their development process. In order for modelling methods for living beings and industry to be as operational as possible, they must ideally self-adapt to their objects of study, which are intrinsically dynamic. We aim, in the next few years, to equip modelling methods with the means to “recycle” them, in reaction to the lifecycles of the objects they helped build.

This unusual retroaction is truly groundbreaking compared to the usual approach, which at best includes referencing between models and their environments of production.

  - Consideration of humans (patient in health or actor in industry) in AI algorithms (learning or use); use of virtual/augmented reality. This study of human behavior could mobilize disciplines such as psychology and anthropology
  - Creation of logical approaches generating dynamic pathology models that are personalized and adaptative (accounting for change over time to predict or adapt to observed changes). Contribution to the field of inductive logic programming and its frontiers, with respect to both theory and application
  - Creation of algorithmic approaches for (i) analyzing dynamic properties (complex attractors, dynamic properties expressing observed or desired behavior) on logical/hybrid models (in the sense that they will mix/connect discrete and continuous evolution) of pathologies/patients; and (ii) eventually control the dynamic behavior observed to push the real system toward a desirable behavior, or to avoid any undesirable one (typically: the increase of tumor cells)
  - New patient prediction algorithms integrating different data
  - Creation of specific in silico patient models in short time spans
  - New molecular modelling methods to optimize the rational identification of molecules (AI and deep learning)
  - Imaging and sensors
    - New radiopharmaceuticals and radiotherapeutics (notably alpha)
    - New imaging approaches (dual-tracer, low statistic, dynamic)
    - Low-statistic detectors in nuclear medicine
    - New automated biomarker extraction tools, new intelligent sensors (deported, connected, and autonomous)
- Production and production process
  - Cell production for therapeutic use: increasing scale
  - Chimeric receptor cells or new locally-produced immunotherapy approaches (development of a production chain)
  - Large-scale production systems (turbulence system)
  - High-capacity reactors for viral production
- Mechanical engineering
  - Image-based biomechanic models (patient-specific)

- Innovative models and therapies
  - Neural avatars (organ-on-a-chip)
  - In vitro bone marrow
  - Solutions for repairing the neuromusculoskeletal system
  - New predictive in vitro and in vivo test to chart health care pathways
  - Gene vectorization towards the central nervous system (neurodegenerative diseases)
  - Development of new protein-protein interaction inhibitors via an integrated approach combining deep learning, molecular dynamics, and drug design on new biological targets of interest
- Gathering non-digital data, cartography, articulation with HSS
  - New algorithms for estimating the user's state and for improving human-machine dialogue

4.5 Required resources

4.5.1 Technical resources

The technical resources at the disposal of the health and industry communities will be mobilized for this research.

4.5.2 Partnerships and collaboration

We distinguish between two major families of collaboration and partnership: those internal to the Nantes scientific community, and those external to it with actors beyond Nantes. While some collaboration methods have been tested, others propose innovative approaches that are adapted to the issues identified.

4.5.2.1 Collaboration internal to the Nantes scientific community

Collaborations, which are integral to these transversal subjects, are a prerequisite. While significant today, they can be expanded further, see the Human resources, organization, management section below.

Beyond collaboration between disciplines from science, technical engineering, and the life sciences, the association of HSS in certain subjects would be relevant. As part of a scientific roadmap encompassing innovation, it would make sense—along the same lines as the Innovation and transfer WP present in certain European projects—to mobilize a pool of experts in management science (economic model), sociology (acceptability), and law, notably for research with a high TRL.

4.5.2.2 Collaborations external to the Nantes scientific community

Collaborations with industrial actors have been put in place, and will be pursued and developed further, notably through new industrial chairs in various topics, including imaging.

Training at the intersection between research and industry will be strengthened, notably in bioprocesses, bioengineering, and digital health.

4.5.3 Human resources, organization, management

To meet these ambitions and implement the present roadmap, a genuine **organizational breakthrough** is needed. Project-based collaborations of varying length between researchers and research units are necessary, but are not enough on their own to raise ambitions and scale for transversal health-industry research topics.

New forms of cross-fertilization and enduring collaboration must therefore be created. Securing funding and resources for long projects (5-7 years) is a first step, but it is important to go even further, for instance by founding **enduring joint "centers"** that allow researchers in industry and health to work together over time. The association of HSS disciplines mentioned above will also be planned in these centers, in order to develop research that is truly interdisciplinary, and to avoid compartmentalized functioning.

Multiple corollaries must be explored to support this change of organizational paradigm, such as the issue of **graduate programs**, which remain structured according to traditional disciplinary nomenclature.

5 Appendix

5.1 Academic disciplines involved

The following scientific disciplines[8] will be involved in each topic:

5.1.1 Ocean engineering

- 02 - Public law
- 05 - Economic sciences
- 23 - Physical, human, economic, and regional geography
- 26 - Applied mathematics and applications of mathematics
- 27 - Computer science
- 28 - Dense environments and materials
- 32 - Organic, mineral, and industrial chemistry
- 37 - Fluid envelopes of the Earth system and other planets
- 60 - Mechanics, mechanical engineering, civil engineering
- 61 - Computer and automation engineering, signal processing
- 62 - Energy, process engineering
- 63 - Electrical engineering, electronics, photonics and systems
- 64 - Biochemistry and molecular biology
- 66 - Physiology

5.1.2 Innovative and decarbonized manufacturing

- 05 - Management sciences
- 16 - Psychology and ergonomics
- 18 - Architecture
- 24 - Spatial planning, urban planning
- 26 - Applied mathematics and applications of mathematics
- 27 - Computer science
- 28 - Dense environments and materials
- 32 - Organic, mineral, and industrial chemistry
- 33 - Materials chemistry
- 60 - Mechanics, mechanical engineering, civil engineering
- 61 - Computer and automation engineering, signal processing
- 62 - Energy science, process engineering
- 63 - Electrical engineering, electronics, photonics and systems

[8] Scientific disciplines based on the reference from the National Council of Universities

5.1.3 Health

- 16 - Psychology and ergonomics
- 26 - Applied mathematics and applications of mathematics
- 27 - Computer science
- 43 - Biophysics and nuclear medicine, imaging
- 44 - Biochemistry, cellular and molecular biology, physiology and nutrition
- 45 - Microbiology, transmissible diseases and hygiene
- 46 - Public health, environment and society
- 47 - Oncology, genetics, hematology, immunology
- 51 - Cardiorespiratory and vascular pathology.
- 54 - Development of pediatric diseases, gynecology-obstetrics, endocrinology, and reproduction
- 64 - Biochemistry and molecular biology
- 65 - Cell biology
- 66 - Physiology
- 67 - Biology of organisms and populations
- 74 - Sciences and techniques of physical and sporting activities
- 86 - Drug science
- 87 - Biological and pharmaceutical sciences

5.1.4 Transversal topics

- 16 - Psychology and ergonomics
- 26 - Applied mathematics and applications of mathematics
- 27 - Computer science
- 28 - Dense environments and materials
- 29 - Elementary components
- 32 - Organic, mineral, and industrial chemistry
- 33 - Materials chemistry
- 43 - Biophysics and nuclear medicine, imaging
- 60 - Mechanics, mechanical engineering, civil engineering
- 61 - Computer and automation engineering, signal processing
- 62 - Energy science, process engineering
- 63 - Electrical engineering, electronics, photonics and systems
- 64 - Biochemistry and molecular biology
- 65 - Cell biology
- 66 - Physiology
- 67 - Biology of organisms and populations
- 74 - Sciences and techniques of physical and sporting activities
- 86 - Drug science
- 87 - Biological and pharmaceutical sciences

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