INCLIVA | VLC
Biomedical Research Institute

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COOPERATIVE SCIENTIFIC PROJECT

2026–2030

This document has been approved by the INCLIVA Governing Board by minutes dated 12 December 2025 and ratified by its Board of Trustees by minutes dated 19 December 2025.

This approval was granted within the framework of the powers conferred upon each of these bodies, and in accordance with the procedures established in the organisation's internal regulations.

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1. GENERAL INTRODUCTION

The INCLIVA Biomedical Research Institute, established through an agreement between the Hospital Clínico Universitario de Valencia (Regional Ministry of Health), the University of Valencia and the Carlos Simón Foundation, is a national and international leader in translational research, driving the transfer of findings from biomedical research into clinical practice. Within the framework of the new 2025–2029 strategic cycle, a **cross-cutting Cooperative Scientific Project (CSP)** is proposed to foster **genuine and effective integration between basic and clinical research groups**, promoting innovation, sustainable collaboration and scientific excellence.

Firstly, and as a fundamental step in the development of this Cooperative Scientific Project, INCLIVA's Scientific Management has reviewed its four core scientific areas (Oncology, Cardiovascular, Reproductive Medicine, and Metabolism and Organ Damage) and has proposed the following areas, with the aim of responding appropriately to the reality of the institute's current critical mass of researchers and in line with current European, national and regional priorities:

1. **Cancer Unit** (spun off from the Oncology Unit to provide a comprehensive approach to cancer)
2. **Cardiovascular Area** (unchanged from the previous Research Project)
3. **Women's Health Area** (derived from the Reproductive Medicine Area, to broaden its scope and reflect current realities in the field)
4. **Rare Diseases Area** (derived from the breakdown of the Metabolism and Organ Damage Area to provide a distinct identity for the groups working in the area and to enable positioning studies with other institutions)
5. **Ageing, Inflammation and Chronic Diseases** (stems from the breakdown of the Metabolism and Organ Damage Area to provide an identity for the groups working in the field and to enable positioning studies with other institutions)

Based on these five fundamental scientific areas, INCLIVA's new Cooperative Scientific Project for the period 2026–2030 is grounded in the European Union's R&D&I strategic frameworks (Horizon Europe), the Spanish Strategy for Science, Technology and Innovation (EECTI) and the Valencian Community's Smart Specialisation Strategy (2021–2027):

This project is structured around **five priority cross-cutting programmes**:

1. Digital Transformation, Artificial Intelligence and Applications in Healthcare Processes (Coordinators: José Luís Górriz and Inma Saurí)
2. Personalised Medicine and Advanced Therapies (Co-coordinators: Valentina Gambardela and María José Terol)
3. Immune-mediated Diseases and Therapies (Co-coordinators: María Jesús Sanz and Mari Carmen Gómez Cabrera)
4. Mental Health and Neuroscience (Coordinators: Juan Nácher and Carmina Montoliu)
5. Infectious Diseases (Coordinators: Anaïs Corma and José Luis Piñana)

Each of these programmes has been designed as a space for scientific and clinical cooperation with common objectives, annual interaction indicators, structured coordination mechanisms and a strong focus on health innovation, the integration of the gender perspective and the use of shared technological platforms.

The R&D&I promotion activities to be carried out, organised by INCLIVA's management units, will at all times focus on enhancing interactions between the groups within these five cross-cutting programmes, with the common aim of increasing research and innovation in the lines of work listed in the document and achieving the interconnection objectives set out therein, whilst also enhancing the activities of the *core facilities* at IIS INCLIVA and the University of Valencia.

2. CROSS-CUTTING PROGRAMME "DIGITAL TRANSFORMATION, ARTIFICIAL INTELLIGENCE AND APPLICATIONS IN HEALTHCARE PROCESSES"

2.1 Coordination

- José Luis Górriz Teruel, principal investigator of the Consolidated Renal Disease Group
- Inmaculada Saurí Ferrer, Coordinator of the INCLIVA Data Science Platform

2.2 Objectives and rationale

2.2.1 Objectives

- To drive innovation in translational research through the integration of artificial intelligence (AI) tools in the analysis of biomedical and clinical data.
- To design and implement predictive models to anticipate clinical outcomes, facilitate patient stratification, optimise therapeutic interventions and improve the quality of healthcare.
- To promote the digitalisation of clinical and research processes with the aim of improving efficiency, quality of care and the sustainability of the healthcare system.
- To facilitate integration and interoperability between clinical and research areas, promoting the secondary use of data to generate new knowledge and improve decision-making.
- Ensure that, within our organisation, the use of clinical and research data complies with ethical and regulatory standards in digital environments, safeguarding patients' rights and the integrity of research.
- To promote inter-institutional collaboration through the integration of projects with universities.
- Development of a Data Space to facilitate interaction with other regional, national and European centres, with the aim of fostering joint participation in collaborative development initiatives.

2.2.2 Scientific justification

The programme aligns with the pillars of the **Spanish Strategy for Science, Technology and Innovation (EECTI 2021–2027)** and the ISCIII calls for proposals that prioritise AI projects applied to healthcare and clinical digitalisation. At the regional level, the **S3 strategy** for smart specialisation identifies biomedicine, digital health and enabling technologies as key drivers for R&D&I in healthcare. Furthermore, this programme is also in line with the **Valencian Regional Government's Digital Health Strategy**, the primary aim of which is to modernise the Valencian public healthcare system through digital technologies, improve patient care and make the system more efficient, resilient and prepared for demographic challenges.

This programme is aligned with the priorities of **the Horizon Europe programme (Health Cluster and Digital Cluster),** which promotes the use of data, AI and digital technologies to transform healthcare systems. n programmes such as EU4Health support and fund initiatives such as the secondary use of data in research and

innovation in the health sector, particularly through the European Health Data Space (EHDS), the **Innovative Health Initiative (IHI)** – the successor to IMI – and the recent European **Artificial Intelligence (AI) in Science** initiative.

The use of AI and digital models will enable INCLIVA to position itself at the forefront of data-driven medicine, facilitating the development of tools for early diagnosis, personalised medicine and organisational efficiency.

2.2.3 Strategic rationale

The implementation of Digital Transformation (DT) and Artificial Intelligence (AI) at the INCLIVA Biomedical Research Institute represents a strategic opportunity to optimise processes, accelerate scientific discoveries and strengthen the social impact of health research. These technologies not only modernise the institute's technological infrastructure, but also profoundly transform the way in which medical and scientific data is generated, analysed and utilised. Among the benefits are:

- AI's ability to process large volumes of clinical, genomic and experimental data, identifying complex patterns that are invisible to traditional human analysis. This enables a better understanding of diseases, earlier detection of risks and more effective development of personalised treatments, which are fundamental in the context of precision medicine.
- The use of predictive algorithms can significantly improve clinical and scientific decision-making, increasing the effectiveness of clinical trials and optimising resources allocated to research.
- The automation of repetitive tasks using digital tools allows scientific and administrative staff to focus their efforts on activities with higher added value, thereby improving institutional productivity.
- Strengthening collaboration between teams, institutions and international networks. System interoperability and remote access to digital platforms enable real-time information sharing, promoting collaboration between researchers and accelerating scientific progress.
- The use of digital solutions improves document management, project planning and regulatory compliance, increasing operational efficiency and the ability to respond to scientific or health challenges.
- Digitalisation enables more robust protection of sensitive data through advanced cybersecurity and access control systems. This guarantees the confidentiality of medical information and the integrity of experimental data, which are fundamental to maintaining the trust of patients, collaborators and funding bodies.
- The institute's social impact is enhanced, reinforcing its role as a key player in improving health at both local and global levels.

Taken together, the integration of Digital Transformation and Artificial Intelligence not only modernises the scientific infrastructure but also redefines INCLIVA's potential as a benchmark for innovation, scientific quality and social commitment in the field of health.

The platform is supported by the International Projects Unit (head: Ana Ferrer), which consolidates the development of projects from the various calls for proposals under European programmes, not only those directly related to health but also those in related fields. Under the Horizon Europe programme, projects have been launched in the fields of internal medicine and cardio-renal medicine (WELLBASED, Hypermarker,

JACARDI, PRIME-CKD, BIOTOOL-CHF), oncology (AIDA, REBECCA, MyPath, ONCODIR, MELIORA, JA PCM), reproductive medicine (eProbes), large joint actions (JACARDI, JADE, JARED), innovation in digital health (InnDIH, INNDIH AI Connect), as well as major national initiatives in the field of AI and data science (IntegraCloud, IntegraDPS). Furthermore, funding has been secured to boost fundraising from European programmes and attract international talent thanks to the EuroBoost project funded by the AEI. The platform is also supported by the National Projects Unit (head: Raquel Llorens), which is responsible for the comprehensive management of regional and national research and innovation projects carried out at IIS INCLIVA. Furthermore, it handles applications for competitive grants, both public and private, as well as managing national and regional grants. The Unit compiles calls for proposals published by various organisations and bodies and distributes them to research staff. And the Innovation Support Unit, which is responsible for the promotion and management of innovation and knowledge transfer. Its functions include identifying ideas and conducting feasibility analyses, developing innovation projects, and protecting and exploiting results.

2.3 INCLIVA research groups involved

- Cardiometabolic and Renal Risk Study Group (Principal Investigators: Dr Josép Redón i Mas and Raquel Cortés, Cardiovascular Unit). They have carried out the BigMedilytics project (H2020 - ICT-15 – 780495), focusing on the application of Big Data to optimise care processes for cardiovascular diseases, and the BODYPASS (ICT-14 - 779780), which breaks down barriers between the healthcare sector and the consumer sector by eliminating existing data silos, and the BigData@Heart project (IMI-IMI2-2015-07-07), which integrates large volumes of clinical data and biomarkers to improve the management of heart failure. Furthermore, this group coordinates the IntegraCloud project, INCLIVA's technological platform for the integration of structured and unstructured healthcare information, and IntegraDPS, which integrates new health departments such as Gandía and Sagunto into the INCLIVA platform. Furthermore, Drs Raquel Cortés and María José Forner have led national projects to identify molecular biomarkers in liquid biopsies associated with early diagnosis, lupus activity and organ damage using omics techniques, the data from which can be integrated with clinical data to develop more effective diagnostic and predictive algorithms. Within this same group, Dr María José Forner and Dr Fernando Martínez are involved in R&D&I projects focusing on cardiovascular diseases and autoimmune diseases. In the former, they have developed the EU-MASCARA FP7 FP7-HEALTH-2011 project, which aimed to examine genetic, proteomic and metabolomic markers alongside markers of inflammation, oxidative stress and cardiac remodelling to study their incremental diagnostic and predictive value over existing diagnostic and predictive algorithms. Finally, the HYPERMARKER project (HORIZON-HLTH-2022-TOOL-11) is currently under development, with the aim of harnessing the potential of pharmacometabolomics to provide 'smart' prescribing of antihypertensive therapy.
- Renal Disease Group (Principal Investigator: José Luis Górriz). This group has developed a system for the early detection of chronic kidney disease based on a clinical decision support algorithm, which automatically detects patients with chronic kidney disease in at-risk populations , assesses disease progression, and refers them to Primary Care or Nephrology as necessary. The algorithm created allows this project to be implemented immediately in other hospitals and health districts within the Valencian Community. The Group is involved in a major network of international clinical trials on the prevention of kidney disease progression.

- Primary Care Research Group (Principal Investigator: Dr Jorge Navarro Pérez, Cardiovascular Area). It has established research lines based on population-based Big Data, particularly regarding chronic diseases, cardiovascular risk, ageing and public health. It conducts longitudinal studies using electronic health records in primary care, in collaboration with other clinical and public health groups.
- Breast Cancer Biology Group (Principal Investigator: Dr Ana Lluch Hernández, Cancer Area). It participates in studies on the digital monitoring of breast cancer patients using smart devices and mobile applications. It collects continuous data on physical activity, sleep, diet, etc., enabling the generation of large volumes of longitudinal and personalised data.
- Gynaecological Tumour Molecular Diagnostics Research Group (Principal Investigator: Dr Aymara Mas Perucho, Women's Health Area). Its research lines include the development of predictive models based on liquid biopsy for the early diagnosis and molecular classification of gynaecological tumours. This involves the management and analysis of complex molecular data, with the potential for the integration of clinical and imaging data.
- Research Group on Psychiatry and Neurodegenerative Diseases (Principal Investigator: Dr Juan Nácher Roselló, Ageing, Inflammation and Chronic Diseases Area). It is collaborating with the Polytechnic University of Valencia on a project for the personalised diagnosis and treatment of psychosis using AI and Big Data. It analyses clinical, neuropsychological and, potentially, neuroimaging and genetic data for the purposes of prediction and stratification.
- Translational Research Group on Oesophagogastric Cancer (Principal Investigator: Tania Fleitas, Cancer Area). This group coordinates the AIDA project ("An Artificially Intelligent Diagnostic Assistant for gastric inflammation") — a European project aimed at creating an AI-driven tool for diagnosing precancerous gastric inflammation, personalised patient monitoring, data-driven medical recommendations, etc. This involves the management of clinical data, possibly imaging, and multiple health data sets, collaboration across various countries and centres, and compliance with data protection regulations. This group also participates in the LEGACy project — an H2020 / transnational project involving populations from the EU and Latin America, focusing on multi-omic characterisation of gastric cancer, molecular profiling, tumour microenvironment, microbiome, as well as epidemiological characterisation, etc. These lines of research require the analysis of large volumes of data, and the integration of biomarkers, molecular and clinical data.
- The General and Digestive Surgery Research Group (Principal Investigator: Dr Luis Sabater Ortí) leads the "3D PANC" study, which compares the accuracy of 3D imaging with CT in the preoperative diagnosis of pancreatic cancer. This is a prospective, multicentre study involving many centres, suggesting large volumes of imaging data and the need for standardised analysis.
- Anaesthesiology and Resuscitation Research Group (Principal Investigator: Dr Rafael Badenes Quiles). This group has led an international, multicentre study on a "Clinical Decision Support System" for COVID-19, which combines symptoms, comorbidities, laboratory tests and clinical data to predict severity, risk of ICU admission, etc. This is a clear application of clinical modelling.
- Human Translational Genomics Research Group (Principal Investigator: Dr Rubén D. Artero Allepuz). This group conducts research into rare diseases using functional genomics, animal models and omics technologies. It generates a high volume of molecular data, requiring bioinformatic processing and offering potential for integration with clinical data.
- Experimental Cardiac Electrophysiology Research Group (Principal Investigators: Javier Chorro and A. M. Alberola)

- Heart Failure Research Group (Principal Investigator: Julio Núñez)
- Research Group for the Prevention of Cardiovascular Risk in Children and Adolescents (Principal Investigator: Empar Lurbe)
- Associated Clinical Group in Digestive Medicine (Principal Investigator: Dr Isabel Pascual Moreno). This group works on complex chronic diseases with extensive data (cirrhosis, NASH, IBD, gastrointestinal cancer), making it ideal for predictive models.
- Associated Clinical Group in Neurology (Principal Investigator: Dr José Miguel Láinez Andrés). Their work focuses on dementia, stroke, epilepsy, migraine… conditions where prediction and monitoring are key.
- Associated Clinical Group in Traumatology and Orthopaedics (Principal Investigator: Dr Antonio Silvestre Muñoz). This group works with the use of imaging, customised prostheses, guided techniques and robotics. It utilises integrable biomechanical and clinical data.
- Associated Clinical Group in Care – INVESTENF-INCLIVA (Principal Investigator: Dr Cintia Borja Herrero). This INCLIVA nursing group generates data on daily living, nursing interventions and frailty-related factors. It adds a social and health outcomes dimension to the programme, which is essential in line with new national priorities.
- Associated Clinical Group in Urology (Principal Investigator: Dr José Martínez Jabaloyas). It conducts studies on hyperplasia, cancer, and the management of clinical, urodynamic and imaging data, and may therefore have an interest in decision models.
- Associated Clinical Group in Nuclear Medicine

2.4 External research groups involved

- University of Valencia
- Polytechnic University of Valencia: Centre for Research in Health Economics and Management (Prof. Vivas)
- Obesity and Diabetes Research Network

2.5 Common research areas

- Multimodal data integration. Fusion of imaging, biobank, omics and clinical data from multiple groups. Joint work between the Bioinformatics, Biostatistics and Data Science Unit to harmonise data from all groups.
- Design of AI algorithms for early diagnosis, prediction of therapeutic response and risk stratification.
- Creation of digital health models based on real-world data.
- Implementation of clinical decision support systems (CDSS).
- Health technology assessment (HTA) and organisational sustainability using AI.
- Impact studies for applications developed by multiple groups (e.g., renal predictive model + cardiac predictive model).
- Clinical trials with integrated tools (e.g. use of CDSS in oncology, nephrology, metabolism) through INCLIVA's clinical research unit.
- Telemonitoring of chronic patients.

2.6 Specific actions

- Creation of a repository of validated predictive models for chronic, oncological and cardiovascular diseases.
- Conducting multicentre studies aimed at integrating artificial intelligence into clinical guidelines and healthcare decision-making.
- Collaborative platforms for interoperable data mining.
- Training of research staff in AI methodologies and biomedical data analysis.

2.7 Health innovations

- Development of personalised predictive risk models for the early detection and management of conditions such as cancer, cardiovascular diseases, heart failure and cognitive decline.
- Monitoring and predicting individual clinical progression, facilitating medical decision-making.
- Optimisation of healthcare resource use through AI-based models.
- Development of analytical/predictive models for estimating and controlling healthcare costs.
- Digital clinical tools for clinical decision support (CDSS) to assist healthcare professionals in clinical decision-making.
- Monitoring interfaces for patient monitoring.

2.8 Actions to promote the integration of the gender dimension

- Systematic inclusion of sex- and gender-specific analysis in predictive models.
- Assessment of gender bias in AI algorithms and correction through mathematical adjustments and equity audits.
- Specific studies on differential responses to treatments based on sex.
- Training of research teams in science with a gender perspective.
- Equal representation in the samples used for model development.

2.9 Annual indicators of interrelationships between groups

Indicator	
Number of activities or meetings to promote collaboration between groups	≥3
Number of projects submitted in competitive calls involving members from at least 2 groups	≥2
Number of joint publications between at least two groups	≥5
Number of datasets shared with researchers	≥2
Number of training courses for group staff in digital skills / AI	≥1

2.10 Interaction with INCLIVA platforms

INCLIVA platform(s)	Proposed interaction and justification
Data Science	Technological core of the programme: development of infrastructure for data ingestion, storage, ETL pipelines and APIs. Interoperable repositories of clinical, biological and population data. Data space. Computational support service for model training and deployment in secure, shared environments. Data analysis. Pseudonymisation process. Development and validation of AI models.
Biobank	Support for access to biological samples from multiple groups. Interoperable data
Precision Medicine Unit, Molecular Imaging and Metabolomics Unit, Chromatography and Mass Spectrometry Unit	Integration of omics analyses and imaging into AI models for decision-making. Data space.
Biomarker Analysis Unit	Correlation between biomarkers and predictive models.
Biostatistics Unit	Development and validation of statistical models.
Bioinformatics Unit	Implementation of AI in large-scale omics and clinical analysis (e.g. to correlate molecular profiles with clinical responses)
Clinical Research and Clinical Trials Unit	Monitoring of clinical trials (e.g. alerts for deviations from the protocol). Telemedicine.

3. CROSS-CUTTING PROGRAMME "PERSONALISED MEDICINE AND ADVANCED THERAPIES"

3.1 Coordination

- Valentina Gambardela: Researcher in the Research Group on Colorectal Cancer and New Therapeutic Developments in Solid Tumours.
- María José Terol: Head of the Haematology and Haemotherapy Section at the Hospital Clínico Universitario de Valencia and leader of the Consolidated Research Group on Lymphoproliferative Syndromes.

3.2 Objectives and rationale

3.2.1 Rationale and strategic approach

Precision medicine and advanced therapies constitute a scientific and healthcare priority at international, national and regional levels, due to their potential to transform the diagnosis, treatment and monitoring of complex diseases (cancer, rare, degenerative and autoimmune diseases, etc.). Within the European framework, the Horizon Europe and Horizon Europe Health programmes prioritise personalised medicine, advanced therapies, genomic data and innovation in digital health. In Spain, the **Strategic Action in Health (AES / EECYT / ISCIII)** allocates funds for biomedical research with an emphasis on translational research, precision medicine and collaborative projects. In 2025, the AES call for proposals has a budget of ~€160 million (potentially expandable to ~€200 million) to fund R&D&I projects in health. At the regional level (Valencia), this must align with the regional strategy for innovation and smart specialisation (RIS3 / S3), which promotes R&D&I in health, digitalisation, biotechnology and shared platforms.

INCLIVA already has a *Precision Medicine Unit (PMU)* offering platforms for genomic sequencing, molecular analysis, omics technologies and bioinformatics. Furthermore, it has multiple scientific and technological platforms (Biobank, Bioinformatics Unit, Molecular Analysis Unit, etc.) that support translational research. It has numerous established and emerging research groups in critical areas: oncology, metabolism, rare diseases, genetics, innovative therapies, etc.

Advances in next-generation sequencing, liquid biopsy, molecular biomarkers, artificial intelligence in medical imaging, etc., are transforming diagnosis, prognosis and treatment. INCLIVA is already involved in projects that combine these elements. Furthermore, there is a growing demand for more effective, less toxic and more personalised therapies, both from patients and from regulatory frameworks, funders and healthcare institutions. Thus, clinical, economic and quality-of-life costs are reduced when treatments are better tailored to the patient's profile, unnecessary treatments or adverse effects are avoided, relapses are detected earlier, etc.

3.2.2 Objectives

- To advance precision medicine through the development of diagnostic, prognostic and predictive biomarkers (including omics signatures).

- To apply emerging predictive and mechanistic models such as organoids and 3D bioprinting, as well as innovative gene-editing technologies (CRISPR/Cas) for the development of advanced therapies.
- To promote the translation of basic research findings into clinical practice, by personalising treatments, optimising dosages, avoiding toxicity and reducing adverse effects.

3.3 INCLIVA research groups involved

- Research Group on Colorectal Cancer and New Therapeutic Developments in Solid Tumours (Principal Investigator: Andrés Cervantes)
- Lymphoproliferative Syndromes Research Group (Principal Investigator: Dr María José Terol)
- Research Group on Myeloid Neoplasms (Principal Investigator: Dr Mar Tormo)
- Haematopoietic Transplantation Research Group (Principal Investigator: Dr Carlos Solano)
- Research Group on Breast Cancer Biology (Principal Investigators: Dr Ana Lluch / Dr Pilar Eroles)
- Molecular Imaging and Metabolomics Research Group (Principal Investigator: Dr Daniel Monleón)
- Histopathology and Tissue Engineering Research Group (Principal Investigator: Dr Manuel Mata Roig)
- Translational Epigenomics and Epigenetics Research Group (Principal Investigator: José Luis García)
- Research Group on Molecular Diagnosis of Gynaecological Tumours (Principal Investigator: Aymara)
- Associated Clinical Group: Care Research Group – INVESTENF-INCLIVA (Principal Investigator: Cintia Borja)
- Associated Clinical Group in Pharmacy (Dr Manuel Alós Almiñana)
- Associated Clinical Group in Urology (Dr José Martínez Jabaloyas)
- Research Group on General and Digestive Surgery (Dr Luis Sabater Ortí)
- Translational Research Group on Paediatric Solid Tumours (Dr Samuel Navarro Fos, Dr Rosa Noguera Salvá)
- Translational Research Group in Oesophagogastric Cancer (Dr Tania Fleitas Kanonnikoff)
- Associated Clinical Group in Nuclear Medicine
- Research Group on Genetics and Biomarkers of Rare Diseases (Lab GeBi) (Principal Investigator: Carmen Espinós)
- Tissue Biochemistry Research Group (Principal Investigator: Juan Viña)
- Osteoporosis Genetics Research Group (Principal Investigator: Miguel Ángel García)
- Maternal-Fetal Communication Research Group (Principal Investigator: Felip Vilella)
- Paediatric Nutrition Research Group (Principal Investigator: Cecilia Martínez Costa)
- Heart Failure Research Group (Principal Investigator: Julio Núñez)
- Experimental Cardiac Electrophysiology Research Group (Principal Investigators: Javier Chorro and A.A. Alberola)
- Research Group on the Prevention of Cardiovascular Risk in Children and Adolescents (Principal Investigator: Empar Lurbe)
- Translational Research Group on Ischaemic Heart Disease (Principal Investigator: Vicente Bodí)

3.4 Common scientific lines and operational actions

This section defines the shared lines of action within the programme and the specific measures to implement them.

3.4.1 Molecular and multi-omic biomarkers

- Development of omics signatures with predictive capacity for the use of targeted anti-tumour therapies, immunotherapy and other advanced therapies in solid tumours and haematological neoplasms
- Liquid biopsy (circulating tumour DNA, exosomes, microRNA, fragmentomics)
- Correlation with digital imaging (radiomics, pathomics and functional imaging)

3.4.2 Advanced preclinical models for personalised medicine

- Derivation and culture of organoids (tumour and healthy tissue)
- Engineering of 3D models and tissue bioprinting
- Functional assays of genetic editing (CRISPR, RNP) in cellular and organoid models
- Co-cultures with microenvironment (stromal cells, tumour-associated fibroblasts and immune system cells)
- Specific selection and development of *tumour xenografts*

3.4.3 Advanced therapies: gene therapy, cell therapy, immunotherapy

- Development of gene delivery vectors (viral, non-viral)
- CAR-T, TCR and modified adoptive cell therapies
- Targeted gene therapies for rare/monogenic diseases
- Assessment of safety, dosing, persistence and toxicity in Phase I trials (*First-in-human*)

3.4.4 Data integration and personalised prediction

- Design of machine learning/artificial intelligence algorithms to integrate 'omic', clinical and imaging data
- Predictive models of response, resistance mechanisms and organ damage
- Digital medicine: decision-making platforms for clinical staff

3.4.5 Clinical validation and adaptive trial design

- Early-phase "basket", "umbrella" or biomarker-adaptive clinical trials
- Phase I/II exploratory studies with integrated biomarkers and pharmacodynamic monitoring studies

3.5 Health innovations

The programme aims to generate high-impact innovations in healthcare, which may include:

- Validatable biomarkers for patient stratification and therapy selection (differential diagnosis, prognosis, response prediction)
- New therapeutic products (modified cells, gene vectors, experimental precision therapies)
- Ex vivo culture methods (organoids, bioprinting) for personalised functional testing
- Non-invasive monitoring methods (longitudinal liquid biopsy, biomolecular sensors)
- Adaptive and strategic clinical trial designs based on biomarkers
- Clinical decision-making platforms integrating clinical, molecular and imaging data (clinician support tools)
- Personalised medicine strategies that reduce adverse effects, overtreatment and healthcare system costs

3.6 Actions to promote the integration of the gender dimension

To ensure that research and innovation are equitable and gender-sensitive, the following is proposed:

- Include sex/gender-stratified analyses in all studies (biomarkers, therapeutic response, toxicity)
- In the design of cohorts and trials, ensure balanced representation of women and men (unless there is documented scientific justification)
- Adopt inclusive language and specify variables for sex (biological) and gender (social) in metadata
- Training and raising awareness among research staff regarding gender bias in science
- Specific encouragement of female researchers' participation (mentoring programmes, female leadership)
- Mandatory recording of gender indicators (proportion of women in leadership roles, female first authorship, mixed co-authorship)
- Review of results from a gender perspective: differences in biomarkers, side effects, therapeutic efficacy
- Encouraging research lines that explore specific aspects of women's health (gynaecological cancer, differential immune responses, hormones)
- Promote internal equality committees to oversee gender integration within the programme
- In internal calls for proposals, apply criteria that favour proposals including gender analysis

These actions ensure that the programme does not reproduce biases and contributes to a more responsible and equitable science.

3.7 Annual indicators of interaction between groups

To measure the degree of integration within the programme and its success, we propose the following **key performance indicators (KPIs)**, with annual targets:

Indicator	**Definition/calculation**	**Annual target**
Number of programme meetings or activities to promote collaboration	Joint sessions	2

No. of inter-group collaborative projects (coordinated within the programme)	Projects involving ≥ 2 programme groups	2
Number of joint publications between programme groups	Articles co-authored by ≥ 2 programme groups	5
Number of joint applications for external funding	Submissions of coordinated national/international proposals	2
Platform sharing index	Platform (technology) hours allocated to programme projects vs total usage	20%
Number of technical staff/researchers shared between groups	Shared recruitment or assignments (technicians, bioinformaticians)	1
Number of thematic seminars/workshops organised	Internal programme events (scientific, methodological)	2
Cross-training (PhD students / postdocs mobilised)	Number of students or postdocs collaborating in ≥ 2 groups	1
Inclusion of gender analysis	Proposals submitted with sex/gender analysis / total proposals submitted	≥ 80%
Translational impact (trials, patents)	Number of emerging clinical trials or patents generated	1

3.8 Interaction with INCLIVA platforms

One of the key elements of the programme is the intensive and coordinated use of INCLIVA's scientific and technological platforms. Below is a detailed description of how each platform will be integrated into the programme, with examples of potential contributions:

Platform	Role or service offered to the programme	Justification / examples of use
Data Science	Design, integration, curation and analysis of large integrated databases (omics, clinical, imaging)	Development of data pipelines, creation of unified databases, quality assurance, ML algorithms
Biobank	Storage and standardised management of biological samples (tissues, blood, plasma, DNA, cells, organoids)	Consent, traceability, pre-analytical quality control, distribution to groups
Precision Medicine Unit	Support in the design and validation of personalised diagnostic strategies	Interface between genomic analysis and clinical decision-making, generation of integrated reports
Biostatistics Unit	Experimental design, statistical analysis, modelling, validation of results	Statistical support for publications, clinical trials, multivariate analysis
Bioinformatics Unit	Sequencing analysis, multi-omics integration, pipelines, genetic annotation	NGS data processing, differential analysis, integration with AI, visualisation

Analytical Liquid Chromatography Unit	LC methods for metabolomics, pharmacokinetics and quantification of small molecules	Quantification of drugs, metabolites, pharmacokinetic profiles in models and human samples
Mass Spectrometry Unit	Proteomic and metabolomic analysis, detection of low-abundance biomarkers	Identification of proteomic/metabolic signatures, radioisotopic quantification ( ) where applicable
Clinical Research and Clinical Trials Unit	Practical support in the design, management and monitoring of clinical trials	Conducting phase I/II trials, clinical coordination, regulatory aspects, authorisations, follow-up
Flow Cytometry Unit at the University of Valencia	Support in the isolation of cell populations with specific biomarkers. Differentiation of circulating immune cells.	Characterisation and separation of cell populations. Cell viability and proliferation. Multiplex panels. Immunophenotyping. Intracellular cytokines.

4. CROSS-CUTTING PROGRAMME "IMMUNE-MEDIATED DISEASES AND THERAPIES"

4.1 Coordination

- María Jesús Sanz, Professor of Pharmacology at the University of Valencia and principal investigator of the Consolidated Research Group on Inflammation.
- Mari Carmen Gómez Cabrera, Professor of Physiology at the University of Valencia and principal investigator of the Consolidated Research Group on Exercise, Nutrition and Healthy Lifestyles

4.2 Objectives and rationale

4.2.1 Rationale and strategic relevance

Immune-mediated diseases (or those with an immunological/inflammatory component) constitute a growing part of the contemporary healthcare challenge. Many chronic degenerative diseases — cardiovascular, neurological, oncological, and rare diseases — share mechanisms of immune dysfunction, chronic inflammation, or alterations in the tissue microenvironment that drive progression, comorbidity, and varied therapeutic responses.

The generation of integrated knowledge linking immunity, the microenvironment and therapies is an urgent necessity to advance towards effective personalised medicine. In this context, a cross-cutting programme at INCLIVA can: foster synergies between groups with complementary expertise, accelerate the clinical translation of immunological discoveries, generate technological innovation in diagnostic and therapeutic tools, promote a gender perspective in immunological research, and consolidate INCLIVA's position in national and European competitive calls for proposals.

4.2.2 Strategic alignment

- European Strategy (Horizon Europe 2021–2027): particularly in the Health and Life Sciences Clusters, which focus on personalised medicine, digital health, immunotherapy and predictive models.
- National (EECYT, ISCIII, State R&D&I Plan): priority areas in personalised medicine, biomedical platforms, systems biology, rare diseases, advanced therapies and clinical trials.
- Regional (RIS3/S3): in the Valencian Community, the regional innovation strategy (RIS3-CV/S3) promotes personalised health, advanced biomedical technologies, biotechnology and big data for healthcare innovation.

This cross-cutting programme therefore addresses both key scientific needs and strategic institutional, regional, national and European priorities.

4.2.3 Scientific objectives

The scientific objectives of the programme are as follows:

- To characterise the common and specific biological and clinical mechanisms involved in the pathophysiology of chronic and degenerative diseases (cardiovascular, neurological, respiratory, cancer, rare diseases, etc.).
- To investigate the interaction between the immune system and the tissue microenvironment in each of these pathologies, analysing how chronic inflammation, immune activation or immunosuppression contribute to their onset, progression and therapeutic response.
- To study the impact of immunological ageing (immunosenescence) on susceptibility to immune-mediated diseases and on the efficacy of targeted therapies, including physical exercise.
- To develop and evaluate new immune-mediated therapeutic strategies, including immunotherapy (monoclonal antibodies, therapeutic vaccines, CAR-T cell therapies, etc.).
- To identify immunological biomarkers for diagnosis, prognosis and therapeutic response, whether common or specific to different conditions, to enable personalised medicine.
- To analyse gender-dependent differences and hormonal influences on immune and inflammatory responses, with an emphasis on how they modulate the onset, progression and therapeutic response of immune-mediated diseases in women (including diseases with higher female prevalence, the impact of the hormonal cycle, pregnancy and the menopause) and on the development of personalised therapies with a gender perspective.
- To generate preclinical experimental models and translational platforms that replicate immunological interactions between different organs and systems, with the aim of validating new therapeutic targets and predicting efficacy and safety in humans.
- To analyse how lifestyle factors (nutrition, exercise, exposure to pollutants) influence immune responses and therapeutic efficacy.

4.3 INCLIVA research groups involved

- Inflammation Research Group (Dr Mª Jesús Sanz Ferrando)
- Exercise, Nutrition and Healthy Lifestyle Research Group (Dr Mª Carmen Gómez Cabrera)

- Healthy Ageing Research Group (MiniAging) (Dr Consuelo Borrás Blasco)
- Cardiometabolic and Renal Risk Study Group (Dr Josép Redón i Mas, Dr Raquel Cortés Vergaz)
- Endothelial Cells Research Group (LINCE) (Dr Carlos Hermenegildo Caudevilla, Dr Susana Novella del Campo)
- Cardiometabolic Risk and Diabetes Research Group (Dr José Tomás Real Collado, Dr Sergio Martínez Hervás)
- Genomics and Diabetes Unit (Dr Felipe Javier Chaves Martínez)
- Breast Cancer Biology Research Group (Dr Ana Lluch Hernández, Dr Pilar Eroles Asensio)
- Colorectal Cancer and New Therapeutic Developments in Solid Tumours Research Group (Dr Andrés Cervantes Ruipérez)
- Skin Cancer Research Group (Dr José Carlos Monteagudo Castro)
- Myeloid Neoplasia Research Group (Dr Mar Tormo Díaz)
- Lymphoproliferative Syndromes Research Group (Dr Mª José Terol Casterá)
- Haematopoietic Transplantation Research Group (Dr Carlos Solano Vercet)
- Translational Research Group on Oesophagogastric Cancer (Dr Tania Fleitas Kanonnikoff)
- Neurological Degeneration Research Group (Dr Carmina Montoliu Félix)
- Metabolic Diseases Research Group (Dr Herminia González Navarro)
- Respiratory Diseases Research Group (Dr Jaime Signes-Costa Miñana)
- Ageing and Physical Exercise Research Group (Dr José Viña Ribes)
- Research Group on Cellular and Organ Pathophysiology of Oxidative Stress (Dr Federico V. Pallardó Calatayud)
- Research Group on Medical Chemistry for Drug Development (Dr Nuria Cabedo Escrig)
- Reproductive Medicine Research Group (Dr Carlos Simón Vallés)
- Research Group on Therapies for Endometriosis and Endometrial Cancer (Dr Raúl Gómez Gallego)
- Associated Clinical Group in Gastroenterology (Dr Isabel Pascual Moreno)
- Vascular Function Research Group (Principal Investigator: José María Vila Salinas)
- Tissue Biochemistry Research Group (Principal Investigator: Juan Viña)

4.4 Common scientific lines and actions for their development

To structure the programme's work, the following cross-cutting scientific lines are proposed, with specific actions:

4.4.1 Line 1: Immune mechanisms and shared microenvironment

Actions:

- Cross-disease comparative studies: analysing immune profiles in tissue, infiltrates and the systemic circulation (cytokines, chemokines, cellular immune status).
- Integrate multi-omic data (transcriptomic, proteomic, metabolomic, cytomic) with clinical data to identify common immunological signatures.

- Correlation studies between the immune profile and prognosis, comorbidities and disease progression.

4.4.2 Line 2: Chronic inflammation, activation and immunosuppression

Actions:

- Longitudinal monitoring of biomarkers of inflammation and immune regulation in patient cohorts.
- Functional studies of immune cells (T cells, macrophages, neutrophils, etc.) isolated from patients and controls.
- *Ex vivo*, *in vitro* and *in vivo* experiments to manipulate inflammatory pathways (e.g. pathway blockade, modulators) and study their effects.

4.4.3 Line 3: Immunological ageing / immunosenescence

Activities:

- Ageing cohorts to characterise immune profiles at different ages.
- Linking markers of immune senescence (e.g. senescent cells, changes in clonal repertoires) to disease incidence.
- Intervention trials in animal models (or pilot trials in humans) with modulators of immune ageing, including physical exercise.

4.4.4 Line 4: Assessment of the impact of innovative therapies on the immune system

Actions:

- Study of the effect of new monoclonal antibodies or other molecules on the immune system.
- Study of the immunological impact of new therapeutic vaccines or vaccine vectors.
- Evaluation of cells targeting specific microenvironmental targets (CAR-T, CAR-NK, modified regulatory cells, etc.) and their impact on other immune actors.
- Preclinical safety and efficacy studies in animal models of new drugs, with an emphasis on effects on the immune system.

4.4.5 Line 5: Immunological biomarkers and personalised medicine approaches

Actions:

- Identification of biomarkers of immune cells, cytokines, molecular signatures and cell receptor profiles in different leukocyte subtypes.
- Validation across multiple cohorts and diseases: search for common or specific biomarkers.
- Integration of biomarkers with AI-based predictive models to optimise therapeutic decision-making.
- Evaluation of therapeutic response based on biomarkers and treatment adjustment.

4.4.6 Line 6: Gender, hormones and immunity

Actions:

- Systematic collection of hormonal and gender variables in all studies.
- Analysis stratified by sex and hormonal status (premenopause, menopause, pregnancy).
- Functional studies on immune cells from women versus men; influence of hormones *ex vivo* and *in vitro*.
- Therapeutic response trials adjusted for sex/gender and hormonal status.

4.4.7 Line 7: Experimental models and translational platforms

Actions:

- Development of humanised animal models or 'humanised mice' with a human immune component.
- Immune organ-on-chip models integrating a tissue microenvironment and immune components.
- Three-dimensional cultures with immune cells and target tissue cells.
- *Ex vivo* assays on human tissues (organs, biopsies) to evaluate immunomodulatory therapies.

4.4.8 Line 8: Lifestyles, immunity and therapeutic efficacy

Actions:

- To assess the influence of diet, body composition, physical activity and exposure to environmental toxins on immunological profiles and systemic inflammatory status.
- Characterisation of immunometabolic biomarkers (cytokines, metabolites, microbiota, oxidative stress, hormones) associated with different lifestyles.
- Controlled interventions (exercise, diet, intermittent fasting, reduction of exposure) to assess their effect on immune function and therapeutic response.
- Multi-omic analysis (metabolomics, transcriptomics, microbiome) of lifestyle-related immune adaptations.
- Study of interactions between ageing, sex and lifestyle in the modulation of immunity.

4.5 Health innovations

This programme has the potential to generate significant innovations:

- Advanced immunological diagnostic platforms (multiplex cytokine panels, cell receptor profiles in different leukocyte subtypes, activation/regulation signatures).
- AI-based clinical decision support tools incorporating immunological, clinical and molecular data to predict risk, progression and therapeutic response.

- Mobile applications or connected systems for immune monitoring in patients, with real-time indicators (e.g. transplants, autoimmune diseases).
- Validation of personalised immunotherapies, tailored to the patient's immune profile (e.g. tailored antibodies, modulating cell therapies).
- Translational models that bridge the gap between discovery and clinical practice, with greater efficiency, predictability of toxicities and improved efficacy.
- Integration of the gender perspective as an innovative element that can lead to more precise therapies for women, who have historically been under-represented.
- Technology transfer and collaboration with industry to license or commercialise diagnostic tools, biomarkers or therapies developed.

4.6 Actions to promote the integration of the gender dimension

To ensure that the gender approach is not a superficial addition, the following are proposed:

- Mandatory inclusion of gender/sex variables in the design of all studies within the programme.
- Stratification of analyses by sex: clinical and immunological results must be evaluated separately for women and men.
- Incorporation of relevant hormonal variables (menstrual phase, contraceptive use, pregnancy, menopause).
- Training in gender perspectives for all researchers and technical staff.
- An internal gender and health committee to review protocols and publications to identify gender biases or gaps.
- Research specific to women: diseases with a female predilection (e.g. certain autoimmune diseases), hormonal influence on therapies.
- Equal representation in leadership: ensuring women's participation in coordination roles, promotions and as principal investigators.
- Incentive policy: prioritise or provide bonuses for programme projects that explicitly include gender-related questions.

4.7 Annual indicators of interaction between groups

To monitor the level of collaboration and the programme's success, we propose the following indicators:

Indicator	**Suggested annual target**
No. of activities or meetings to promote collaboration between groups	≥2
Number of new inter-group projects (≥2 groups)	≥2
Joint publications between programme groups	≥5
Clinical trials incorporating immunological/multi-omic data	≥1
Immunological biomarkers identified and validated	≥1
Technological tools / applications developed	1

Training and mobility activities between groups	≥2
Percentage of studies with sex/gender analysis	≥80%
Results transferred to clinical practice	To be determined

4.8 Interaction with INCLIVA and UCIM platforms and their role

To achieve efficiency, reproducibility and translation, the programme must be integrated with the scientific and technological platforms of INCLIVA and the Central Medical Research Unit (UCIM) (Scientific and Technological Platforms – INCLIVA – Biomedical Research Institute)

INCLIVA platform(s)	Proposed interaction and justification
Data science	Integrate clinical, molecular, immunological and imaging data. Design AI pipelines for classification, prediction and clustering.
Biobank	Provide well-characterised samples (tissues, blood, cells, fluids) with clinical and immunological metadata. Ensure quality, traceability and shared access between groups.
Precision Medicine Unit	Apply findings from immune profiling to personalise immune-mediated therapies and guide clinical decisions.
Biomarker Analysis Unit	Cytokine measurement, immune profiles, receptors, multiplex panels, analytical validation.
Biostatistics Unit	Robust statistical design, gender-adjusted analysis, cross-validation, statistical power
Bioinformatics Unit	Omics data processing, integration of heterogeneous data, visualisation, reproducible pipelines.
Body Composition Unit	Assessing body composition variables that may influence immune status (fat mass, lean mass) as adjustment covariates
Analytical Liquid Chromatography Unit	Support in metabolomics and the quantification of small molecules related to immunity.
Mass Spectrometry Unit	Identification and quantification of proteins, metabolites and advanced immune molecular signatures.
Clinical Research and Clinical Trials Unit	Organisation, follow-up, monitoring and execution of clinical trials that integrate immunological discoveries
Flow Cytometry and Cell Culture Unit (UCIM)	*Ex vivo* and *in vitro* functional studies of different leukocyte subpopulations and other elements associated with the immune system.
Animal Housing and Experimental Surgical Theatres Unit (UCIM)	Development of translational animal models necessary to evaluate the immune component of the pathologies under study, as well as the testing of new therapies.

Genomics and Epigenetics Unit (UCIM)	Genetic and epigenetic studies of human and animal samples. Identification of alterations associated with the disease or the applied therapy.
Biomedical Imaging and Metabolomics Unit (UCIM)	*In vivo* imaging using non-invasive techniques to obtain anatomical and metabolic information (cellular function). This enables studies of disease progression and the efficacy of treatments. Metabolomic analysis will help to obtain quantifiable profiles of liquid, solid and semi-solid samples.
Microscopy Unit (UCIM)	Characterisation of human and animal samples using immunofluorescence and immunohistochemistry techniques.

5. CROSS-CUTTING PROGRAMME "MENTAL HEALTH AND NEUROSCIENCE"

5.1 Coordination

- Juan Nácher, Professor of Cell Biology at the University of Valencia and principal investigator of the Consolidated Research Group on Psychiatry and Neurodegenerative Diseases.
- Carmina Montoliu, Professor of Cell Biology at the University of Valencia and principal investigator of the Consolidated Research Group on Neurological Degeneration.

5.2 Objectives and rationale

5.2.1 Rationale and strategic relevance

Neuropsychiatric disorders and neurodegenerative diseases represent one of the emerging priorities in public health and biomedical R&D&I.

There is a gap between basic advances in neuroscience (molecular, cellular, circuit-level) and their effective clinical translation. A cross-cutting programme can catalyse the connection between groups working with preclinical models, patients, technological platforms and digital innovation.

Given that INCLIVA already has the Cross-cutting Programme on Neurological Impairment, this new Neuroscience and Mental Health programme can function as an 'umbrella framework' that integrates this dimension of neurological impairment with the broader psychiatric, cognitive and mental health dimensions.

5.2.2 Strategic alignment

Horizon Europe / Horizon Europe (EU Framework Programmes): Research into mental health, brain neuroscience and diseases of the nervous system is a priority within the so-called "Health, Demographic Change and Wellbeing" pillar and in Pillar II of "Global Challenges and a Competitive Europe".

Spain / ISCIII / EECYT (Spanish Strategy for Science, Technology and Innovation): Mental health and nervous system disorders feature as strategic priorities in ISCIII calls for proposals, as well as in mental health research plans.

Valencian Community / S3 / Regional RIS3: The Valencian Community's Smart Specialisation Strategy (RIS3) includes, within its biomedicine and health pillar, innovation priorities in 'digital health' technologies, personalised medicine, biomarkers, big data and social wellbeing — which align with a neuroscience and mental health programme. In addition, the Valencian Community's Mental Health Strategy (Valencian Mental Health and Addictions Plan 2024–2027) is currently in force, aiming to improve access to quality care and the treatment of addictions and mental health problems, with a focus on prevention, equity, comprehensive care for children and adolescents, and the expansion of human resources.

In short, this programme ensures that INCLIVA's research groups direct their efforts towards one of the emerging scientific and health priorities, facilitating the acquisition of European, national and regional funding.

5.2.3 Scientific objectives

The scientific objectives of the programme are as follows:

- To improve the prevention, treatment and rehabilitation of severe mental disorders, cognitive impairment and neurobehavioural disorders. To promote early diagnostic strategies and personalised therapeutic approaches in neurological and psychiatric disorders.
- To improve the early diagnosis, treatment and prevention of cognitive and functional decline associated with chronic liver diseases (liver cirrhosis and metabolic dysfunction-associated liver disease, MASLD), diabetes and major surgery. To identify mechanisms, therapeutic targets and biomarkers for the onset of such cognitive and functional decline, and to design and test new diagnostic and therapeutic procedures to prevent or reverse its onset.
- To conduct translational research in neuroscience to better understand the molecular, cellular and brain network mechanisms involved in psychiatric and neurological disorders.
- To study the interaction between genetic, epigenetic, environmental and social factors in the development of neuropsychiatric and neurodegenerative diseases.
- To promote integrated models of comorbidity between neurological and psychiatric diseases (e.g. Alzheimer's, Parkinson's with depression, cognitive impairment in patients with psychiatric disorders) to understand intersections and synergies.

5.3 INCLIVA research groups involved

For this new Cross-cutting Programme, the aim is to retain those groups that already collaborated during the Cross-cutting Programme on Neurological Impairment and to include those that were not previously involved but which can contribute value to the lines of research. Furthermore, there must be a commitment to optimal basic-clinical integration.

- Research Group on Psychiatry and Neurodegenerative Diseases (Dr Juan Nácher Roselló)
- Neurological Deterioration Research Group (Dr Carmina Montoliu Félix)

- INCLIVA – FIPF Joint Biomedical Research Unit (Principal Investigators: José Tomás Real, Carmen Espinós, Carmina Montoliu and Vicente Felipo)
- Associated Clinical Group in Neurology (Dr José Miguel Láinez Andrés)
- Associated Clinical Group in Gastroenterology (Dr Isabel Pascual Moreno)
- Anaesthesiology and Resuscitation Research Group (Dr Rafael Badenes Quiles)
- Nursing Research Group. INVESTENF-INCLIVA (Dr Cintia Borja Herrero)
- Research Group on Cardiometabolic Risk and Diabetes (Dr José Tomás Real Collado, Dr Sergio Martínez Hervás)
- Research Group on Personal Autonomy, Dependency and Severe Mental Disorders (Dr Rafael Tabarés Seisdedos)
- Research Group on Ageing and Physical Exercise (Dr José Viña Ribes)
- Research Group on Exercise, Nutrition and Healthy Lifestyles (Dr MCarmen Gómez Cabrera)
- Research Group on Healthy Ageing (Dr Consuelo Borras Blasco)
- Inflammation Research Group (Dr Mª Jesús Sanz Ferrando)
- Cardiometabolic Research Group in Primary Care (Dr Jorge Navarro Pérez)
- Clinical Cardiology Research Group (Dr Juan Sanchis Forés)
- Associated Clinical Group on Insomnia and Circadian Rhythms (Principal Investigator: M. de Entrambasaguas Barretto)
- Human Translational Genomics Research Group (Dr Ruben Artero Allepuz)
- Research Group on Cellular and Organ Pathophysiology of Oxidative Stress (Dr Federico Vicente Pallardo Calatayud)
- Translational Epigenetics and Epigenomics Research Group (Dr José Luis Garcia Gimenez)
- Research Group on Genetics and Biomarkers of Rare Diseases (Dr Carmen Espinós)
- Research Group on Neurobiology and Molecular Pathophysiology in Rare Diseases – NeuroFisER (Principal Investigator: Pilar González Cabo)
- Associated Clinical Group in Otorhinolaryngology (Principal Investigator: Jaime Marco).

5.4 Common scientific lines and actions for their development

To structure the programme's work, the following cross-cutting scientific lines are proposed, with specific actions:

5.4.1 Research Area 1: Integrative neurobiology of psychiatric and neurodegenerative diseases

- Study of molecular and cellular mechanisms (synapses, plasticity, oxidative stress, axonal transport, neuroinflammation).
- Use of cellular models (organoids, 3D cultures), transgenic animals, and human models of neuronal iPSCs.

- Integration with platforms for transcriptomics, epigenomics, proteomics, metabolomics, biobanking, data science, biostatistics, bioinformatics, chromatography and spectrometry.

5.4.2 Line 2: Multimodal biomarkers for early diagnosis and progression

- Identification of cerebrospinal fluid (CSF), plasma and exosome biomarkers, and imaging markers.
- Identification of biomarkers in human brain cells (olfactory epithelium, iPSCs).
- Combination of neuroimaging data (MRI, PET), electrophysiology, neuropsychology and molecular biomarkers.
- Validation in longitudinal cohorts and multicentre studies.

5.4.3 Line 3: Risk models, prediction and stratification using artificial intelligence

- Use of big data, machine learning and deep neural networks to predict risk, stratify patients and forecast progression.
- Development of predictive tools integrated with clinical platforms (for example, using the INCLIVA Data Science Platform).
- Brain integrity models, connectomics, correlation with clinical-demographic and environmental data.

5.4.4 Line 4: Neuroscience of neurological impairment associated with systemic diseases

- Improving the early diagnosis, treatment and prevention of cognitive and functional decline associated with chronic liver diseases (liver cirrhosis and metabolic dysfunction-associated liver disease, MASLD), diabetes and major surgery.
- Identify biomarkers for the early detection of cognitive and functional decline (peripheral markers, neuroimaging techniques, neurophysiological techniques, biomarker combination panels, etc.).
- To identify the mechanisms by which:
    - Peripheral inflammation leads to neuroinflammation
    - Neuroinflammation leads to functional, structural and neurotransmission alterations in the brain
    - Brain alterations lead to cognitive and functional decline
- Identify therapeutic targets to reverse or prevent cognitive and functional decline.
- To design and test new therapeutic approaches to reverse or prevent cognitive and functional decline.
- To study common mechanisms of neurodegeneration between primary CNS diseases and systemic pathology (e.g. oxidative stress, mitochondrial dysfunction, neuroinflammation).

5.4.5 Line 5: Population studies, brain epidemiology and community mental health

- Population-based studies in the Valencian Community to estimate prevalence, neuropsychiatric risk factors and cognitive incidence.
- Integration with primary care and collaboration with INCLIVA's Primary Care Group.
- Assessment of social determinants, gender and inequalities in mental health.

5.5 Health innovations

This programme has the potential to generate significant innovations:

- Development of digital mental health tools (cognitive monitoring apps, early warning systems).
- Integration of artificial intelligence and clinical decision interfaces for diagnostic support and patient monitoring.
- Predictive biomarkers: developing diagnostic kits (blood tests, exosomes, nanoparticles) that can be transferred to clinical practice.
- Cognitive rehabilitation protocols based on neurofeedback, virtual reality and adaptive stimulation.
- Collaborative care models: integration of neuroscience with primary care and community health, incorporating preventive models and digital monitoring.

5.6 Actions to promote the integration of the gender dimension

To ensure that the gender perspective is not merely a superficial addition, the following are proposed:

- In each line of research, include analyses stratified by sex/gender (women/men), as well as an exploration of specific biological mechanisms (hormonal, epigenetic, social).
- When recruiting cohorts, ensure an appropriate gender balance and avoid exclusionary biases.
- Implement requirements for the dissemination of results segmented by sex for publications and conference participation.
- Include specific projects focused on disorders with gender bias (e.g. depression in women, anxiety, sleep disorders, neurodegeneration with sex differences).
- Periodically assess whether there are differences in outcomes, adherence, and therapeutic response by gender, and adjust strategies accordingly.

5.7 Annual indicators of interaction between groups

To monitor the level of collaboration and the success of the programme, we propose the following indicators:

Indicator	**Suggested annual target**
Number of activities or meetings to promote collaboration between groups	≥2
Training activities/presentations for the various groups	≥1
Number of new inter-group projects (≥2 groups)	≥2
Joint publications between programme groups	≥5
Percentage of studies with sex/gender analysis	≥80%
Results transferred to clinical practice	To be determined

5.8 Interaction with INCLIVA platforms and their role

To achieve efficiency, reproducibility and translation, the programme must be integrated with INCLIVA's scientific and technological platforms:

INCLIVA platform(s)	Proposed interaction and justification
Data science	For the storage, integration and real-time analysis of clinical, imaging and biomarker data, and longitudinal follow-up. To develop scorecards, integrated predictive models and dashboards for researchers and clinicians.
Biobank	Collection, storage and distribution of biological samples (plasma, CSF, tissues, exosomes) from neuropsychiatric cohorts. Managing consent, traceability and quality of human samples for biomarkers. To provide samples for longitudinal studies and internal projects.
Precision Medicine Unit	Application of personalised neurological/psychiatric medicine strategies: genotype-phenotype correlation, pharmacogenomic prediction. Integration of omics data (genomics, transcriptomics, proteomics) and personalisation of therapies.
Biomarker Analysis Unit	Measurement of biomarkers of interest (plasma proteins, metabolites, exosomes, brain molecules) using specialised equipment. Providing high-quality data for biomarker validation in clinical cohorts.
Biostatistics Unit	Robust statistical design, gender-adjusted analysis, cross-validation, statistical power
Bioinformatics Unit	Omics data processing, integration of heterogeneous data, visualisation, reproducible pipelines.
Analytical Liquid Chromatography Unit	Support for metabolomics analysis, brain lipids, small metabolites in plasma/CSF. Development of quantitative methods for neurological metabolites.
Mass Spectrometry Unit	Proteomic identification, analysis of low-abundance metabolites, quantification of brain molecules. Validation of biomarkers using highly sensitive techniques.
Clinical Research and Clinical Trials Unit	Organisation, follow-up, monitoring and conduct of clinical trials in neuroscience and mental health

6. CROSS-CUTTING PROGRAMME "INFECTIOUS DISEASES"

6.1 Coordination

- Dr Anaïs Corma, Joan Rodés Research Fellow at INCLIVA's Cardiometabolic and Renal Risk Study Group.
- Dr José Luis Piñana, researcher at INCLIVA's Haematopoietic Transplantation Research Group.

6.2 Objectives and rationale

6.2.1 Rationale and strategic alignment

Infectious diseases represent one of the priorities defined in the Spanish Strategy for Science, Technology and Innovation (EECTI) 2021–2027 under the Health thematic area: in particular, precision medicine, new diagnostics and therapies, antimicrobial resistance, and emerging diseases.

At European level, the Horizon Europe programme, particularly **Cluster 1: Health**, emphasises prevention, diagnosis, treatment and surveillance of emerging and re-emerging infectious diseases, as well as pandemic preparedness.

At regional level, the Valencian Community has the RIS3-CV (Smart Specialisation Strategy), where "New technologies and knowledge for the prevention, diagnosis and prognosis of diseases" is a priority, as well as innovation in health, the integration of active ageing, chronic diseases, etc.

6.2.2 Programme objectives

The specific objectives proposed are as follows:

- To study the molecular and cellular mechanisms of microbial pathogenesis, antimicrobial resistance and immune response.
- To improve the prevention, early diagnosis, monitoring and treatment of emerging infections and chronic infectious diseases, particularly in immunocompromised patients.
- Strengthen the capacity to respond to epidemic outbreaks through molecular surveillance and the development of new therapeutic and vaccine strategies.

6.3 INCLIVA research groups involved

Below are the INCLIVA groups that may be involved, with particular attention to the researchers listed:

- Cardiometabolic and Renal Risk Study Group, led by Drs Pepa Galindo and Anaïs Corma. Their areas of research include the characterisation of cardiovascular risk and renal dysfunction in patients with HIV infection, the assessment of comorbidities in HIV patients and their impact on the development of frailty and quality of life, the evaluation of the risk of h r renal dysfunction in people on PrEP (pre-exposure prophylaxis), and the characterisation of the natural history of viral hepatitis (in relation to

the development of cardiometabolic and renal damage and clinical events). They also collaborate on studies into Chagas' disease and its implications for cardiac and digestive diseases. Within this same group is Dr David Martí who, although his main work focuses on MASLD (metabolic steatohepatitis) and metabolism-related liver diseases, also participates in studies seeking to improve the clearance of the Hepatitis C virus at the DS Clínico-Malvarrosa.

- Haematopoietic Transplantation Research Group (coordinated by Carlos Solano Vercet and including Dr José Luis Piñana, coordinator of this cross-disciplinary programme). Dr Piñana is a clinical researcher specialising in infections in haematological patients, with an emphasis on viral, fungal and bacterial infections, immunosuppressive factors, and the response to and benefits of vaccination in immunocompromised individuals. He coordinates a research programme integrating clinical epidemiology, immunovirology, molecular diagnostics, immune reconstitution, prophylaxis and personalised antimicrobial treatment. His main lines of research include 1) community-acquired respiratory viral infections in recipients of allogeneic haematopoietic stem cell transplants, CAR-T therapy recipients and patients with haematological malignancies, 2) Vaccination in immunocompromised patients: effectiveness of the influenza vaccine, immunogenicity against SARS-CoV-2 and RSV, and optimisation of post-transplant schedules; 3) advanced viral diagnostics: implementation of multiplex and digital PCR for the diagnosis and viral load of respiratory viruses, metagenomic NGS for the study of mutation acquisition in respiratory viruses; 4) viral biomarkers associated with immune reconstitution, 5) the relationship between immunosuppression, lymphopenia, lymphocyte reconstitution and susceptibility to infections, and 6) adoptive cell therapy (infusion of memory T cells or virus-specific T cells) to prevent and treat severe opportunistic infections in immunocompromised patients. His research has contributed to the development of national and international guidelines on the definition of infectious processes, prevention, diagnosis and treatment of infections in immunosuppressed patients and those with haematological cancer, establishing him as a national authority on infections in haematology and cell therapies.
- Molecular Microbiology and Microbial Pathogenesis Group, coordinated by Dr David Navarro Ortega. This group is explicitly focused on the study of the basic aspects of infectious diseases, pathogenic microorganisms, pathophysiology, innovative diagnosis, and the immunobiology of the infected patient. Its main lines of research are: (1) immunobiology of cytomegalovirus infection in patients undergoing allogeneic haematopoietic stem cell transplantation and those with haematological malignancies, (2) virome analysis, (3) immunobiology of SARS-CoV-2, (4) the design and evaluation of diagnostic algorithms, the applicability and actions associated with the results of analytical techniques, and the development of new diagnostic strategies, (5) the molecular characterisation of *Neisseria gonorrhoeae,* and (6) the analytical validation of diagnostic techniques. In addition to Dr Navarro, there are several emerging and established researchers: Dr Estela Giménez, who collaborates on studies of CMV infection in transplant patients, participates in CMV-related theses, and works on SARS-CoV-2, etc.; Dr Eliseo Albert, who works on viral infection (CMV, anellovirus, SARS-CoV-2) in immunocompromised patients or transplant recipients. He also participates in MALDI-TOF studies for *Pseudomonas* and antimicrobial resistance; Dr Ignacio Torres Fink, who has also participated in work on SARS-CoV-2 viral load in respiratory samples and the MALDI-TOF technique for the rapid characterisation of Pseudomonas in blood.
- The Epigenomics and Translational Epigenetics Group, led by Dr José Luis García Giménez (emerging group). Its research focuses on sepsis (neonatal and adult), including immune mechanisms and

biomarkers of infection/sepsis, which links it directly to the field of infectious diseases. It includes clinical research staff from the Intensive Care Unit at the Hospital Clínico (Edurne Carbonell).

- Colorectal Cancer and New Therapeutic Developments in Solid Tumours Research Group (Principal Investigator: Andrés Cervantes)
- Neurological Degeneration Research Group (Principal Investigator: Dr Carmina Montoliu Félix). Potential collaboration on how chronic or acute infections affect neurological degeneration and contribute to neurodegeneration.
- Respiratory Diseases Group (Principal Investigator: Dr Jaime Signes-Costa Miñana). Potential for collaborations on lung infections, respiratory viruses, co-infections and respiratory surveillance.
- Translational Research Group on Oesophagogastric Cancer (Principal Investigator: Dr Tania Fleitas Kanonnikoff). INCLIVA's infectious disease groups can collaborate with Tania Fleitas and the AIDA project by contributing expertise in the diagnosis, treatment and resistance of *Helicobacter pylori*. They can also participate in clinical trials, microbiome analysis and the validation of AI models. Their joint work would enable the personalisation of therapies and improve the management of precancerous gastritis.
- Associated Clinical Group in Digestive Medicine (Dr Isabel Pascual Moreno)
- Associated Clinical Group in Neurology (Dr José Miguel Láinez Andrés)
- Associated Clinical Group in Urology (Dr José Martínez Jabaloyas)
- Care Research Group. INVESTENF-INCLIVA (Dr Cintia Borja Herrero)
- Cardiometabolic Research Group in Primary Care (Dr Jorge Navarro Pérez).

6.4 Common research areas and actions for their development

These scientific lines form the core around which the actions of the cross-cutting programme will be organised. Each line will include specific actions.

6.4.1 Line 1: Pathogenesis and antimicrobial resistance

- Basic studies of resistance mechanisms (enzymes, mutations, genetic transfer).
- Functional characterisation of emerging and re-emerging pathogens.
- Studies of host-pathogen interactions, innate and adaptive immune responses.
- Development of cellular and animal (in vivo) models for validation.

6.4.2 Line 2: Early diagnosis and biomarkers

- Validation of biomarkers for infection, inflammation and prognosis.
- Development/improvement of rapid diagnostic platforms for genetic or protein detection (PCR or LAMP, microarrays, metagenomics, antigen tests, MALDI-TOF).
- Liquid biopsy, genomics of direct pathogens, detection of resistance.

6.4.3 Line 3: Prevention, therapies and vaccines

- Research into new vaccines or boosters adapted to emerging variants.
- Development of therapeutic strategies, including combination therapies, antibody-based therapies, antivirals, and alternative antimicrobials.
- Immunomodulatory therapies.
- Use of adjuvants, nanotechnologies, and emerging vector platforms.

6.4.4 Line 4: Molecular surveillance and epidemiology

- Monitoring of emerging pathogens through sequencing
- Integration with clinical data
- Predictive modelling and early warning systems.

6.4.5 Line 5: Clinical studies and translation into practice

- Clinical trials of new diagnostic/therapeutic interventions and vaccines.
- Multicentre/international studies.
- Improvement of clinical protocols, guidelines based on molecular evidence.
- "Diagnostic stewardship", optimisation of the use of diagnostic technologies.

6.4.6 Line 6: Technological innovation and digital platforms

- Development of artificial intelligence and machine learning for diagnosis, prognosis and monitoring.
- Integration of big data, omics analysis and advanced bioinformatics.
- Use of precision medicine platforms, biomarkers, mass spectrometry, biobanking, etc.
- Telemedicine, digitalisation, real-time monitoring.

6.5 Innovations in healthcare

This section covers planned innovations, whether technological, organisational, process-related or concerning healthcare products, including those that may lead to technology transfer:

- Development of next-generation diagnostic tests (metagenomics, multiplex PCR, next-generation sequencing applied directly to clinical samples).
- Prediction systems based on artificial intelligence/machine learning to identify outbreaks, individual infection prognosis and risk of resistance.
- Digital health platforms for remote monitoring, follow-up of patients with chronic infections, and treatment adherence.
- New treatments: adaptive vaccines, innovative therapies, alternative antimicrobials, monoclonal antibodies, immunomodulatory therapies.
- Organisational innovations: improved clinical protocols, optimisation of diagnostic workflows ('diagnostic stewardship'), efficient use of laboratory resources, integration of animal and environmental health.

- Technology transfer: patents, spin-offs, collaboration with the pharmaceutical/biotechnology industry and diagnostic companies.

6.6 Actions to promote the integration of the gender dimension

The gender perspective is essential in both basic and clinical research. Specific proposals:

- Include sex/gender-stratified analyses in all clinical studies (incidence, clinical presentation, response to treatment, adverse effects).
- Ensure balanced representation of women in cohorts, trials and diagnostic sampling.
- Assess gender differences in risk factors, environmental exposure, access to diagnosis and treatment, and adherence.
- Promote female leadership in the research groups involved, ensuring equal opportunities in the allocation of resources, participation in committees, publications and project leadership.
- Training and raising awareness among research staff regarding gender bias, bias in study design and data collection.
- Incorporate gender analysis into innovation objectives, for example, diagnostic devices that take into account sex/gender-related physiological differences.

6.7 Annual indicators of intergroup collaboration

To assess the degree of collaboration, effectiveness, impact and continuous improvement, the following indicators, measurable annually, are proposed:

Indicator	**Unit of measurement / suggested annual target**
Number of collaborative projects between at least two programme groups	≥ 1 new project/year
Number of joint publications between the groups involved	≥ 3 indexed publications/year
Number of internal scientific events (seminars, workshops) specific to the programme	≥ 1/year
Technology transfer or translation of results: patents, prototypes, clinical practice guidelines, industry partnerships arising from programme lines	≥1 every 2 years
Shared use of technology platforms (number of services/technologies used by ≥ 2 groups)	At least 1 interaction/year
Inclusion of gender analysis in projects: proportion of projects with sex/gender analysis	≥ 80% of programme projects include such analysis

6.8 Interaction with INCLIVA platforms and rationale

To achieve the objectives, the programme must make intensive and coordinated use of the scientific and technological platforms of INCLIVA and UV. The planned interaction is described below.

Platform	Function / type of support for the programme
Biobank	Supply, storage and management of human (and potentially animal) biological samples with associated clinical data for genomic studies, biomarkers and longitudinal studies.
Precision Medicine Unit	Integration of a personalised approach to the diagnosis, treatment and prevention of infections; patient stratification; identification of individual risk or response profiles.
Biomarker Analysis Unit	Detection and validation of biomarkers for infectious diseases, inflammation, immune response, prognosis and therapeutic monitoring.
Molecular, Cellular and In Vivo Analysis Unit	Basic experimental studies (cell and animal models), pathogenesis testing, functional resistance studies, and validation of therapies and vaccines in preclinical models.
Biostatistics Unit	Statistical study design, sample size calculation, analysis of clinical and molecular data, modelling, validation of predictors.
Bioinformatics Unit	Analysis of omics, genomic and metagenomic data; analysis pipelines; storage/exploitation of big data; integration of clinical and public health data.
Analytical Liquid Chromatography Unit	Analysis of metabolites, small bioactive compounds, drug pharmacokinetics, toxicological analysis.
Mass Spectrometry Unit	Detailed identification of proteins and metabolomes; detection of microcomponents or circulating molecules as biomarkers; proteomic signatures.
UV Flow Cytometry	Multiparametric analysis of cells and microorganisms (immunophenotyping, viability and apoptosis, etc.).

7. APPROVAL AND ENTRY INTO FORCE

This document shall be effective from the date of its ratification until it is replaced by a new version.