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A collection of scientific advances in the research lines of CIC bioGUNE

Future Medicine

CIC bioGUNE
MEMBER OF BASQUE RESEARCH & TECHNOLOGY ALLIANCE

Contents

The Center

CIC bioGUNE is a multidisciplinary research center in Life Sciences that brings together expertise in biology, chemistry, medicine, and computational sciences, covering the full spectrum from fundamental to translational research. Its mission is to uncover the molecular mechanisms underlying disease and to translate this knowledge into the development of innovative therapies. Research at CIC bioGUNE is organized around four key areas of biomedicine—Cancer, Metabolic Diseases, Rare Diseases, and Infectious Diseases—and is structured within two core programs: Metabolism and Cell Signaling in Disease and Molecular Recognition and Host–Pathogen Interactions.

Recognized for its scientific excellence, CIC bioGUNE has been awarded the prestigious Severo Ochoa Seal of Excellence by the Spanish Ministry of Science and has received special acknowledgment from the Spanish Association Against Cancer (AECC) for its contributions to cancer research. Guided by a spirit of collaboration, CIC bioGUNE fosters partnerships with researchers, clinicians, and technology specialists at local, national, and international levels. The center is an active member of the Basque Research and Technology Alliance (BRTA) and operates within a diverse network of academic institutions, clinical organizations, and research and technology centers.

Our work is supported by state-of-the-art infrastructures and cutting-edge technological platforms. These include advanced facilities for nuclear magnetic resonance (NMR), designated as ICTS, electron microscopy, monoclonal antibody production integrated with our animal facility, and comprehensive core platforms for genome, proteome, and metabolome analysis.

General View

Direction

CIC bioGUNE's mission is to establish a leading European hub in biosciences, leveraging cutting-edge technologies to drive innovation in life sciences and health. By enhancing collaboration within the Basque Research and Technology Alliance (BRTA) and partnering with academic, social, and healthcare entities in the Basque Country, CIC bioGUNE optimizes resources to deliver a high-value scientific and technological offering that strengthens the region's biotech and pharmaceutical sectors.

Our research spans from gene studies to animal models, focusing on biomolecular structure, key mechanisms of health and disease, and their clinical applications. With a strong emphasis on precision medicine, CIC bioGUNE aims to unravel the molecular basis of immune defence, cell proliferation, and development to advance healthcare solutions.

Advanced NMR Metabolomics: Mapping the Landscape for Precision Health and Preventive Medicine

José M. Mato and Óscar Millet, *Precision Medicine and Metabolism Laboratory*

The field of metabolic health is undergoing a profound transformation, driven by high-throughput Nuclear Magnetic Resonance (NMR) spectroscopy. This technique is moving beyond traditional biomarkers to provide a detailed, quantitative view of an individual's physiological state, establishing itself as a cornerstone for a new, dynamic framework in precision medicine that shifts from reactive healthcare to proactive, personalized prevention.

The foundation for this approach is the large-scale characterization of the human metabolome. A landmark study in *EBioMedicine*[1] provided an essential baseline by performing comprehensive NMR-based lipoprotein analysis on over 30,000 individuals. This work established detailed reference values for 112 specific lipoprotein parameters, stratified by age and sex. It revealed that the metabolome follows distinct, sex-specific trajectories throughout life, with key inflection points (around ages 44 and 60 in women, and 60 in men) that align with biological aging models. The study confirmed the clinical utility of these profiles, showing that very-low-density lipoprotein (VLDL) parameters were most sensitive for stratifying cardiovascular risk according to the SCORE2 algorithm.

Beyond lipids, NMR uniquely enables the quantification of a composite panel of inflammatory biomarkers from a single serum sample. Research in *PLoS One*[2] characterized such a panel, finding pronounced sexual dimorphism in the SPC2 biomarker (associated with HDL), which was consistently higher in women and inversely correlated with Body Mass Index (BMI). This evidence underscores the necessity of using sex-specific models for accurately assessing subclinical inflammation, a key driver of chronic diseases.

The transformative power of this metabolic mapping is unlocked through multi-omic integration. A study in *NPJ Genomic Medicine*[3] demonstrated that combining NMR-derived serum lipoproteomics and urine metabolomics with genomic data provides far superior risk stratification than any single approach. By applying this integrated method to clinically healthy individuals, researchers identified distinct metabolic subgroups, one of which exhibited a genetic and metabolic signature for dyslipoproteinemias, revealing latent cardiovascular risk long before any clinical symptoms appear.

Building on these maps, the field is advancing towards predictive health analytics using molecular aging clocks. As reviewed in *NPJ Metabolic Health and Disease,*[4] NMR-based metabolomic clocks can estimate biological age with remarkable accuracy, often outperforming chronological age in predicting mortality and morbidity. The latest models are designed to be both predictive and interpretable, identifying the specific metabolic pathways, such as shifts in energy metabolism, lipoprotein remodeling, or inflammation, that are driving accelerated biological aging. This creates a critical window for personalized, preventive action.

In conclusion, the convergence of large-scale metabolomic mapping, inflammatory biomarker discovery, multi-omic integration, and predictive modeling is forging a new paradigm. NMR spectroscopy is at the heart of this shift, providing the data density, precision, and practicality needed to move towards a future where medicine is fundamentally aimed at preserving wellness and preempting disease.

From Omics to Trajectories: Incoming Trends in Preclinical and Multi-omic Precision Medicine

Urko M. Marigorta, *Integrative Genomic Laboratory*

At the Integrative Genomics Lab, we focus on understanding the invisible layers of complex disease. We posit that identifiable molecular trajectories and regulatory shifts emerge long before symptoms or treatment responses are clinically apparent. This year we have deepened our strategic focus, building on several projects aimed at clarifying health-to-disease transitions using longitudinal, multi-omic data. Rather than pure analytical exercises, our goal is to explain the mechanisms and causal pathways that drive immune-mediated disorders, grounding our interpretations in physiology and evolutionary reasoning.

In this context, three key developments in genomic data science are influencing how we pursue this mission. The first one involves the consolidation of the deep change in population biobanks. Rather than massive genomic repositories, top notch initiatives such as the UK Biobank are expanding into multi-omic databases that couple genomics with large-scale proteomics, metabolomics, and longitudinal phenotyping. Fueled by massive cash injections from big pharma, these datasets are growing in depth and coverage, and undoubtedly, multi-omic biobanks already are the essential infrastructure to uncover causal biomarkers.

Coupled with the multi-omic biobank consolidation, the increasing availability of longitudinal data collected years before diagnosis is transforming our understanding of preclinical disease trajectories, well before symptom onset. Recent plasma studies have uncovered novel proteins involved in cardiovascular pathogenesis, illustrating how longitudinal molecular data can highlight early causal drivers and therapeutic targets.[5] Indeed, integrative proteo-metabolomic studies combined with Mendelian randomization pinpoint causal proteins and metabolites shaping risk across disease domains,[6] and combination of polygenic and proteomic risk scores are boosting the potential of predicting disease onset.[7] These developments signal a decisive transition, whereby molecular drift in the preclinical window is no longer invisible, and multi-omic longitudinal resources are the central tool allowing the shift from precision to preventive multi-omic medicine.

Finally, as multi-omic datasets expand in scale and modality, the field increasingly depends on computational tools to manage this complexity and extract biological insights. Incoming high-performance software allows for efficient handling of heterogeneous data spanning thousands of features across tissues, individuals, and timepoints.[8] In parallel, advances in deep learning, as shown by long-context models such as DeepMind's AlphaGenome,[9] improve the prediction of key regulatory and functional properties directly from DNA sequences at million basepair resolutions.

Looking ahead, new developments will converge towards a shared goal to make early disease states increasingly measurable and interpretable. Rather than identifying "who has a disease", the field will aim an understanding of how individual trajectories diverge long before symptoms appear. Towards this purpose, readouts of molecular drift will have to be integrated with clinical and environmental contexts to interpret how disease onset can be anticipated. Our contribution will lie in clarifying the mechanisms that underpin health-to-disease transitions, helping to move precision medicine upstream (towards genuinely anticipatory approaches).

Computationally Guided Rejuvenation: Emerging Strategies for Safe and Targeted Interventions

Antonio del Sol and Sascha Jung, *Computational Biology Laboratory*

Aging arises from the gradual loss of tissue homeostasis, driven by interconnected changes in epigenetic regulation, cellular identity, immune function, and microenvironmental signaling, ultimately leading to the development of age-related diseases. As these diseases already constitute more than half of the global healthcare burden, the need for safe and effective rejuvenation strategies continues to grow. In recent years, partial reprogramming has emerged as a promising approach for reversing age-associated cellular dysfunction. However, safety concerns still impede direct clinical translation. At the same time, the field has begun to move beyond gene therapies, with a conceptual shift toward computational models that help design safe and tissue-specific rejuvenation strategies acting across multiple aging mechanisms.

A notable development this year has been the integration of aging clocks with high-throughput small-molecule screens to discover rejuvenating compounds with translational potential. For example, a brain-specific transcriptional aging clock has been developed to score thousands of compounds for their ability to revert age-associated gene expression patterns.[10] As a result, a combination of three compounds has been identified that was demonstrated to phenotypically rejuvenate brain cells and improve cognitive function in a preclinical aging model. A related study generalized this strategy to any human cell type and identified more than 300 chemical compounds that exhibit rejuvenating effects.[11] These advances highlight how aging clocks can be operationalized as screening tools for early-stage therapeutic discovery.

In parallel, we have witnessed a notable evolution of aging clocks themselves. Whereas earlier clocks primarily estimated biological age, modern clocks provide interpretable descriptions of tissue-specific aging processes and are increasingly used as actionable readouts in interventional studies. Their ability to detect pathway-specific rejuvenation signatures makes them ideal tools for evaluating the efficacy of novel therapies, including senolytics, metabolic modulators, and controlled reprogramming approaches.[12,13] Concurrent to the development of novel computational approaches, the first translational pipelines for rejuvenation interventions have emerged. Small-scale human studies of senolytics have moved into Phase-1 clinical trials and reported exploratory biomarker readouts and safety data from blood and cerebrospinal fluid measures.[14] In addition, partial reprogramming strategies have been further optimized in preclinical settings for the precise temporal control and tissue-specific delivery using inducible, cyclic expression systems[15]. Although full clinical translation remains ahead, these studies show the field shifting toward rigorously designed translational pipelines that combine molecular biomarkers with mechanistically informed intervention strategies.

In the coming years, computational approaches will increasingly serve as the organizing framework that guide the design of multi-target interventions, optimize combinations maximizing rejuvenation while minimizing risks and support personalized treatment strategies that reflect each tissue's unique aging trajectory. As a result, rejuvenation biology is expected to transform from an exploratory science into a programmable, clinically actionable field.

Programmable and High-Fidelity Genome Writing: Toward Safer and Predictable Synthetic Biology

Raúl Pérez-Jiménez, *Synthetic Biology Laboratory*

Genome engineering is increasingly constrained not by efficiency, but by the need for precision, predictability, and genomic safety. Traditional CRISPR-based approaches rely on double-strand DNA breaks to introduce genetic changes, a strategy that has proven powerful but intrinsically linked to undesired mutations, chromosomal rearrangements, and activation of DNA damage responses. As genome editing technologies move closer to clinical and industrial translation, the field is shifting toward break-free, programmable strategies that enable controlled genome rewriting with minimal collateral damage.

Prime editing has emerged as a key innovation in this transition, enabling precise substitutions, insertions, and deletions without generating double-strand breaks. However, its widespread application has been limited by the frequent appearance of insertion and deletion (indel) by-products. A recent study demonstrated that these errors arise from competition between the edited 3′ DNA strand and the unedited 5′ strand during repair, revealing a previously underappreciated mechanistic bottleneck in prime editing fidelity.[16] By engineering Cas9 nickase variants with relaxed nick positioning, the authors were able to bias strand resolution toward the edited product, promoting degradation of the competing unedited strand. This protein-engineering strategy culminated in the development of the "very precise prime editor" (vPE), which achieves up to a 60-fold reduction in indel formation and edit-to-indel ratios exceeding 500:1 while maintaining high efficiency across diverse cell types and editing contexts. Importantly, vPE also exhibits reduced off-target activity and robust performance in functional cellular assays, demonstrating that nuclease engineering can fundamentally redefine the safety profile of prime editing.

In parallel, the field has begun to address a complementary challenge: the precise insertion of large DNA sequences without double-strand breaks. A recent advance introduced a laboratory-evolved CRISPR-associated transposase system, evoCAST, capable of RNA-guided gene insertion in human cells.[17] Using phage-assisted continuous evolution, key components of a bacterial CAST system were adapted for efficient function in eukaryotic genomes, resulting in up to 30% integration efficiency across multiple genomic loci and a dramatic improvement over the wild-type system. EvoCAST enables high-purity, programmable insertion of therapeutic genes at clinically relevant sites, with minimal off-target effects and robust activity across cell types.

Together, these advances illustrate a broader conceptual shift in genome engineering, from inducing DNA damage to writing genetic information with molecular precision. By combining high-fidelity prime editors with evolved transposase systems, synthetic biology is moving toward a future in which genome modification becomes a predictable, modular, and safe engineering discipline.

Trained Immunity as a Dynamic Continuum: Moving Beyond Outdated Dichotomies

Juan Anguita, *Inflammation and Macrophage Plasticity Laboratory*

Work published in 2025 has refined the conceptual and mechanistic landscape of trained immunity, with particular emphasis on how microbial components and metabolites

influence both peripheral and central programs. Several reviews have clarified terminology and biological scale. For example, Damani-Yokota and Khanna[18] distinguish short-lived, tissue-restricted macrophage memory from long-term programs rooted in hematopoietic stem and progenitor cells (HSPCs), establishing peripheral and central trained immunity as complementary layers. Their review further highlights the translational potential of leveraging trained immunity not only for infection and vaccination, but also for chronic disease and cancer. Liao and cols.[19] underscore that trained immunity exists along a continuum ranging from beneficial enhanced responsiveness to maladaptive, chronically primed inflammatory states. This framework aligns closely with our group's findings,[20] which experimentally demonstrate that trained immune responses are highly plastic and tunable, reinforcing the idea that the same molecular circuits can yield protective or pathological outcomes depending on context, stimulus intensity, and metabolic conditions. This duality is exemplified by BCG-trained macrophages that exhibit maladaptive hypercoagulability following LPS stimulation.[21] The concept of long-term memory has also been expanded to tissue specific stem cells, including those in the gut, as well as non-immune cells such as epithelial cells.[22] These studies position trained immunity within infection, autoimmunity, and metabolic disease, emphasizing microbial and metabolite-derived cues as systemic drivers of chronic inflammatory memory.

Mechanistic studies have extended these principles by showing that microbial components can directly reprogram the bone marrow. Robles-Vera and cols.[23] recently demonstrated that intestinal barrier disruption permits Enterococcus faecalis translocation to the bone marrow, eliciting Mincle-dependent progenitor training. Microbiota-linked metabolites have emerged as equally potent modulators. Yang and cols.[24] integrate SCFAs, bile acids, TMAO and tryptophan derivatives as upstream regulators of trained immunity in chronic inflammatory states. These studies highlight the close relationship between the functional disruption of microbiota and innate immune responses in the long-term. In this context, our group[25] recently proposed a unified model linking microbial ligands, metabolites and barrier physiology to both peripheral and central memory, while Pederson and cols.[26] outline systems-level strategies combining metagenomics, metabolomics and immune profiling to map these consequential microbiota–HSPC interactions.

Collectively, these studies converge on a model in which microbial components, microbial translocation events, and microbiota-derived metabolites act along a peripheral–central axis to calibrate innate immune memory. This positions microbiota-based interventions, metabolite modulation and barrier-focused strategies as opportunities for reshaping pathological or protective trained immune states.

Shedding Light on the Sugar Code: Imaging Advances and Emerging Glycoimmune Therapies

June Ereño-Orbea, *Cancer Glycoimmunology Laboratory*

Glycoscience, the study of how glycans (sugars) shape cell behaviour, is moving fast, driven in part by new super-resolution imaging tools. Monosaccharides, the ångström-scale building blocks of glycans, assemble into the complex structures that form the glycocalyx, a dense sugar coat surrounding every cell. This layer has a major impact on immune recognition, cancer progression, infection, and inflammation. Yet the field still faces a major challenge: we have lacked the ability to see these sugars in their native molecular context. Glycans are incredibly diverse and flexible, and traditional methods (mass spectrometry, EM, crystallography, NMR, or standard fluorescence imaging) fail to provide both high resolution and cellular context simultaneously. Without molecular-level visualization, linking specific glycan structures to cell functions remains difficult. A major turning point in 2025 came with techniques capable of imaging the glycocalyx at near-molecular resolution. A landmark study[27] combined sequential-imaging–based resolution enhancement with metabolic labeling of specific monosaccharide analogues, achieving ~9 Å resolution in an optical microscope. For the first time, individual sugars on live-cell surfaces could be directly visualized, revealing nanoscale features long hypothesized but never seen. This ability to selectively tag and image defined monosaccharides opens up exciting possibilities for studying how glycan architecture regulates receptor clustering, phagocytosis, viral entry, and immune checkpoint signaling.

Progress in glycoimmunology, the branch of glycobiology focused on immune responses, was also highlighted throughout the 2025 Gordon Research Conference on Glycobiology (Italy) and the Glyco27 Conference (Canada), where I had the chance to hear outstanding talks from the groups of Dr. Stark (Massachusetts Institute of Technology ((MIT), USA), Prof. Rabinovich (Institute of Biology and Experimental Medicine (IBYME), University of Buenos Aires (Argentina)), and Dr. Läubli (University of Basel (Switzerland)). Their work showcased how tumours exploit "glycoimmune checkpoints," where glycans and glycan-binding receptors suppress anticancer immunity. The laboratory of Stark presented antibody–lectin chimeras (AbLecs), engineered molecules that block inhibitory Siglecs and boost macrophage phagocytosis, outperforming combinations of classical antibodies. Because they are modular, AbLecs can be paired with PD-L1-targeting antibodies, creating a powerful link between glyco-immunology and conventional checkpoint inhibition. Rabinovich focused on galectin-1, a secreted lectin that shapes immune suppression by modulating T-cell differentiation, dendritic cell interactions, and myeloid-cell programs. His group's analysis of cancer datasets revealed that high galectin-1 expression correlates with elevated myeloid-derived suppressor cell (MDSC) activity and worse clinical outcomes, especially in colorectal cancer. Blocking galectin-1 reprogrammed these suppressive cells, reduced tumor growth, and even reversed fibrosis in myelofibrosis models.

Together, these developments point toward a genuinely "sweet" future for immunotherapy, one where decoding and targeting glycan interactions play a central role in next-generation cancer treatments and immune-modulatory strategies.

New Advances in Glycosciences

Ana Ardá, Ana Gimeno, Jesús Jiménez-Barbero and Luca Unione, *Chemical Glycobiology Laboratory*

Glycan-mediated molecular recognition underlies numerous biological processes, including cell adhesion, immune regulation, pathogen–host interactions, and the control of protein trafficking and stability. Research in the Chemical Glycobiology Lab focuses on elucidating the structural basis of these interactions, primarily involving glycan-binding proteins (lectins) and immune-related glycoconjugates,[28,29,30,31] as well as glycans implicated in bacterial[32] and viral infections.[33] Particular attention has been devoted to galectins (Gals), key players in decoding the glyco-code. We have contributed to defining how Gal-9 binding to HLA-DR on dendritic cells regulates immune synapse formation and T-cell proliferation.[34] In parallel, tandem-repeat Gals,[35] as Gal-4,[36] Gal-8,[37] or Gal-9,[38,39,40] the chimera-type Gal-3,[41] or the prototype galectin Gal-1[42,43,44,45] have emerged as promising therapeutic targets, supported by growing evidence of their immunosuppressive roles in cancer.

In 2025, significant efforts were devoted to the study of GlycoRNA, a recently described class of glycoconjugates first reported in 2021. Although its existence and characterization remain debated—particularly due to purification challenges and the detection of non-RNA glycoconjugates[46,47] —several studies

have proposed potential biological functions or introduced new analytical tools.[48,49] Notably, N-glycosylation of small RNAs has been suggested to prevent recognition by innate immune receptors, enabling non-inflammatory clearance of dead cells.[50] In addition, reported interactions with endogenous lectins point to possible roles in immune regulation.[51]

Technological innovation remains central to advancing glycoscience, given the intrinsic diversity and complexity of glycans. NMR studies in our lab have enabled monitoring of glycan–lectin interactions in living cells.[52] Furthermore, recent advances in super-resolution microscopy are transforming the study of the glycocalyx, allowing visualization of its spatial heterogeneity and molecular organization. Single-molecule techniques such as Glyco-STORM[53] and Lectin-PAINT[54] provide multiplexed, super-resolution maps of surface glycoproteins[55] and glycan epitopes,[56] achieving sub–10 nm precision and enabling quantitative cell glycotyping beyond conventional lectin assays.[57] Complementary bottom-up models of synthetic glycocalyces, visualized by interferometric scattering microscopy,[58] reveal how glycan composition influences membrane mechanics and diffusion. Finally, computational approaches such as glycan spatial-coordinate simulations[59] integrate experimental data to predict glycocalyx architectures. Together, these advances position glycocalyx imaging as a key frontier in cell biology and biomedical research. Finally, from the AI-perspective, the open access GlyContact code allows exploring glycan structures within their 3D space, opening new avenues to get new insights into their biological functions.[60]

We look forward to future developments in this exciting field and are excited about the current developments in our lab, which we will show in the coming months!

Adjuvants and Vaccines Intersect Chemistry and Immunology

Alberto Fernández-Tejada, *Chemical Immunology Laboratory*

The clinical success of anticancer and antiviral vaccines often requires the use of an immunological adjuvant, a substance that helps stimulate and direct the body's immune response to the vaccine, making it work better. However, few adjuvants are sufficiently potent and non-toxic for clinical use; moreover, it is not really known how they work. Current vaccine approaches based on weak carbohydrate and glycopeptide antigens are not being particularly effective to induce the human immune system to mount an effective fight against cancer. Despite intensive research and several clinical trials, no such carbohydrate-based antitumor vaccine has yet been approved for public use. In this context, the research topic in the Chemical Immunology group has a double, far-reaching goal based on applying chemistry to address the above clear gaps in the adjuvant/vaccine field.

Saponins derived from the South American tree bark Quillaja Saponaria (QS), e.g QS-21, increase the immunogenicity of the vaccine antigen, boosting the immune response. QS-21 is approved as a component of the AS01 adjuvant system (a liposomal formulation together with MPLA (monophosphoryl lipid A) in malaria (RTS,S antigen), shingles and RSV (respiratory syncytial virus) vaccines, for which it has been associated with a lower risk of dementia.[61] More recently, a related mixture of saponin and MPLA adjuvants has been developed, which forms a cage-like nanoparticulate structure resembling saponin-based immune stimulating complexes (ISCOMs). This adjuvant combination, termed SMNPs, has been found to elicit dose-dependent HIV vaccine responses in non-human primates,[62] highlighting its relevance for potential human use in the future. Another formulation incorporating saponin adjuvants that has gained clinical approval is the Matrix-M nanoparticulate system used in Novavax's COVID-19 vaccine. This adjuvant has also been evaluated as part of a novel anti-sporozoite malaria vaccine candidate in combination with the R21 antigen,[63] marking the first-in-human trials with similar or improved efficacy than the commercial RTS,S/AS01 vaccine. Moreover, a recent work has been published on the mechanism of Matrix-M, showing that it triggers inflammasome activation and enables antigen cross-presentation by inducing lysosomal membrane permeabilization.[64] Another study has investigated the mode of action of saponin-based adjuvants formulated as ISCOMs, finding cell-specific uptake by CD11b+ dendritic cells and bone-marrow derived macrophages (BMDMs) via clathrin-mediated endocytosis, which resulted in induction of lipid bodies and antigen translocation, leading to antigen cross-presentation and subsequent CD8+ T-cell activation.[65]

Regarding the development of carbohydrate-based vaccines, there have been a couple of studies published this year, both involving conjugation of the corresponding immunogen to the CRM197 carrier protein and coadministration with QS-21 as an adjuvant. In the first case,[66] the Globo-H hexasaccharide antigen was prepared via chemoenzymatic synthesis and its CRM197 conjugate was evaluated formulated with various adjuvants, discovering a mixture of QS-21 and a synthetic 3-O-deacyl-MPLA derivative (3D-MPL) as the best adjuvant combination for inducing robust antitumor immunity. Most recently, we have developed a semi-synthetic vaccine platform incorporating tumor-associated taMUC1 glycopeptides displayed in monovalent form or as tetravalent clusters

on synthetic cyclopeptide scaffolds grafted onto CRM197.[67] In mouse immunizations, the tetravalent conjugate coadministered with QS-21 induced high levels of functional antibodies reactive against cancer cells expressing the native taMUC1 glycoprotein, providing a new conjugate vaccine approach based on a scaffold-assisted antigen presentation strategy.

In 2025, a structure-activity relationship study has been published describing the impact of the length of the saponin side chain on adjuvant activity, which led to the identification of two promising analogues with longer carbon chains (i.e. n=14, 12) than a simplified QS-21 variant (TQL-1055, n=10).[68] Moreover, two very interesting review articles have reported the most recent advancements in saponin-based adjuvants and their mechanisms of action,[69,70] which sets the stage for the submission of our latest studies in the field that we aim to publish in the upcoming year.

Technologies and Concepts to Understand Cancer Cell Signaling and Metabolism

Arkaitz Carracedo, *Cancer Cell Signaling and Metabolism Laboratory*

Cancer remains a major health and societal challenge and requires individualized clinical management in the era of precision medicine. In line with this notion, the study of the fundamental bases of cancer requires more granularity, which calls for better experimental models and more advanced computational and experimental approaches. We have focused our literature survey and update for 2025 on three main research areas:

Cancer metabolism. Cancer cells reprogram their metabolic landscape to adapt to microenvironmental constrains. A major metabolic process activated in cancer cells downstream oncogenic signals is polyamine biosynthesis. This year unprecedented polyamine-activating molecular pathways have been reported in prostate cancer, linking androgen signaling to the production of this family of metabolites.[71] Since polyamine production requires the availability of key substrates (methionine, arginine, ornithine) whether nutritional interventions can be exploited to reduce the biosynthesis of these metabolites rises as a clinically relevant question. A recent report demonstrates that

a tumor type that is highly dependent on polyamines, neuroblastoma, can be treated through dietary restriction of arginine and proline, thus strengthening the notion that nutritional plans could be used adjuvant to pharmacological treatments.[72] In line with this notion, caloric restriction in specific diets could promote ketosis, which might influence nutrient availability in tumor cells. Interestingly, a report in 2025 demonstrates that tumor cells can use ketonic bodies (beta hydroxybutyrate) as an alternative nutrient source through an unprecedented acetyl Coa synthesis route.[73]

Molecular processes underlying disease aggressiveness. The field has come to realize that cancer cell state is a major determinant of disease aggressiveness. This is especially relevant when tumor cells face different microenvironmental stresses, including therapies. Cancer cell state can be influenced by genomic or epigenomic changes. Cancer cells exposed to anticancer treatments exhibit a window in which they remain alive without signs of therapy resistance. This growth arrest phase is termed drug tolerance and is thought to represent the seed for the appearance of resistant mutant cells. Recently, a study reported a comprehensive analysis of drug tolerance in triple negative breast cancer in the search for common molecular traits of these cells, which led to the identification of FOSL1 as a major driver of this phenotype.[74] The transition of drug tolerant persister cells to resistance cells is poorly understood, and it would require genetic mutations to consolidate. Using a drug-tolerant cancer cell model system, a recent study discovered that these drug tolerant cells activate DNA Fragmentation Factor B (DFFB) upon sublethal apoptotic stress, which supports the acquisition of mutations.[75] The complexity of measuring DNA damage and mutations increases when monitoring precancerous lesions or normal tissues, which has inspired new methodologies to assess this process with high resolution.[76,77]

Technology-driven enhanced cancer resolution. Cancers are heterogeneous organ-like structures, inhabited by tumor and non-tumoral cells. In turn, we need single cell resolution to better understand the changes that underlie the biology of the disease. Whereas single cell sequencing is well established and broadly utilized, proteomics remains a bulk strategy. This year, single cell proteomics has shown great advances, which has allowed the study and classification of neutrophils in glioblastoma.[78] Similarly, single cell-level technologies that retain topographical information in the tumor have been instrumental to study tumor-stroma interaction, as is the case in a recent publication focused on prostate cancer.[79] Lastly, the increasing number of molecular layers creates analytical bottlenecks, that promote the development of new computational strategies to integrate data, such as the MORE R package.[80]

Regulatory Programs, Disease States and Computational Views of Tumour Diversity

Isabel Mendizabal, *Precision Cancer Multiomics Laboratory*

Prostate cancer is unusual among common malignancies in that it lacks a strong set of recurrent genomic drivers. This makes it a useful system for studying how regulatory architecture, cellular context and tissue organization, not only mutations, shape tumour behaviour. Our work approaches this from three angles: understanding the regulatory programs behind progression, comparing molecular features across prostate disease states, and using computational methods to relate molecular profiles to tissue architecture. We posit that this integrative approach is essential for building more precise, biologically informed cancer management.

In 2025, a unifying message was that epigenetic information reveals aspects of tumour evolution that genetics alone cannot. A large study showed that cell-population variability in DNA methylation patterns trace the branching and timing of tumour growth and capture lineage history invisible to DNA sequencing.[81] Work in colorectal cancer reported that early immune evasion can arise from epigenetic reprogramming even with minimal genomic alterations,[82] while lung cancer studies demonstrated that methylation patterns modulate how genomic alterations influence clonal diversification.[83] Together, these findings illustrate how regulatory layers integrate environmental cues to drive differences between disease states and shape evolutionary trajectories.

A second theme this year was the growing ability to modulate regulatory programs in a targeted manner. In prostate cancer, H2B N-terminal acetylation is a mark supporting enhancer-driven transcriptional programs and disrupting collapsed oncogenic activity.[84] In immune cells, combined genetic and epigenetic editing reshaped T-cell identity.[85] Although our group does not focus on editing, these studies highlight why detailed maps of regulatory states matter. They reveal vulnerabilities that may become therapeutically actionable as these technologies mature.

The rapid advance of AI in oncology became unmistakable in 2025. One study even showed that a clinical agent built on the same technology behind ChatGPT (GPT-4) could reach treatment recommendations comparable to specialist tumour boards.[86] In pathology, emerging models can infer molecular and microenvironmental features that escape visual inspection for refined grading and support outcome prediction, although concerns about the limitations in generalization, bias and clinical validation remain.[87,88] These developments resonate with our third research line, namely that as tumours are now profiled through increasingly rich molecular and imaging data, computational pathology and AI are becoming essential tools for interpreting tumour organisation.

Looking to 2026, progress will likely come from approaches that treat cancer as a system shaped by its molecular signals and tissue environment. This year's studies highlight how these dimensions jointly influence tumour behaviour and create fertile ground for work at the molecular-pathology interface. Our work follows this direction by uniting multiomics, disease-context comparisons and computational models of tumour organization.

HER2-Targeted Antibody-Drug Conjugates in Breast Cancer: Mechanisms, Efficacy and Resistance

Samuel Pasco, Uxue Armendariz and Ana Ruiz-Sáenz, *Cancer Therapy Resistance Laboratory*

Breast cancer (BC) is the most common cancer among women, and approximately 30% of cases are classified as HER2-positive (HER2+), characterized by overexpression of the HER2 oncogene that drives tumor progression. HER2 has been a key therapeutic target since the 1990s, leading to the development of trastuzumab, the first HER2-targeted monoclonal antibody, which revolutionized treatment by inhibiting HER2 signaling and engaging the immune system.[89] For decades, trastuzumab has significantly improved clinical outcomes for HER2+ BC patients.

More recently, antibody-drug conjugates (ADCs) have emerged as a major innovation. By linking HER2-targeted antibodies to highly potent chemotherapeutic agents, ADCs enable precise delivery of cytotoxic payloads directly to cancer cells, enhancing efficacy while minimizing off-target toxicity. The principal first- and second-generation HER2-targeted ADCs are trastuzumab-emtansine (T-DM1) and trastuzumab-deruxtecan (T-DXd), respectively. T-DXd has shown remarkable success in BC trials compared to,[90] trastuzumab,[91] and T-DM1.[92] Beyond its

success in BC, T-DXd has also demonstrated efficacy in HER2+ gastrointestinal[93] and other solid tumors.[94] More surprisingly, its success in HER2-low cancers[95] is upending the current understanding of targeted therapy mechanisms. One possible explanation is the unique design of T-DXd: its topoisomerase I inhibitor payload is permeable and linked via a cleavable linker that releases the drug inside lysosomes, allowing it to diffuse into neighboring tumor cells and exert a potent "bystander effect". Additionally, the payload can also be cleaved extracellularly, activating tumor-resident macrophages and further contributing to its antitumor activity.[96]

Despite its success, many patients fail to respond. Identified T-DXd resistance mechanisms include loss of HER2 expression and impaired antibody binding;[97] truncation of HER2's extracellular domain which promotes an immunosuppressive phenotype;[98] activation of compensatory DNA repair pathways;[99] mutations in DNA repair gene SLX4[100] and circular RNA-mediated inhibition of ferroptosis.[101] While there is an increased focus on tumor immune infiltration, questions remain about the cancer-immune crosstalk determining treatment success, particularly for T-DXd which retains its ability to engage the immune system.[102] High expression of B cell/immunoglobulin signature, which is incorporated into the HER2DX molecular assay that predicts response to trastuzumab-based therapy, associates with an ~50% reduction in fatality regardless of age, subtype, or tumor stage.[103] Regarding T-DM1, in tumors with high immune infiltration before treatment, the immune score remained largely unchanged, whereas in tumors with low immune infiltration before treatment, there was a significant increase in immune infiltration after treatment,[104] suggesting mechanisms beyond leukocyte infiltration contribute to response.

As more data on ADCs becomes available, particularly in HER2-low patients and in other cancer types, we expect more developments in identifying determinants of response and resistance to ADCs. Furthermore, the possibility of multiload ADCs[105] would allow for inhibiting additional resistance pathways to improve therapy outcomes.

Breast Cancer Heterogeneity and Resistance to Therapy

Maria dM Vivanco, *Cancer Heterogeneity Laboratory*

An impressive collection of data of varied sources has been accumulating over the last few years in breast cancer research. However, accurate survival prediction in breast cancer remains a key challenge in oncology. Models that integrate clinical, molecular, and imaging data, often called multimodal artificial intelligence (AI) models, could help guide breast cancer management in several influential ways: risk stratification, personalised treatment selection, early identification of resistance and generation of recommendations to support clinicians.[106]

Comprehensive integrated analysis of multi-omics data is increasingly used in cancer research, however, combining data from multiple modalities is complex and machine learning approaches are being instrumental for survival prediction.[107,108] We have recently taken advantage of the publicly available datasets from The Cancer Genome Atlas (TCGA), which integrate clinical, omics, and histopathology imaging data for thousands of breast cancer patients. We integrated these data and used multimodal deep learning models (combining robust preprocessing, late-fusion strategies, and rigorous validation) to identify biologically relevant features linked to patient survival that highlight the potential of multimodal approaches to advance prognostic modelling in breast cancer.[109] It is hope that further and more sophisticated integration approaches can contribute to increasingly personalised breast cancer management, reducing overtreatment and improving outcomes and quality of life.

Network medicine considers the complexity of disease and biological systems to overcome the limited view that aimed to identify a single drug target for each disease.[110] Breast cancer is notorious for its complexity and massive impact in society, with 2,308,897 new cases diagnosed in 2022 worldwide.[111] Current challenges in breast cancer management include inter- and intratumor heterogeneity, which hinder accurate diagnosis and effective treatment. In particular, intratumour heterogeneity and the presence of cancer and dormant stem cells contribute to the emergence of resistance to existing therapies, and create difficulties in determining the most effective combinations of systemic treatments.[112,113,114,115]

Cancer onset, progression, and metastasis are profoundly shaped by microenvironmental cues within the tumor niche. Among these, the extracellular matrix (ECM), a complex, dynamic, three-dimensional (3D) macromolecular network, plays a pivotal role in regulating cell behaviour and driving tumour growth and dissemination.[116,117,118] Once regarded as a passive scaffold, ECM is now recognized as a key regulator of tissue homeostasis and tumorigenesis. Comprising over 300 macromolecules, collectively termed the matrisome, the ECM orchestrates biochemical and biomechanical cues that govern cell morphology, signaling, and intercellular communication.[119] Dynamic ECM remodeling underpins mammary gland organization and stemness, while its dysregulation drives tumor initiation, progression, and metastasis.[120]

Developing advanced 3D in vitro cancer models incorporating ECM-based bioscaffolds offers a promising strategy to bridge the gap between preclinical research and clinical trials by closely recapitulating the tumor microenvironment.[121,122,123] Such platforms enhance the physiological relevance of drug testing by replicating cell-cell and cell-matrix interactions observed in vivo, ultimately enabling more accurate predictions of therapeutic efficacy.[124] Despite extensive insights into epithelial–microenvironment crosstalk, improved culture models remain essential to capture tissue heterogeneity and accelerate the development of preventive strategies and selective combinatorial therapies for breast cancer.[125]

Harnessing Immunity in Liver Cancers: Breakthroughs and Risks of Checkpoint Inhibitors

Malu Martínez-Chantar, *Liver Disease Laboratory*

Immunotherapy has transformed cancer treatment worldwide, particularly with the rise of immune checkpoint inhibitors (ICIs). These therapies unlock the immune system's ability to fight cancer and have shown remarkable results in several tumors, including hepatocellular carcinoma (HCC) and biliary tract cancers. However, these liver tumors often develop in patients with chronic liver disease, which makes treatment more complex. In these cases, doctors must carefully balance the potential benefits of ICIs with the risks of worsening liver function or triggering immune-related side effects. Adding to the challenge, the liver itself is also a common site of toxicity for ICIs used in cancers outside the liver, and there is still no reliable way to predict who is at risk. This creates an urgent need for new tools to guide therapy and protect liver health.

Throughout 2025, scientific progress has deepened our understanding of both the efficacy and toxicity of ICIs in liver disease. Studies continue to support the use of anti-PD-1 and anti-CTLA-4 therapies in HCC, particularly in combination with anti-VEGF agents, which improve response rates and survival.[126,127] However, new work has focused on how chronic inflammation and fibrosis shape the liver's immune environment, potentially reducing ICI effectiveness. Immunosuppressive cell populations, such as regulatory T cells and myeloid-derived

suppressor cells (MDSCs), are abundant in cirrhotic livers and may hinder anti-tumor responses.[128]

At the same time, 2025 has brought significant insights into ICI-induced liver injury, a growing concern in patients with or without liver tumors. The immune-related hepatitis seen with ICI therapy differs mechanistically from classical autoimmune hepatitis and presents variably depending on the baseline liver status.[129] For instance, patients with cirrhosis may show silent hepatic decompensation without classical signs of hepatitis, complicating diagnosis and management. Recent research has also compared liver toxicity in cancer patients with underlying hepatitis B/C infection versus those with non-viral liver disease, revealing distinct immune signatures and patterns of injury.[130]

Molecular profiling and single-cell sequencing have been critical tools in mapping these differences. For example, altered expression of PD-L1 in non-parenchymal liver cells, and reduced activity of intrahepatic CD8+ T cells, may contribute to poor response and increased toxicity. Research also highlights the role of gut-liver immune interactions, suggesting that microbiome composition influences both ICI efficacy and hepatotoxicity (2).

Looking ahead to 2026, we expect the field to focus on identifying predictive biomarkers to better select patients for ICI therapy and personalize immunosuppression when toxicity occurs.[131] Ongoing trials are testing combination strategies that include TGF-β inhibitors, IL-10 modulators, and microbiome-directed therapies to enhance antitumor immunity while minimizing liver injury. There is also rising interest in prehabilitation protocols—optimizing liver health before immunotherapy—to reduce the risk of decompensation.

From a societal perspective, these innovations promise to extend survival and quality of life for liver cancer patients and those with chronic liver disease receiving ICI therapy. However, equitable access to these diagnostics and therapies remains a key concern, particularly in low-resource settings. The challenge for 2026 will be to translate these immunological insights into safe, scalable clinical practice.

Modifications by Ubiquitin-Like Proteins in Health and Disease, Tools and Strategies

Rosa Barrio and James D. Sutherland, *Ubiquitin-likes and Development Laboratory*

Our lab investigates how development and disease are controlled by Ubiquitin-like (UbL) post-translational modifications (PTMs), which regulate key cellular processes by altering protein stability and function. Studying these transient, low-abundance modifications is challenging. To overcome this, we have pioneered biotin-based tools,[132,133,134,135] including our pioneering platform, BioE3,[136] to identify targets of E3 ligases. This work is crucial for advancing Targeted Protein Degradation (TPD), a therapeutic strategy that harnesses the cell's own machinery to eliminate disease-causing proteins. We apply these methods to study rare diseases, such as Townes-Brocks Syndrome (TBS, caused by SALL1 mutations) and other rare disorders linked to E3 ligase dysfunction. Research is increasingly focusing on E3 ligases due to their diversity and specificity, as well as on deubiquitinases (DUBs) and non-protein substrates of ubiquitination.[137]

The BioE3 strategy has enabled the study of complex E3 ligases, such as Cullin4-CRBN.[138] This work revealed that treatment with the molecular glue pomalidomide rewires the cellular ubiquitin landscape, a critical consideration when applying Targeted Protein Degradation (TPD) strategies in humans. Furthermore, BioE3 was adapted for use in miniaturized microfluidic devices (Picowells), facilitating the screening of new molecular glues that degrade GEMIN3 by recruiting the Von Hippel-Lindau (VHL) E3 ligase.[139] This miniaturized approach will accelerate the discovery of novel chemical molecules for use as protein inhibitors or as warheads for new degraders.

Concurrently, new high-throughput strategies are emerging to identify targets for molecular glue degraders[140] and to screen chemicals that bind E3 ligases with different affinities,[141] highlighting the growing need for innovative methods to optimize drug discovery. The field is advancing rapidly, with new degraders being developed for various diseases[142] and PROTACs such as ARV-471 and ARV-766 (targeting the estrogen and androgen receptors, respectively) now in Phase III clinical trials.[143]

Simultaneously, the frontier of non-protein ubiquitination continues to advance. Specific E3 ligases are key to this process, enabling the ubiquitination of non-protein molecules. Key examples include DELTEX E3 ligases targeting nucleic acid-linked adenosine diphosphate ribose (ADPr) and the SCFFBS2/ARI1H complex modifying N-acetyl glucosamine residues on Nrf1. These findings demonstrate that E3 ligase specificity underpins this unconventional yet significant biological mechanism. For instance, Bejan et al. studied the crosstalk between mono-ADP-ribosylation and ubiquitination (MARUbylation)[144] on various PARP proteins. Non-proteins ubiquitination may occur during DNA damage, immune responses, or bacterial infection. Kloet et al. identified the zinc-finger E3 RNF114 as an interactor of ubiquitinated ADP-ribose that can elongate its ubiquitin chains, suggesting RNF114 acts as a reader of ADPr-Ub during DNA damage.[145]

Finally, studying the etiology of rare diseases is crucial for understanding their causes, consequences, and for developing strategies to improve patients' lives. Recent progress in Townes-Brocks Syndrome (TBS) includes a comprehensive analysis of new patients, mutations, and phenotypes,[146] including an exhaustive study of the Japanese TBS population.[147] Research in animal models has uncovered the role of SALL factors as negative regulators of growth and lipid storage (Drosophila).[148] Intriguingly, truncated SALL1 sequesters SALL4 into heterotetramers that are defective in DNA binding, providing new insights into TBS etiology.[149]

The TPD field will continue to grow in the coming year. Key priorities include identifying novel E3 ligases with diverse specificities, such as those in specific subcellular localizations, cell types, or organs, as well as developing new methodologies to identify chemical binders for those E3s. A new challenge for TPD is the application of this strategy to diseases beyond cancer, such as neurodegeneration or rare diseases. On the other hand, the characterization of non-protein ubiquitination is still in its infancy, and we expect to see new developments in the modifications of sugars, lipids, and nucleic acids. A specific challenge will be the development of new strategies to identify these modifications *in vivo*.

From Bench to Bedside: Navigating Technical and Regulatory Hurdles in Extracellular Vesicle Applications

Juan Manuel Falcón, *Exosomes Laboratory*

Standardization and quality control remain critical challenges in advancing EV-based therapies and other uses in humans. Despite the MISEV2023 guidelines,[150] harmonizing protocols for isolation, characterization, and quantification across various settings remains difficult. The inherent variability and heterogeneity of EV populations further hinder reproducibility and clinical translation. Additionally, scalable manufacturing of clinical-grade EVs with consistent purity and stability is essential to support therapeutic applications. Cargo loading and targeting are major technical challenges in EV-based therapies. Effectively incorporating therapeutic agents while preserving EV structure

and achieving precise delivery to target cells while avoiding unintended immune responses is essential for their safety and efficacy. Robust regulatory and safety frameworks are needed to guide the clinical translation of EV-based therapies. Thorough safety and immunogenicity assessments are crucial to ensure these therapies are safe, effective, and consistent.

During 2025 more than 3500 publications on extracellular vesicles covered the development in isolation methodology, characterization, diagnostics, and therapeutics applications. Mukerjee et al.[151] advance the field by benchmarking next-generation isolation technologies—particularly microfluidic and immunoaffinity systems—that significantly improve purity-to-yield ratios and enable standardized, automatable workflows suitable for clinical laboratories. Li et al.[152] highlight breakthroughs in multiplexed exosome biomarker detection platforms and demonstrate improved cancer diagnostic accuracy through integrated proteomic and miRNA signature panels, with specific emphasis on early-stage tumor detection. Youssef et al.[153] describe key advances in precision oncology, detailing improved exosome engineering strategies—including CRISPR-loaded vesicles and tumor-targeting surface modifications—while also emphasizing AI-assisted biomarker discovery workflows that refine patient stratification. Xu et al.[154] provide a critical overview of manufacturing and regulatory advances, outlining improved quality-control assays, potency metrics, and nonclinical evaluation pipelines that bring exosome therapeutics closer to regulatory approval. Moni et al.[155] present updated evidence on diagnostic and prognostic exosomal biomarkers, demonstrating stronger correlations between vesicle-derived cargo and clinical outcomes across multiple cancer types, while identifying biomarker panels with the highest reproducibility. Mohiyuddin et al.[156] expand understanding of exosomes in brain-cancer management, emphasizing improved drug-loading techniques, BBB-penetrating design strategies, and preclinical evidence of reduced neurotoxicity compared to synthetic nanoparticles. Mukerjee et al.[157] advance diagnostic engineering by introducing new chipset-based exosomes sorting and quantification platforms with higher sensitivity for low-abundance biomarkers and describe conceptual progress toward exosome-based cancer nanovaccines.

Collectively, the 2025 studies mark meaningful progress in the technological, analytical, and translational maturity of extracellular vesicles science and reinforce their emerging role as clinically actionable tools in diagnostics and therapeutics. While the potential of EV-based applications across regenerative medicine, skincare and immunomodulation is undeniable, progress depends on addressing critical challenges in standardization, regulatory oversight, mechanistic understanding and delivery targeting. As the field matures, a multidisciplinary approach, bridging cell biology, immunology, nanotechnology and clinical research, as well as engineering, ecology understanding will be essential for unlocking the full therapeutic promise of EVs.

Metabolons Inside the Cell

Mikel Valle, *Cryo-EM of Biological Macromolecules Laboratory*

A metabolon is a transient multi-enzyme complex in a cell where sequential enzymes of a metabolic pathway associate to efficiently pass intermediates from one to the next. This organization, known as metabolic channelling, increases reaction rates, reduces the need for water to hydrate individual enzymes, and ensures that products are channelled directly to the next enzyme's active site avoiding dilution in the cell's cytosol. Metabolons are held together by non-covalent interactions and structural elements like the cytoskeleton or cellular membranes. These complexes are dynamic and can be difficult to study because they dissociate into subunits once removed from their cellular context.

The challenge to study metabolons has limited the research to the characterization of partial complexes such as the human Citrate Synthase-Malate Dehydrogenase 2[158] or full complexes using in silico approaches such as the purinosome.[159]

With our previous experience in the structural characterization of several oligomeric enzymes by cryo-EM, our current aim is to explore these transient metabolons using endogenous cellular content directly isolated from cell lysates after the stabilisation of the metabolons with a crosslinking treatment in the cells. The first required tool is the method to label genes of interest for affinity purification of the corresponding protein, and this has been recently reported using CRISPR/Cas technology.[160] This way, we can avoid the use of cloned or overexpressed material, since this approach cannot deal with multielements that associate via complex regulation. The combination of stabilized complexes, the use of tagged proteins, and the isolation of endogenous samples will pave the way to fill this knowledge gap in the near future.

Prion Diseases Enter the Therapeutic Era: Recent Progress and Future Perspectives in Prion Disease Research

Joaquín Castilla and Hasier Eraña, *Prion Research Laboratory*

Prion diseases or Transmissible Spongiform Encephalopathies (TSE) are rare, rapidly progressing, and invariably fatal neurodegenerative disorders that became the paradigm of protein-misfolding diseases. They were the first in which the causal agent was shown to be an endogenous protein existing in two conformations: a physiological globular form (PrPC) and a misfolded amyloid form capable of converting the normal protein in a self-propagating cycle, ultimately causing neuronal death. Since the early 2000s, it has been recognized that other, more prevalent neurodegenerative diseases with protein aggregates share key mechanisms with TSEs, including misfolding, templated propagation, and the existence of distinct amyloid conformers underlying different phenotypes.

In 2025, these parallels have been further reinforced, with new evidence for distinct strains in synucleinopathies and tauopathies,[161,162,163] the seeding capacity of Aβ oligomers,[164] and the continued adaptation of amyloid seeding assays (ASAs) to other diseases and tissues.[165,166,167,168] ASAs for prion diseases are also being optimized through alternative substrates[169] and adapted for use in fixed tissues.[170,171] New biomarkers have emerged, including miRNA signatures[172] and β-synuclein for differential diagnosis.[173] As the field enters its therapeutic era—with one clinical trial ongoing and others expected soon—prognostic, diagnostic, and monitoring markers are gaining importance, such as functional rating scales,[174,175] ASAs for tracking disease progression,[176] and prodromal indicators.[177] Therapeutic research has accelerated, with efforts to reduce PrPC levels, including ASO distribution studies in primates[178] and gene-editing strategies,[179] alongside alternative approaches such as protein binders.[180] Advances in prion biology also marked 2025, with new insights into fibril assembly and disassembly,[181,182] cofactor roles in prion formation,[183] glycosylation-dependent strain properties,[184] and neurotoxicity mechanisms.[185,186,187,188,189] Large cohort studies explored genetic,[190,191] clinical, and environmental determinants of disease occurrence and survival.[192] In animal prion diseases, Chronic Wasting Disease (CWD) remains central, with progress in diagnostics,[193,194,195] interspecies transmission,[196,197] and genetic susceptibility.[198,199]

Looking ahead, the first results of the ongoing clinical trial will likely shape 2026, and complementary therapeutic strategies may gain relevance. Diagnostic and prognostic

research will continue expanding to support clinical readiness and natural-history studies. CWD will remain a major focus in animal prion research, while thanks to the refinement of in silico, in vitro, in cellula, and in vivo models we expect an improvement of our understanding of spontaneous prion formation, internalization, propagation, and neurotoxicity. Thus, although therapeutic and diagnostic progress in human prion diseases is likely to dominate 2026, fundamental discoveries in prion biology will also contribute to a highly dynamic year for the field.

Advances in IBS: From Carbohydrate Maldigestion to Multi-Ancestry Genomic Studies

Cristian Díaz Muñoz, Ibone Rubio Sánchez-Pajares and Mauro D'Amato, *Gastrointestinal Genetics Laboratory*

Irritable bowel syndrome (IBS) is a disorder of gut-brain interaction that affects around 10% of the global population, significantly impacting patients' quality of life and placing a burden on healthcare systems. Its hallmark symptoms are well recognized: recurrent abdominal pain, bloating, and bowel habit abnormalities (i.e., diarrhoea and/or constipation). Yet its underlying biology remains elusive. The pathophysiology of IBS is complex and multi-factorial involving microbial dysbiosis, gut-brain axis miscommunication and perturbed digestion among others. In 2025, research at the Gastrointestinal Genetics Lab has helped overcome some of these challenges by advancing mechanistic insights into IBS, with a clear commitment to turning them into actionable solutions for clinical practice.

Main accomplishments from our lab have continued to provide strong evidence linking genetic variation in the sucrase-isomaltase gene (SI) to IBS risk.[200] SI encodes a brush-border disaccharidase with two catalytic domains essential for carbohydrate digestion. Large-scale biobank analyses show that only variants affecting the sucrase domain associate with increased IBS risk and symptom severity, with carriers often avoiding sucrose-rich foods.[201] Building on these findings, we examined the common Val15Phe SI variant, which reduces enzymatic activity by ~35%, in a pilot sucrose challenge test. Carriers showed diminished glucose response and a trend toward higher IBS burden, supporting SI genotyping combined with functional tests as a non-invasive strategy to detect SI dysfunction.[202] Our next focus is to characterize how SI variants alter enzymatic activity and drive symptom variability, a key step toward developing precision-nutrition approaches.

We have also shown that other human carbohydrate-active enzymes (hCAZymes) may also influence IBS risk. Evidence from patients treated with carbohydrate-restricted diets shows that those carrying multiple impaired hCAZyme alleles experience the greatest benefit, introducing the concept of "carbohydrate maldigesters" and strengthening the case for personalized dietary strategies.[203,204]

Besides these important advances, large-scale hypothesis-free genetic studies remain essential to uncover novel pathophysiological mechanisms in IBS. Over the past five years, we have conducted genome-wide association studies (GWAS) of IBS and related endophenotypes, leading to the identification of gene targets and actionable pathways with therapeutic potential.[205,206] Building on this foundation, we are now expanding our efforts to explore IBS, functional constipation and gut motility traits across diverse ancestries and over millions of individuals, aiming to reveal shared genetic signatures across populations and uncover ancestry-specific disease triggers. In our most recent study, we demonstrate causal effects of stool frequency on IBS and other gastrointestinal disorders and highlight common tractable molecular mechanisms controlling gut motility, including vitamin B1 metabolism, bile acids synthesis, and cholinergic signalling.

In summary, our research reveals key biological mechanisms predisposing to gastrointestinal disease and highlight modifiable pathways as potential targets for personalized nutrition and pharmacological intervention.

From Noise to Flow: The Deterministic Turn in Generative Protein Design

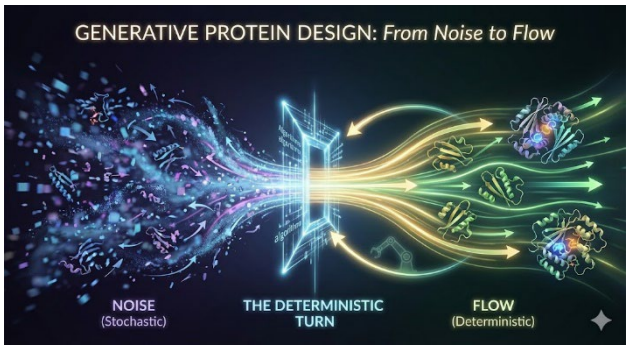
Gonzalo Jiménez-Osés, *Computational Chemistry Laboratory*

The year 2025 marks a definitive inflection point in computational structural biology, transitioning from the "structure prediction revolution" to a discipline of deterministic functional engineering. While early tools like AlphaFold 2 mastered static structure prediction, practitioners faced the "Validity Gap", where geometric feasibility often failed to translate into thermodynamic stability or function in wet labs. Consequently, the field coalesced around three grand challenges: the affinity bottleneck in drug discovery requiring precise binding free energy predictions; the fidelity of inverse folding to capture dynamic "breathing" motions rather than rigid scaffolds; and the scale complexity barrier that previously limited generative models to small proteins, failing to address complex enzymes or multi-domain receptors. To address these, the industry adopted unified "co-folding" architectures treating proteins, nucleic acids, ligands, and ions as coupled inference problems. AlphaFold 3 (AF3) democratized this, modeling post-translational modifications and complex interactions as a universal biological tool.[207] For drug discovery, Boltz-2 widened the energetics bottleneck. Unlike predecessors that only predicted binding pose, it predicts binding affinity with accuracy comparable to physics-based Free Energy Perturbation but at 1,000x speed, enabling the crucial distinction between nanomolar drugs and micromolar duds.[208] Concurrently, Chai-1 emerged as a lean alternative achieving state-of-the-art accuracy in single-sequence mode, a breakthrough for designing synthetic "orphan" proteins lacking evolutionary history.[209]

A defining narrative of 2025 is the migration from stochastic Diffusion to deterministic Flow Matching algorithms in Generative Protein Design. This paradigm, learning direct probability paths, enabled unprecedented generation speed and stability. RFdiffusion2 applied this to engineer atomic-level catalysis, solving the "inverse rotamer" problem to scaffold complex "theozymes" (theoretical active sites of enzymes) with activity orders of magnitude higher than prior attempts.[210] Scaling further, NVIDIA's La-Proteina utilized partially latent flow matching to jointly generate atomistic structures and sequences. By reasoning about side-chain packing constraints during backbone generation, it broke the length barrier to robustly design proteins up to 800 residues.[211] The therapeutic sector was deeply impacted by Chai-2's "zero-shot" antibody design. Achieving a 16-20% experimental hit rate—a massive leap from historical 0.1% figures—it effectively compresses discovery campaigns to a single 24-well plate.[212] Parallel to structural advances, ESM3 revolutionized protein language modeling by simulating 500 million years of evolution. It generated novel functional proteins, such as distinct fluorescent variants, exemplifying "programmable biology".[213]

Operationalizing these models, 2025 saw AI agents acting as "virtual scientists," epitomized by the Virtual Lab project where autonomous agents executed design-build-test cycles. These agents successfully designed SARS-CoV-2 nanobodies by dynamically selecting toolchains and analyzing *in silico* metrics. Crucially, this autonomy was industrialized through Robotic Cloud Labs (RCLs) like Adaptyv Bio. These established "closed-

loop" infrastructures where AI directly triggers liquid handling robots via API to physically validate designs, creating a seamless feedback loop. This integration paves the way for "Zero-Shot" Therapeutics in 2026. By leveraging models with double-digit hit rates to design drugs de novo without iterative screening, this paradigm promises to make rare disease treatments economically viable and clinically scalable.



Structural Virology: Not Trendy, Yet Timeless

Nicola GA Abrescia, *Structure and Cell Biology of Viruses Laboratory*

The past years have underscored - once again - the critical importance of virology and immunology research. Societal responses to emerging and re-emerging viral threats rely on decades of accumulated fundamental knowledge and uninterrupted technological progress. Current concerns about avian and human influenza, together with the recent alarm in Spain over African swine fever virus (ASFV) detections in Catalonia - an animal pathogen of immense agricultural and economic impact - illustrate how rapidly viral threats can destabilize public confidence, disrupt agricultural systems, and challenge public-health preparedness. In this context, the study of viruses - whether they infect Bacteria, Archaea, or Eukaryotes, and whether approached from basic, clinical, or translational perspectives - remains indispensable. At the Abrescia Lab, we investigate the molecular mechanisms that drive viral pathogenesis using advanced structural methods. Our research centres on three interconnected areas: virus assembly, virus–cell entry, and virus–antibody recognition. By deciphering the principles of virus assembly, we aim to inform molecular strategies capable of disrupting viral morphogenesis. Broadening the structural picture of the viral world, or virosphere, also reveals evolutionary relationships invisible at the sequence level.

Understanding virus–cell entry mechanisms offer opportunities to interfere with these essential key–lock processes. Antibodies can act as precise molecular tools for such interventions, and clarifying their recognition and neutralisation mechanisms enhances their translational value. To address these questions, we employ an integrative structural approach that combines X-ray crystallography, electron microscopy (EM), and functional studies. Regarding AHSV, we remain the only research group in the Western world to have resolved its structure by cryo-EM in 2020,[214] along with fierce competition from several leading Chinese laboratories heavily investing in ASFV structural biology. Also, a long-standing focus of our group has been the direct visualisation of viral processes within infected cells. Our early work in 2012 marked a milestone for the Basque Country,[215] establishing electron tomography for the first time within a regional research centre. Today, we continue to push in-cell structural virology forward using state-of-the-art cryo-EM and cryo-ET technologies to map the cellular landscape under viral siege and to decode assembly mechanisms in their native context. The knowledge we generate not only advances fundamental understanding of viral molecular mechanisms but also provides a foundation for developing practical tools - antivirals, diagnostics, and vaccines - that benefit both human and animal health. Our work fully aligns with the One Health vision, addressing interconnected societal challenges through innovative research aimed at mitigating the threats posed by viral infectious diseases, a timeless threat faced nowadays by everyone on the globe.

In 2025, structural biology and virology advanced across multiple fronts. Cryo-EM and cryo-ET pushed further in situ, capturing virus assembly and organization directly inside cells and revealing how glycoproteins, matrix layers and host membranes coordinate during budding and maturation.[216] Parallel progress came from the routine integration of AI structure-prediction tools, such as AlphaFold and Rosetta, with cryo-EM maps and crosslinking/MS data, enabling the construction of complete, testable models of large viral assemblies and membrane proteins that had previously resisted structural determination.[217] High-resolution studies of complex viral and natural RNA architectures - including novel RNA nanocages - provided near-atomic insights into how tertiary contacts scaffold capsid assembly and genome packaging, while new bacteriophage structures illuminated modular infection machinery, from portal–neck complexes to tail and baseplate systems, expanding our understanding of viral mechanical strategies.[218,219,220] Methodological innovations in image analysis, including unsupervised morphology-based classification, improved subtomogram averaging and more effective missing-wedge compensation, made it possible to resolve distinct conformers and flexible features within heterogeneous viral populations. These developments, together with new mechanistic insights into major human pathogens such as coronaviruses and influenza viruses-spanning receptor engagement, polymerase conformational states and assembly pathways - directly informed vaccine antigen design and antiviral strategies.

Looking ahead to 2026, our goal is to consolidate and expand our structural work on both animal and human viruses, strengthening the translational bridge toward next-generation vaccinology. By integrating our biological cryo-FIB milling workflows and the emerging pipeline for cellular cryo-electron tomography, we aim to map infection processes with unprecedented precision in physiologically relevant environments. In parallel, the combined use of soft X-ray tomography and high-resolution cryo-correlative microscopy will enable us to track, in whole cells, how distinct viruses enter, traffic, and initiate replication - and how antiviral or vaccine-elicited immune factors modulate these steps. Although not trendy, we are committed to highlighting the fundamental importance of structural virology for human and animal health, ensuring society understands both the challenges ahead and the critical value of preparedness in addressing the next pandemic.

TECHNOLOGIES

Genomics in Motion: Integrating Microbiome, Epigenetics and Multi-Omics for the Future

Ana M Aransay, *Genome Analysis Platform*

Genomes are not fixed instruction manuals but living systems that interact with environmental cues, microbial partners, and epigenetic regulation. Modern genomics has two global challenges to shape the field: deciphering how microbial communities influence host biology and developing accurate methods to measure chemical marks on DNA. These questions guided the Genome Analysis Platform's efforts in metagenomics and epigenomic profiling.

First, we focused on benchmarking methods to characterize microbial communities by comparing several existing techniques to identify the most accurate and cost-effective approaches. We found that different strategies for studying the human fecal microbiome can strongly influence the results, highlighting the need for standardization.

We also advanced gentler, more precise approaches for DNA methylation analysis. Traditional methods often damage DNA, which limits their use with precious or degraded samples. Therefore, we evaluated enzymatic conversion methods in combination to Reduce Representation Methylation (RRMeth) analysis using different restriction enzyme combinations. We observed that Reduce Representation Enzymatic Methylation sequencing (RREM-seq) provided clearer and more reliable methylation patterns, particularly in oncology samples.

The Platform's contributions also extended to collaborative publications in (i) bulk transcriptomics;[221,222,223,224,225,226] (ii) characterization of microRNAs for biomarker discovery;[227,228,229] (iii) single-cell transcriptomic descriptions in evolution of neuron systems,[230] in prostate tumours[231] and to understand immune responses;[232] (iv) epigenomics;[233] (v) fine-tuned approaches of DNA-sequencing and cell line identification[234,235,236] and (vi) phylogenetic studies of prion genes.[237]

Looking to 2026, genomics will become more integrated and user-friendly. Core facilities will combine gene and microRNA

expression with enzymatic DNA methylation and, where relevant, microbiome composition and activity (metagenomics and metatranscriptomics), generating unified multi-layer analyses to better understand how biological systems respond to health and environmental changes. Long-read sequencing will enhance data quality for challenging samples, while single cell multi-omics and spatial transcriptomics will allow unprecedented tissue-level insights. Automated and AI-assisted bioinformatics will make complex datasets easier to interpret. These developments will expand opportunities in precision medicine, environmental genomics, and biotechnology, positioning genomics platforms as hubs for integrative, high-impact research.

The Evolving Landscape of Proteomics: Toward Sample Miniaturization and the Rise of Complementary Non–Mass-Spectrometry Approaches

Félix Elortza, *Proteomics Platform*

Over the past year, proteomics has advanced rapidly not only in mass spectrometry but also in SOMAmer- and Proximity Extension Assay (PEA)–based platforms. These complementary methodologies are shifting proteomics from descriptive atlases toward mechanistic, population-scale, and clinically actionable readouts.

Mass-spectrometry platforms continue to gain momentum thanks to innovations in hardware, software, and sample-preparation strategies. Notably, sample preparation remains a critical step in any proteomics workflow. At the Proteomics Platform of CIC bioGUNE, we have been refining our internal protocols to address projects with low abundance starting material. One area of significant improvement has been immunopurification-based sample preparation using magnetic beads. We have implemented a simple, streamlined on-bead digestion method inspired by Mohammed et al.[238] The resulting protocol is less labor-intensive, reduces contaminants through minimal handling, and achieves substantial gains in sensitivity.[239]

Furthermore, recognizing that limited sample availability can be a major constraint, and based on Ye et al.,[240] we have established a workflow applicable to low-microgram—or even sub-microgram—tissue samples. Our first application focused on generating a single-organ proteome map of *Drosophila melanogaster* larvae. In collaboration with Rosa Barrio's lab, we successfully profiled the smallest organ studied, the ring gland, identifying over 2,500 proteins; for larger organs such as the brain, we detected more than 5,000 proteins. Collectively, we mapped over 8,000 proteins, constituting one of the deepest *Drosophila* proteomic datasets to date (article in preparation). We now aim to apply this minimalistic workflow to cultured cells—e.g. primary cell lines where cell amount is often a limited material—and to clinical biopsies, where minimally invasive sampling is essential.

In parallel, non–mass-spectrometric approaches for differential studies and biomarker discovery in plasma have reached the market. The leading technologies are SOMAmer-based assays (SomaScan) and the Proximity Extension Assay (PEA by Olink). SomaScan offers exceptionally high multiplexing and broad dynamic range with minimal sample requirements but relies on aptamer–target interactions, making it susceptible to cross-reactivity and less effective at resolving proteoforms. Olink provides high specificity and sensitivity through dual-antibody PEA technology, though at the cost of lower multiplexing and dependence on antibody availability, with quantification remaining largely relative. While the application portfolio for these platforms is expanding, some limitations like sample type, post-translational modification analysis, and study cost should be considered.

Additionally, Artificial Intelligence and Machine Learning are increasingly enhancing clinical proteomics by improving protein detection, reducing noise, and automating quality control.

All these improvements support the discovery of disease-associated protein signatures and enable the integration of proteomics with other omics and clinical data to strengthen predictive models.

Technological and Methodological Advances in Mass Spectrometry–Based Metabolomics

Sebastiaan van Liempd, Oihane E. Alboniga, Camila Salazar, Diana Cabrera and Juan Manuel Falcón-Pérez, *Metabolomics Platform*

Metabolomics continued to advance through improvements in mass spectrometry and platform capabilities. Technological progress included enhanced Time-of-Flight (ToF) instruments achieving resolutions up to 100,000, faster scan rates, and expanded dynamic range. Ion mobility MS enabled separation of enantiomers and structural isomers, while single-cell metabolomics emerged as a critical tool for studying cellular heterogeneity. Mass spectrometry imaging and oligonucleotide analysis remained essential for spatial and therapeutic studies, complemented by machine learning for large-scale data interpretation.

At CIC bioGUNE, the metabolomics platform strengthened infrastructure with new LCMS equipment, including ToF and Orbitrap systems, supporting both targeted and untargeted analyses. In 2025, the platform processed over 3,600 samples across 100 projects, achieving 13,000 injections. Methodological advances included expanding the metabolite library to 700 standards, launching robust assays for polyamines and multi-pathway profiling, and implementing isotope-labeled flux analysis. These cover both lipids (>500) and polar (>200) metabolites. This allows us to quickly identify significant markers in untargeted analyses. We extended our transsulfuration assay to include more sulfur-containing compounds derived from methionine and cysteine. Additionally, we launched a highly robust and sensitive assay for polyamines,[241] which played a pivotal role in an upcoming *Nature* publication by Mikel Pujana Vaquerizo et al.[242] Another recent development is a multi-pathway assay that simultaneously measures metabolites involved in glycolysis, the pentose phosphate pathway, and the TCA cycle. Notably, most current requests involve stable isotope-labelled metabolite tracking, underscoring the trend toward dynamic metabolic flux analysis.

Beyond internal services we have collaborated with universities and companies. Many of these external collaborations were based on our core services, i.e. measurement of methionine cycle and tricarboxylic acid (TCA) cycle metabolites. We have expanded our services to include measuring serum and issue concentrations of drugs and their metabolites to further pharmacokinetic/pharmacodynamic (PKPD) studies. These collaborations extended to pharmacokinetic studies and multi-omics integration, reinforcing the trend toward precision medicine and dynamic metabolic research. Overall, 2025 emphasized incremental improvements rather than disruptive innovations, with a clear focus on single-cell approaches, machine learning, and systems biology as drivers for future metabolomics applications.

Recent Advances in Liquid State NMR

Tammo Diercks, *NMR Platform*

Liquid state NMR spectroscopy is a most versatile analytical technique to access a unique wealth of molecular information at atomic resolution and native-like condition. Recent advances in our areas of key interest are summarised below.

New NMR methodology includes a pre-scan inversion recovery filter to distinguish flexible vs structured protein regions,[243] relay to vicinal ^{1}H to observe TROSY effects for aromatic $^{13}C(^{19}F)$[244,245] or imino ^{15}N,[246] and bandselective HA decoupling for ^{15}N TROSY signal sharpening.[247] *J*-resolved spectra may be homodecoupled experimentally[248] or by processing algorithms that also reconstruct pure absorption mode.[249]

For NMR data processing, new tools remove diagonal signals,[250] baseline distortions,[251] and magnetic field noise[252] or inhomogeneity bias.[253] Multiexponential relaxation analysis[254] benefits from denoising[255] and improved decay models.[256] UnidecNMR identifies peaks in ≤ 4D spectra.[257]

^{19}F NMR exploits the extreme spectral dispersion and sensitivity of fluorine, e.g., with F-probes to discriminate chiral compounds[258,259,260,261] or FSB dye to resolve fibril polymorphism.[262] In proteins, CF_3-tags were attached selectively on Cys[263] to probe Pro cis/trans isomerism[264] and vesicle immersion,[265] on Trp,[266] or broadly on exposed XH.[267] F-aminoacids introduced in proteins include 3-CF_3-Phe,[268] 4-F-Trp,[269] 5-F-Trp,[270,271] diverse F-Trp[272,273] and F-Phe isomers,[274] and CF_3-Met.[275] Applications to membrane proteins were reviewed.[276]

In-cell NMR exploits background-free ^{19}F NMR detection of, e.g., injected F-probes to quantify cellular SO_2,[277] Cu^{2+}/Ni^{2+},[278] or NH_3,[279] 2-FDG to trace altered metabolism in cancer cells,[280] or F-ligands for affinity ranking.[281] In proteins, 4-CF_3-Phe enabled ^{19}F NMR to study drug complexes[282] or folding,[283] and F-tagged Cys to measure pseudo-contact shifts.[284] A protein overexpressed with ^{13}C labeled precursors was observed by $^{13}CH_3$-TROSY.[285] An RNase inhibitor cocktail extended RNA aptamer lifetimes[286] for ^{13}C,^{15}N labeling and HSQC detection.[287] A paramagnetic relaxation agent erased all extracellular signals to observe the intracellular metabolome;[288] double-difference STDD NMR revealed on-cell ligand binding.[289]

For NMR metabolomics, reviews covered blood sample preparation,[290] reproducibility and reporting,[291] and NMR methodology to enhance resolution and sensitivity.[292] A single plasma or liver sample enabled dual NMR and MS analysis.[293] Selective 1D TOCSY disclosed N-glycan signals.[294] A new method simultaneously deconvolutes all components from their mixture spectra,[295] HSQCid derives molecular structures from ^{13}C-HSQC,[296] and nmRanalysis assists in NMR metabolite profiling.[297] The 1D CPMG, diffusion edited, and *J*-res projection spectra were predicted from just the standard ^{1}H spectrum.[298]

For ^{31}P NMR, new software predicts the local environment from,[299] and solvent corrections for ^{31}P shifts,[300] or quantifies mRNA directly from ^{31}P FIDs.[301] A review on quantitative ^{31}P NMR,[302] SOPs for phosphometabolite extraction,[303] phospholipid quantification in infant formula,[304] and (glycero)phospholipid identification by 2D ^{1}H,^{31}P HMBC[305] or hetTOCSY[306] were presented.

Towards Autonomous Structure Determination

Isaac Santos and Adriana L. Rojas, *Electron Microscopy (EM) and Crystallography Platforms*

The work at the Electron Microscopy (EM) and Crystallography platforms focuses on understanding the function of macromolecules at both the atomic and cellular levels using electron microscopy (EM) and X-ray crystallography. Our facilities are accessible to all research groups within the center and also provide services to external users.

In electron microscopy, we specialize in sample vitrification, grid screening, and automated imaging with SerialEM, enabling high-quality two-dimensional (2D) and three-dimensional (3D) analyses supported by advanced data-processing tools. These techniques are also applicable to cellular and tissue samples, offering detailed ultrastructural insights.

We have extensive expertise in evaluating nanocarriers, exosomes, and adeno-associated viruses (AAVs) relevant to gene therapy, including integrity assessments and statistical analyses of filled/empty ratios. Our ISO 9001:2015 certification, renewed for the third consecutive year, reflects our commitment to quality. In X-ray crystallography, we offer crystallization as a service, as well as data collection and structure determination as part of collaborative projects.

Recent advances in sample preparation, automation, and hybrid structural methods have accelerated progress across cryo-EM and crystallography. Micropatterning has emerged as a powerful strategy to control cell or macromolecule positioning on EM grids, improving vitrification and cryo-FIB milling while reducing preferred orientations and enabling optimized ice thickness.[307] Cryo-EM now allows visualization of dynamic macromolecular assemblies relevant to drug discovery, capturing transient interactions critical for rational design.[308]

Artificial intelligence (AI) is reshaping data analysis by automating particle picking, improving classification, and enabling enhanced 3D reconstruction with minimal user intervention. Frameworks such as GOLEM extend AI applications to ligand–protein interaction studies, and deep-learning tools are increasingly effective for automated model building from cryo-EM maps.[309] These developments point toward autonomous and high-throughput structure determination.

Parallel advances in microcrystal and serial crystallography expand capabilities for small or fragile samples. Improvements in microcrystal growth, delivery systems, and time-resolved diffraction enable the visualization of biomolecular dynamics, complementing cryo-EM studies of flexible assemblies.[310]

Looking ahead, the convergence of AI, automation, and hybrid imaging will further transform structural biology. Enhanced deep-learning tools and high-throughput instrumentation may soon enable near-real-time interpretation of molecular motion, while in-situ cryo-ET and automated cryo-FIB will facilitate visualizing molecular complexes within native tissues.[311] In X-ray crystallography, especially XFEL-based serial femtosecond approaches, advances in beamline design and pump-probe methods are expected to deliver femtosecond temporal resolution with reduced radiation damage.[312]

Beyond technical progress, automation, cloud-based workflows, and AI-assisted modeling are lowering barriers for non-expert users.[313] The synergy of cryo-EM, XFEL crystallography, and data science promises to accelerate drug discovery, deepen mechanistic understanding, and address challenges in health, energy, and materials science. Structural biology is entering a new phase where automation, accessibility, and interdisciplinarity—not just resolution—define discovery.

Front and Last Page Image:
BioDUB: new strategy to identify specific targets of deubiquitinases.

U2OS (human osteosarcoma) cell, transfected with the deubiquitinase CYLD (in green) fused to BirA enzyme that biotinylates the substrates. In red, we see the substrates biotinylated. Overlay between the BirA-CYLD and the biotinylation material appears in yellow. The nucleus of the cell is labelled in blue. Images are acquired with a Leica SP8 confocal microscope, objective 63X, zoom 3X.

Middle Page Image:
Illustration created with Nano Banana Pro (p. 12)
From CIC bioGUNE's Visual Repositor (p. 14)

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