the SUNDARI JOURNAL

SHINEDocs Unveiling New Discoveries and Research Innovation

#3 2025

Summary

One Year of SUNDARI: A collective Milestone

One year ago, SUNDARI was launched as a bold experiment, a new voice for our SHINEDocs community and beyond, created with heart, curiosity, and a desire to connect the dots of our research, amplify their significance, and inspire future innovations. Since then, it has evolved into something far more impactful than the sum of its pages.

With the support of our contributors, readers, and now a growing editorial team, we've built not just a journal, but a vibrant space for science, ideas, and identity. A heartfelt thank you to all who believed in this vision from the beginning and to those just joining the adventure.

This anniversary issue comes at a time of transition and momentum. With new voices joining the board, we are entering a new phase of visibility and collaboration. The goal remains the same: to reflect who we are, share what we do, and invite others into our scientific journey. Here's to a new chapter of stories, discoveries, and community

The SUNDARI Journal.

DIRECTOR'S INSIGHTS

Jean-Philippe STEPHAN (PhD)
Senior Director Research Pharmacology Unit
Institut Servier d'Innovation Thérapeutique

I am excited to introduce this new volume which depicts a detailed and insightful overview of the In Vitro Pharmacology (IVP) department, standing as a crucial pillar of our research efforts. Using an array of cellular models and assays, the IVP department plays a critical role in the discovery and validation of therapeutic targets and drug candidates in the fields of oncology, immunology, and neurology.

To further refine Servier's scientific and experimental expertise, the IVP department collaborates extensively with R&D sites around the world. These partnerships enable the sharing of knowledge and resources, fostering innovation, and accelerating the development of new therapies. Additionally, IVP works closely with start-ups from the Spartners incubator located at the Saclay site, creating a dynamic environment where cutting-edge ideas can flourish.

Recently, the IVP department went through an evolution of its organization to further enhance its agility and foster even greater collaboration. This change also aims at anticipating pharmaceutical research transformation with the promise to deepen our understanding of complex diseases and improve patient care.

In alignment with this forward-thinking vision, the SHINEDocs community brings together diverse fields and shares valuable insights to promote scientific innovation and knowledge. This unique group of young researchers is dedicated to fostering curiosity, mutual learning, and the application of innovative methods to achieve groundbreaking scientific discoveries. In this volume, you will have the opportunity to travel across various global sites and gain a glimpse into the work of SHINEDocs members. Through short presentations of their research, you will see how they are at the heart of our relentless push for innovation. The wide range of their work, from oncology and neurology to chemistry, reflects the diverse and stimulating nature of our R&D efforts. Their contributions highlight the vibrant and dynamic landscape of scientific exploration within our organization.

Our journey in pharmaceutical research is fueled by our dedication to enhancing patient well-being. Each of you, through your dedication and inventive mindset, embodies these core principles, playing an indispensable role in our collective pursuit of scientific progress.

As we move forward, let us continue to embrace our complementary strengths, push the boundaries of science, and embark on this exciting journey together. Our collaborative efforts and shared passion for innovation will undoubtedly lead to remarkable advancements and improved outcomes for patients around the world. Work hard! Play hard!

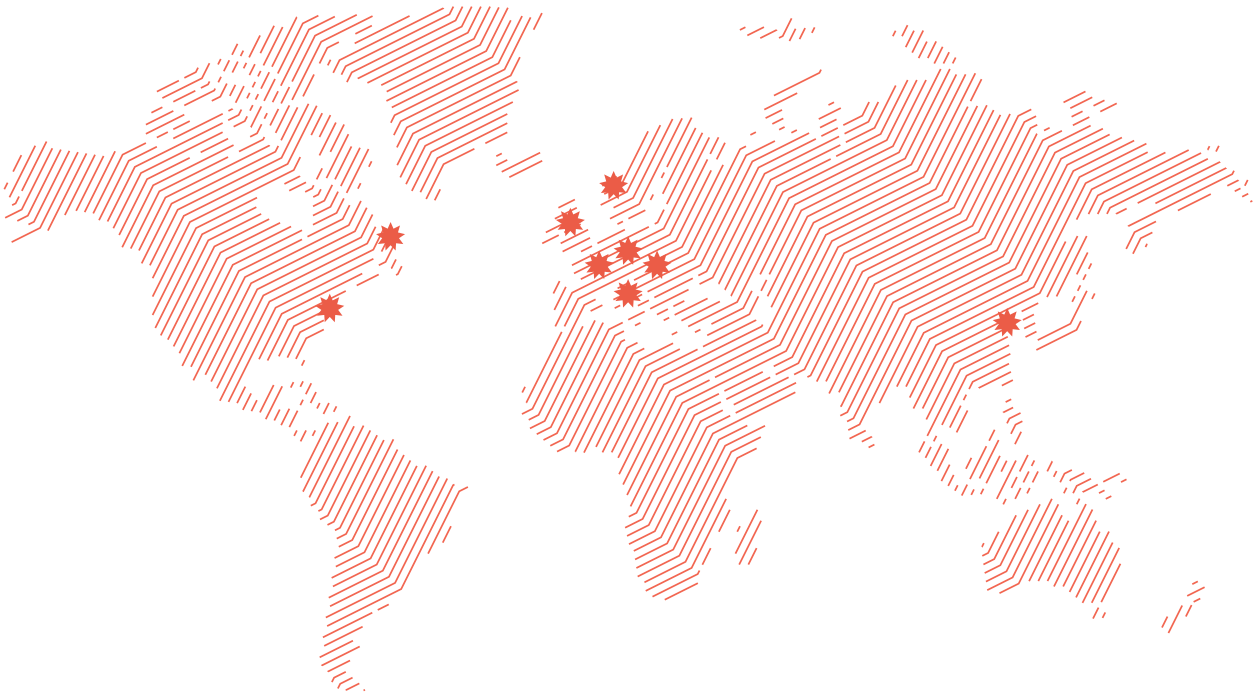
SHINEDocs' Global Presence

SHINEDocs around the World

26
members from the United States, China, United Kingdom, Germany, Canada, Denmark, Hungary, Italy, **and more...**

82
ShineDocs
60% Postdocs
40% PhD Students

56
ShineDocs in France
39 Saclay
17 Other sites



The dynamic SHINEDocs community is distinguished by its constant commitment to innovation. With PhDs researchers, Servier is opened to many successful collaborations. The SHINEDocs' members work together and their spirit of collaboration and passion for innovation create an environment commited to therapeutic progress. Here is an overview of the community in 2025.

UPCOMING EVENTS

SEPTEMBER/OCTOBER 2025

15-16.09

Molecular Analysis for Precision Oncology Congress

Maison de la Chimie, Paris

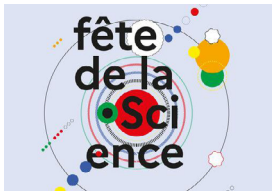
Conference regrouping experts in oncology, molecular diagnostics and precision medicine discussing advances in the molecular understanding of cancer, facilitating precision oncology.

22-23.09

21st Global Biomarkers and Clinical Research Summit

Millennium Hotel Paris CDG, Paris

Summit about multi-omics integration, precision medicine and advances in oncology.



03-13.10

Fête de la Science 2025

France, overseas territories and international

Theme "Intelligence(s)" exploring the many facets of intelligence and inviting us to rethink what it truly means to be intelligent, beyond human boundaries.

07-08.10

RARE 2025 Meeting: Screening, diagnosis and treatment: new tools and new hope

Cité Universitaire Internationale, Paris

A rare disease community bringing together public decision-makers, patient and caregiver representatives, healthcare and research professionals, as well as stakeholders from the pharmaceutical, medical device, and health technology sectors.

GUIDING LIGHTS

IVP implication along the Drug Discovery Process

By implementing multiple cellular models, biochemical assays and a large panel of molecular tools, researchers can pursue the identification/validation of therapeutic targets and the discovery/optimization of potential drug candidates on biological systems outside of a living organism. This controlled environment allows for precise manipulation of certain biological parameters, providing valuable insights into the mechanisms of action, efficacy, and safety of new compounds.

Béatrice Bastard,
Céline Wagner
and Sophie Turban

The In Vitro Pharmacology (IVP) department actively contributes to numerous projects across all research therapeutic areas: oncology, immuno-oncology, and neurology, providing critical data from Concept to Late Research/Early Development phases. Combining scientific and technological/experimental expertise, IVP works in close collaboration with many experts across the R&D organization and externally with the pharma/biotech industry and multiple academic institutions around the world. Within a specific therapeutic area, IVP collaborators evaluate several therapeutic modalities pursued at Servier. These include small-molecule drugs which interact with specific proteins or enzymes within cells, modulating their activity to achieve therapeutic effects; various antibody formats (mono, bi, tri, multi-specific & antibody drug conjugates (ADC)), targeting specific tumoral or immune antigens like proteins on the surface and antisense oligonucleotides, which are short synthetic strands of nucleic acids designed to bind to specific mRNA sequences, blocking the translation of target proteins.

IVP collaborators are engaged in several target discovery projects,

Jessica Soamalala,
Jayson Alves Bordelo and
Manon Tissier

including CRISPR screens and artificial intelligence (AI)-based approaches. Leveraging multiple functional genomics methodologies combined with adapted cellular models, the department is also heavily involved in the validation of many targets in our Concept project portfolio. In this early phase, IVP validates the biological hypothesis in the context of specific indication(s) and leverages biochemical tools and assays to help understand underlying molecular processes, enabling a Go/No Go Early Research decision based on clear milestones.

IVP experts are also fully committed to the success of projects from Early to Late Research tackling multiple critical requirements to successfully move the project forward. In vitro studies enable researchers to evaluate large numbers of molecules quickly and cost-effectively, identifying those with the highest potential for success. High-throughput screening (HTS) techniques are particularly useful in this regard. The department is equipped with state-of-the-art robotic platforms, allowing rapid testing of hundreds of thousands of small-molecule compounds for various types of biological activities. Later, IVP also supports the optimization of the molecules to select the lead candidate(s). Beyond cellular and biochemical assays implemented to support the Design/Make/Test/Analyze (DMTA) cycle, experts within the department are performing additional investigations to understand and characterize the mechanism of action of the candidates and to contribute to the identification and validation of the biomarker hypothesis. Often, this work continues during the Early Development phase to further validate the biomarker hypothesis and to investigate the rationale for additional indications.

Improving disease relevance of our models, a constant challenge

Considering the complexity of biological processes, IVP investigators are constantly working at improving cellular models (2D cell culture, induced pluripotent stem cell (iPSC) derived cells (e.g., neurons), 3D cell culture, patient-derived organoids and patient explants) to select the most appropriate modality for each stage of the project. Among these models, postdocs are setting up and characterizing patient-derived models in solid tumors including organoïds, tumor fragments and so-called tissue slices which offer the advantage of maintaining the full tumor microenvironment with its intact architecture. This approach represents a crucial step towards enhancing our understanding of solid tumors heterogeneity and refining experimental models for translational studies. This work will be a valuable strength for 1) identifying standards of care vulnerabilities to uncover new therapeutic targets 2) guiding the selection of optimal therapeutic strategies and 3) identifying or positioning Servier's assets based on a more nuanced comprehension of the disease.

The integration of artificial intelligence (AI) into pharmaceutical research is revolutionizing the field, impacting many stages of the drug discovery journey. AI algorithms can analyze vast amounts of data from in vitro studies, identifying potential therapeutic targets, drug candidates, and biomarkers with unprecedented speed and accuracy. Progressively, this accelerates the drug discovery process, allowing researchers to focus on the most promising targets and compounds.

To conclude, the role of the In Vitro Pharmacology department in drug discovery is becoming more important than ever considering the evolution of AI-based approaches and the strong reliance on disease-relevant in vitro data. Through interdisciplinary collaboration, researchers can translate in vitro findings into effective treatments that improve patient outcomes. The synergy between evolving experimental approaches and AI-driven approaches is paving the way for a new era in pharmaceutical research, characterized by increased efficiency, precision, and innovation.

GUIDING LIGHTS

David PIWNICA (PhD)
Director, Head of In vitro Pharmacology Department
Institut Servier d'Innovation Thérapeutique

"The Immuno-Oncology group conducts in vitro studies from early-stage target validation to the preparation of regulatory submissions. Together, our group leverages advanced screening and biomarkers discovery, and develops complex ex vivo models to enable future breakthroughs"
Vincent Lombardi

"From targets to candidates, neurology in vitro pharmacology seeks to uncover hits, validate biology, to shape the next generation of neurological treatments. In synergy with IVP teams, we deliver actionable insights that guide decision-making across the discovery portfolio"
Fernando Ramon Olayo

"Leveraging patient-derived data and in vitro patient-derived models, our team aims to enhance translational relevance, accelerate advanced oncology therapeutics, and prioritize high-confidence targets from early discovery."
Nicolas Molinié

"We support in vitro biology and pharmacology across all phases of oncology programs, including screening, mechanistic studies, novel small molecule/ADC identification, and translational biomarker/combination strategies."
Gaylor Boulay

"We used advanced technologies (cytometry, imaging, cell engineering, gene editing) for target ID & validation, with an emphasis on glioma therapeutics in oncology. We also establish key cellular models and investigating target biology to advance projects and enrich the oncology research pipeline."
Sophie Turban

RESEARCH HIGHLIGHTS

Understanding the Complex Landscape of Head and Neck Cancer: Why It Matters for Treatment

The most common form of head and neck cancer, known medically as squamous cell carcinoma of the head and neck (SCCHN), is one of the most common types of cancer worldwide. It affects the tissues lining the mouth, nose, and throat, and it has been linked to agents like tobacco, alcohol and the human papilloma virus. While early-stage SCCHN can often be treated effectively, the situation becomes much more challenging when the cancer returns or spreads to other parts of the body. This advanced stage is referred to as recurrent or metastatic (R/M) SCCHN.

At this advanced stage, doctors often turn to immunotherapy—a type of treatment that helps the body's immune system fight cancer. However, despite some success stories, the reality is that only 10-30% of patients respond positively to immunotherapy, and even fewer experience long-term benefits. This leaves a crucial question: Why do some tumors respond to treatment while others do not?

To tackle this question, Servier and the Institut Curie (the academic partner of my PhD) joined a European initiative: the IMI IMMUCAN consortium. This project has gathered and analyzed tumor samples from hundreds of patients at different stages of SCCHN and other types of tumors. These samples include everything from early, localized tumors to those that have spread extensively and have been heavily treated. By studying the genetic and molecular characteristics of these tumors, we aim to uncover what makes these cancers tick—especially at the advanced stages where treatment options are more limited.

One of the most significant discoveries is how different treatments affect the immune environment within these tumors. We found that systemic treatments—those that target the whole body, like chemotherapy—reduce the number of immune cells that infiltrate the tumor and potentially fight it. Specifically, chemotherapy drugs like platin and taxanes have the most pronounced effect in reducing these immune cells. This finding can have important implications in the way we study, understand and treat these tumors, especially in the context of immunotherapy, as the immune cells are crucial for success in these therapies. Other findings reveal some key differences between tumors that are still localized and those that have spread. For example, certain cancer-related pathways are more active in tumors that have not yet metastasized, and other pathways become more prominent only when the cancer returns after initial treatment, especially in conjunction with the presence of supportive cells like fibroblasts.

These insights underscore a critical point: recurrent and metastatic tumors are not just advanced versions of their original selves. They have evolved and changed, gaining new characteristics that make them more resistant to treatment. Therefore, understanding these changes is vital for developing better therapies and making informed treatment decisions.

In conclusion, this research highlights the importance of studying head and neck cancers at their most advanced stages. By profiling these tumors more thoroughly, we hope to pave the way for more effective treatments that can offer longer-lasting benefits to patients facing this challenging disease.

By Daniel Herrero Saboya
PhD student at TxM Computational Medicine

RESEARCH HIGHLIGHTS

Revolutionizing Chemical Research: The Era of High-Throughput Experimentation

By Raphael Steimbach
Post-doctoral fellow in Chemistry

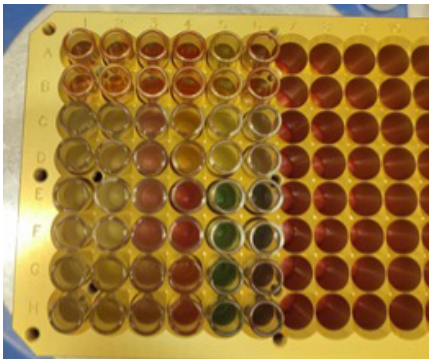
High-Throughput Experimentation (HTE) is a modern approach to the art of chemical synthesis. Synthetic chemists combine chemical building blocks to assemble compounds that have never been made before to find novel therapeutics against debilitating diseases. HTE accelerates drug discovery by enabling chemists to synthesize more compounds faster. This increases the probability of discovering the molecule that patients need. In my PostDoc at the Servier Drug Design Small Molecules (DDSM) unit, I am building an HTE platform to increase the efficiency of medicinal chemistry and thus speed up the Design-Make-Test-Analyze (DMTA) cycle for small molecule therapeutics across all indications. The HTE platform supports medicinal chemists in two aspects of chemical research: **1. Reaction condition screening** and **2. Parallel synthesis.**

Reaction condition screening

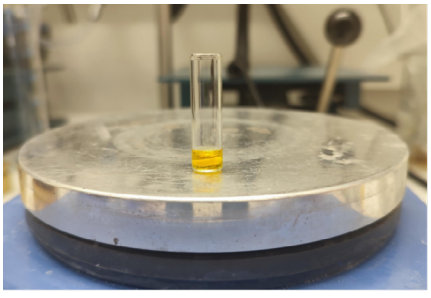
Reaction condition screening is often needed in chemical research, because standard procedures to combine building blocks into new products require adjustment of the reaction conditions depending on the product and building block structures. Finding working reaction conditions to synthesize a new chemical compound can be challenging and time-consuming due to the many factors that influence the outcome of a chemical reaction.
The desired product forms only with the right combination of reaction solvent, catalyst, temperature, and certain additives. With dozens of solvents, catalysts or additives to consider, the number of possible reaction conditions quickly reaches hundreds of combinations. Only a few might be successful, and the right combination is hard to predict, especially for novel compounds. HTE can overcome this challenge by performing numerous chemical reactions in parallel, increasing the chance of finding the right combination of reaction parameters.

Parallel synthesis

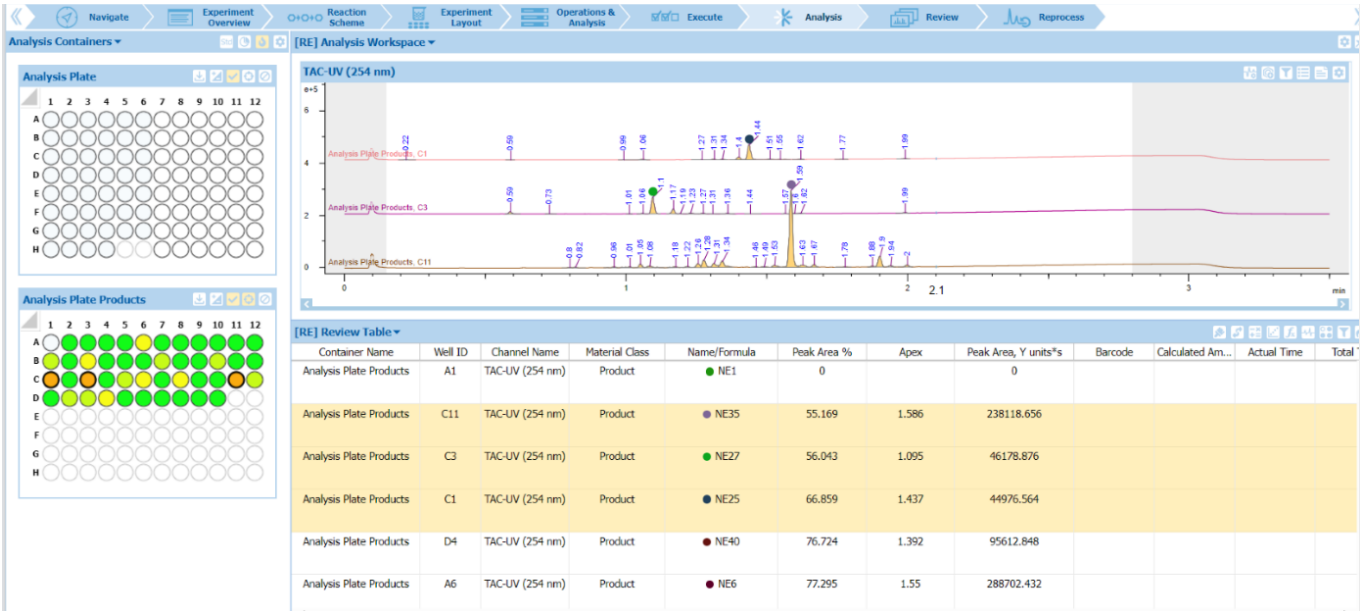
Once successful reaction conditions



48 chemical reactions in glass vials, supported in standardized 96-well reactor plates.



Single miniaturized reaction vial containing 0.1 mL reaction mixture and a rotational stir bar. The vial is placed on a traditional stirring plate for size reference.



Screenshot of the specialized HTE software Katalyst D2D, currently in test phase.

have been found, they can be used in parallel synthesis. This aspect of the HTE platform enables chemists to synthesize many diverse molecules in a chemical series. Currently, the HTE platform can perform parallel synthesis from 48 and up to 96 reactions in one experiment. The chemical space of possible therapeutics is vast, and often thousands of test compounds must be prepared to identify the perfect drug candidate. This makes high-throughput parallel synthesis an essential technology in modern drug discovery.

Rethinking chemical synthesis

The key to increasing throughput in chemistry is miniaturization to the minimum product quantity required to obtain the desired biological or analytical data. HTE is a formidable challenge as it requires the orchestration of the complex connection between experimental design, reaction setup, chemical analysis, purification, and logistics of chemicals, as well as data handling.

The success of HTE hinges on the efficiency of the slowest step, requiring collaboration between departments and the use of a diverse set of methods. These include alternative chemical dosing using ChemBeads or evaporated stock solutions, automated purification and state-of-the-art analytical instruments. The IT and data handling aspects are further challenges in HTE, especially the integration of different systems into a seamless workflow. This is only possible with specialized and often custom-made software tools. In the laboratory, reactions are performed on standardized plates rather than traditional round-bottom flasks to ensure compatibility with different devices along the workflow. Engineering of custom laboratory hardware and on-site manufacturing by 3D-printing is used to rapidly innovate and solve problems in the workflow.

HTE at Servier now and in the future

We have developed an HTE platform that can perform up to 180 reactions per week at mg-scale to screen reaction conditions and produce up to 96 new molecules in parallel, including purification and quality control. The platform is available to all therapeutic areas employing small-molecule modalities.

The next step towards higher throughput is further miniaturization to match the miniscule material requirements of modern analytical techniques and biological activity assays. Sub-milligram quantities often suffice to generate in vitro activity data for early phase test substances. Adapting the synthesis scale to this amount significantly reduces costs and increases throughput. However, working at such small scales requires special analytical techniques to quantify novel substances in solution, as sub-milligram quantities are difficult to measure accurately by weight. Therefore, establishing a direct-to-testable-stock-solution workflow to break through the "milligram-floor" is the next milestone for the HTE platform.

RESEARCH HIGHLIGHTS

Deep behavioral and locomotor characterization of a SCA3 mouse model

By Marius Halliez
Post-doctoral fellow in In Vivo Pharmacology Department

Spinocerebellar Ataxia Type 3 (SCA3) is a rare neurodegenerative disease with currently unmet therapeutic needs: there is no existing curating modality today. SCA3 affects less than 10 people out of 100000 with varying prevalences across the globe. Patients initially suffer from a loss of balance and fine movement along with difficulties in swallowing and slurred speech. Symptoms gain in intensity within one or two decades up to the point where a wheelchair is mandatory and death ensues.

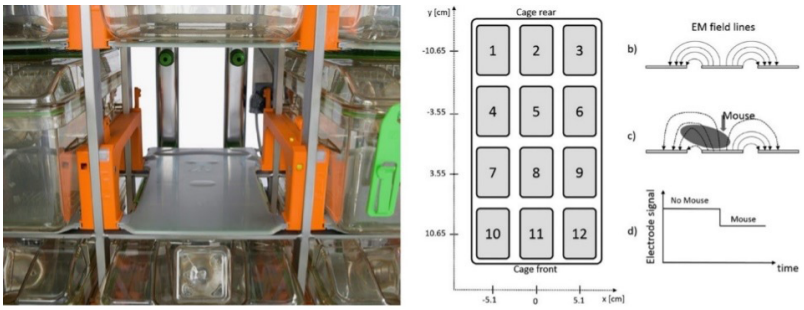
SCA3 is a genetic inherited disease. As any other autosomal-dominant disease, SCA3 passes from a generation to the following one. If one member of a couple suffers from SCA3, there is a 50 % probability that their children will inherit the SCA3-causing gene and will develop the disease. SCA3 results from the aberrant expansion of a trinucleotide CAG tract in exon 10 of the ATXN3 gene. This mutation leads to (i) an abnormal ATXN3 mRNA prone to aggregation and causing disruption of RNA metabolism and (ii) a mutated Ataxin-3 protein carrying an elongated polyglutamine tract. Consequences of such protein modifications are correlated with a toxic gain-of-function notably due to the formation of nuclear aggregates ultimately leading to neurodegeneration. The first brain regions affected are the cerebellum, corresponding to the main control center for coordinated movement and balance, as well as the brainstem. With disease progression, other brain areas eventually become affected such as the cerebral cortex and deeper structures.

During the disease, patients visit the hospital to get an assessment of their symptoms intensity. In-clinic tests correspond to supervised tasks evaluated by a neurologist. Such exercises include walking down a straight line, turn around and come back or simply standing still with eyes opened. At the end of this test battery, a SARA (scale for the assessment and rating of ataxia) score is generated, the higher the score the worst the symptoms. With the rise of portable devices and smartphones, data generated at home during real-life situations could be a great add-on to what is already performed at the hospital. Although less accurate than in-clinic recordings, they are more representative of the patient's real-life experience.

As an in-vivo pharmacologist, I am not working with patients nor data from clinic evaluation. My objective is to characterize a mouse model of SCA3 to prove that it is suitable to assess the potency of new therapeutics in dampening symptoms. A good mouse model for pharmacology studies carries the same target as humans, is generated using a reminiscent biological mechanism giving rise to the pathology in patients and recapitulates similar symptoms compared to what is observed in clinic. The MJD84.2 SCA3 mouse strain ticks all these boxes: (i) it expresses a human version of the mutated ATXN3 gene coding for

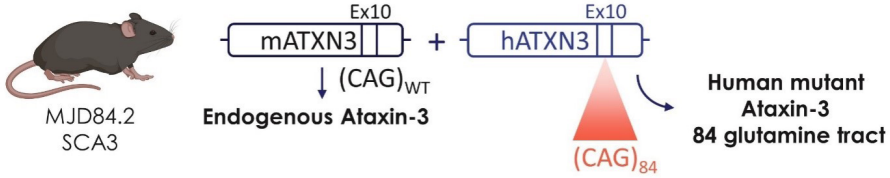
Ataxin-3 with an extended glutamine tract and (ii) suffers from gait and locomotor deficits which is why this is the most widely used model in SCA3 in vivo studies since 2002. These phenotypic symptoms were observed in numerous publications, but this is critical to note that all the generated data result from supervised tests in a highly controlled environment. These particular conditions have always been mandatory for animal experimentation ultimately leading to biased results occulting the true nature of the animal phenotype.

In Servier, one of my missions is to implement and validate a new system of home-cage telemetry to track mouse activity in their housing environment. This tool continuously records animal activity using a set of 12 capacity-sensing electrodes located under each cage. The generated data are abundant and precise enough to derive metrics such as level of animal activity or distance traveled up to the minute scale. Compared to regular animal experimentation in controlled conditions, these so-called connected cages offer many benefits including data generation during night-time (the active period for mice) as well as unbiased, continuous, autonomous and long-term recordings. One purpose of such a system is to generate relevant readouts in animal models of a given disease and to compare them to what is done in-clinic or at-home in patients. The ultimate goal of physiopathological animal characterization is to anticipate the effects of innovative therapies on the elicited symptoms, suggesting potential efficacy on patient burden.



Picture 2. On the left is represented a picture of a mouse cage slot in the Tecniplast DVC® Rack for home-cage monitoring. The gray board contains 12 electrodes arranged in a grid as represented in the diagram. When a cage is inserted in a slot, the board is positioned right under the floor of the cage. A miniature electromagnetic field is generated between each electrode. Electrodes record individually the intensity of the electromagnetic fields at 4 Hz. When the mouse is above an electrode, the intensity of the electromagnetic field is modified thus enabling the localization of the mouse in its cage with a high temporal resolution.

In a recent study, I used the homecage telemetry system to study the MJD84.2 SCA3 mouse strain. In the effort of completing existing information from the literature and to dig deeper in this model characterization, I recorded cohorts of symptomatic animals along with control mice as a refence group. Preliminary analysis suggests that the daily traveled distance per animal appears lower in SCA3 animals, a consistent observation given the locomotor symptoms found in patients. Furthermore, with the access to continuous recordings, analysis of the level of animal activity at different times of the day gives a clue about the circadian rhythm in these mice. In an animal facility, the main stimulus which governs this rhythm in experimental animals is light. Results from a 10 consecutive days analysis suggest than SCA3 mice display altered levels of activity especially during night-time and periods around light switch. Eventually, this work will supplement existing studies on this mouse strain and provide deep enough information to consider an experimental setup were performances of MJD84.2 animals treated with drug candidates for SCA3 will be representative of the treatment efficacy.



Picture 1. A yeast artificial chromosome (YAC) carrying the human mutated ATXN3 gene with an extended CAG tract in exon 10 was used to generate the MJD84.2 SCA3 mouse model. This YAC led to the random insertion of the transgene in the mouse genome, thus leading to a mouse strain that expresses both endogenous murine wild-type Atxn3 and the human mutated version of the gene. The animals used in physiopathological studies are homozygous: both alleles contain 2 copies of the human mutated ATXN3 leading to the overexpression of the human gene compared to the murine version.

RESEARCH HIGHLIGHTS

Exploring New Chemical Space in Drug Libraries via Gold Catalysis.

By Emilie Gentilini
PhD student in Organic Chemistry

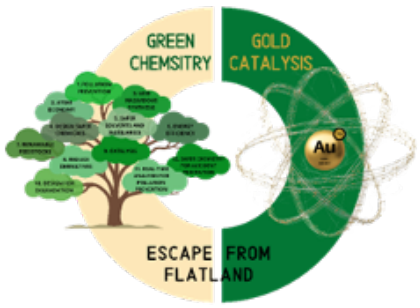
Drug Discovery is a complex and multi-faceted process which is confronted with several challenges. Increasingly complicated biological targets and antibiotic resistance, but also growing environmental concerns make the design of new active compounds more and more difficult. To respond to these issues, it is essential to push the boundaries of 'druggability' and encourage chemists to explore new possibilities. A crucial and challenging step in this direction is enhancing the diversity of the molecular libraries used in the early stages of drug discovery. Indeed, when we look at the databanks of drug candidates, the vast majority of the molecules tend to have a linear or planar geometry, and there are far fewer spherical-shaped molecules. However, harnessing the three-dimensionality could increase the success rates in discovering new drug candidates, especially for complex biological targets. This is the concept of "Escape from Flatland", proposed fifteen years ago by Lovering and co-workers from Wyeth Research, Chemical Sciences. The idea is to increase the complexity of the molecule, and not necessarily by increasing the molecular weight, but to focus on other parameters such as the Fsp3– the fraction of sp3 carbons as a proportion of all the carbons in the molecule – or the number of chiral centers. Furthermore, the creation of more sophisticated libraries could be inspired by the diversity of active compounds found in nature. Natural compounds often exhibit complex three-dimensional architectures that are critical for their biological activity, suggesting that similar structures might be more effective in synthetic drug discovery. In this context, designing such scaffolds might be an interesting route to find new medicinal chemistry-relevant structures.

Challenges of Green Chemistry in Medicinal Research

On another hand, alongside these scientific challenges, there is an increasing ecological awareness driving the need for more sustainable practices in chemistry. Green chemistry aims to reduce or eliminate the use and generation of hazardous substances in chemical processes. It involves prioritizing waste reduction, energy efficiency, the use of renewable resources, and minimizing hazardous substances. Nevertheless, implementing green chemistry principles in medicinal research presents several challenges. Chemists must develop new reactions and processes that not only meet these sustainability goals but also maintain or enhance the efficiency and selectivity required for drug discovery, even more so in a drive to increasing molecular complexity. This often requires a delicate balance between innovative chemical methodologies and practical considerations such as scalability and cost.

Gold Catalysis: An efficient and Sustainable Tool

In this context, our Project focuses on gold catalysis, leveraging its potential to address both the complexity and sustainability challenges in drug discovery. Gold catalysis is a growing field that has proven to be a powerful tool to form new carbon-carbon and carbon-heteroatom bonds, enabling quick access to complex polycyclic structures and moving away from planarity in a more sustainable manner. Indeed, gold catalysis itself aligns with green chemistry principles by using a reagent in catalytic quantities, by allowing the recycling of catalyst, which therefore minimizes resource consumption and waste generation. Unlike its periodic table neighbors, gold exhibits significant stability, allowing reactions under mild conditions which means reducing energy requirements and the need for special equipment, diminishing the energy consumption and carbon footprint of chemical processes. Additionally, gold's unique reactivity provides excellent regio- and stereoselectivity, offering precise control for the formation of specific products compared to other metals. Its availability and non-toxic properties are also remarkable. This enables the development of more efficient and selective chemical reactions and access to highly functionalized molecular motifs. Thus, gold's unique reactivity and properties make it a highly valuable tool for designing therapeutic agents on an industrial scale.



Innovative Molecular Scaffolds: From Theory to Practice

Our research aims to prepare bridged polycyclic structures starting from simple substrates. The purpose of my PhD is to develop a divergent synthesis of various bi-, tri-, and even hexacyclic structures with novel and original frameworks. From a single starting substrate possessing different functional groups able to react together, we designed conditions to reach each of the 8 potential polycyclic scaffolds selectively. The idea is to build, efficiently, complex and innovative building blocks with patterns found in numerous natural substances that have shown biological activity. Taking into account Lipinksi's rule of 5, we ensured that our compounds have functional groups for further functionalization, able to enhance the drug absorption and distribution. In simple terms, the aim of our project is to build complex frameworks and then decorate them with specific features to design promising drug candidates. Our methodology is based on gold catalysis but other metals that showed similar reactivities such as silver or indium catalysts have been employed. By playing between the metal, the ligand or the solvent, we can drive the formation of one of the polycyclic derivatives. By diversifying different starting materials, we are able to obtain hundreds of scaffolds with a high degree of three-dimensional complexity.

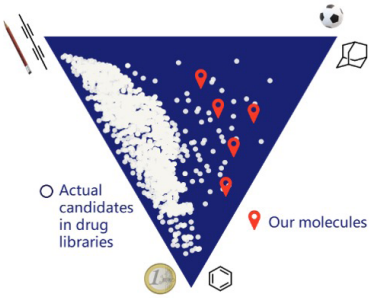


Illustration of the molecular geometry in the actual drug libraries.

During my PhD, the aim is to provide Servier a diverse array of promising molecules to enrich the molecular libraries. By adding these novel molecules, we aim to increase the structural diversity and complexity of Servier's database, hoping to enhance the success rate of drug discovery through more innovative candidates for biological testing.

To conclude, our innovative gold-catalyzed methodology allows for rapid and efficient access to highly complex structures while adhering to green chemistry principles. With this project, we aim to provide to Servier an access to unprecedented three-dimensional scaffolds and open new perspectives for chemical diversity and structural complexity of drug candidates.

NEW MEMBER'S SPOTLIGHT

Louise Rethacker
Immuno Oncology & Oncology Therapeutic Area, R&D Servier Paris-Saclay Institut, Gif sur Yvette, France

Uncovering Tumor-Intrinsic Pathways Differentially Regulating αβ and γδ T Cell Activation

T cells are key players in the tumor immunosurveillance, recognizing and eliminating tumor cells through their T-cell receptor (TCR). The two main subsets, αβ and γδ T cells, differ in their TCR composition and antigen recognition mechanisms. While αβ T cells rely on MHC-restricted antigen presentation, γδ T cells recognize antigens in a non-MHC-restricted manner. However, the tumor-intrinsic factors that differentially regulate γδ and αβ T cell activation remain poorly understood. Genome-wide CRISPR screening provides a powerful method to identify genes and pathways involved in this activation.

Primary human αβ and γδ T cells are co-cultured with the same cancer target to compare their responses and identify key genetic hits that differentially influence activation. To activate αβ TCR, CD8 T cells are transduced with a TCR specific for the NY-ESO-1 antigen, expressed by the melanoma cell line A375, used as a tumor model to assess T cell activation. In parallel, Vγ9Vδ2 T cells are activated and expanded using zoledronate stimulation. After expansion, both T cell populations are co-cultured with A375 cells stably expressing Cas9 and the CRISPR library. Surviving cancer cells are then sequenced to identify enriched gRNAs, allowing for a comparative analysis between the two T cell subsets. This approach aims to uncover tumor-intrinsic mechanisms shaping αβ and γδ T cell responses, as well as cancer cell antigen processing required for Vγ9Vδ2 T cell activation. The findings could offer new insights into T cell-tumor interactions and reveal potential targets to enhance cancer immunotherapy.

SPACE: Surface Proteomics for AML-derived Cells Explores potential new targets and biomarkers through multi-omics strategy

Acute Myeloid Leukemia (AML) is a highly heterogeneous disease, presenting significant challenges in treatment, with many patients lacking viable therapeutic options. In the pursuit of novel therapeutic targets, particularly for antibody drug conjugates and T-cell engagers, comprehensive mapping of the cell surface proteome is critical to differentiate between blasts and healthy cells. This study outlines two innovative proteomic strategies developed to identify and quantify the cell surface proteome in patient-derived blasts. The first strategy involves membrane isolation through centrifugation, while the second employs non-transmembrane biotin labeling of surface proteins' extracellular domains on living cells followed by streptavidin enrichment. Both methodologies proceed with the digestion of isolated membrane proteins into peptides, which are subsequently identified via state-of-the-art mass spectrometry coupled with liquid chromatography. These approaches have successfully identified over 2000 membrane proteins, including 80 cluster dissociation (CD) proteins, in the OCI-AML-3 cell line. Once optimized, the protocol will be applied to AML patient samples to further elucidate the cell surface proteome profile in AML. Additionally, samples' RNA will be sequenced, and proteomics and genomics data layers will be merged to provide a comprehensive mapping of the molecular landscape of AML. This method holds significant potential for uncovering new therapeutic targets, ultimately contributing to the development of more effective treatments for patients.

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NEW MEMBER'S SPOTLIGHT

Charlotte Job
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Identification of Therapeutic Targets from Single-Cell RNA-Seq Data Using Biologically Interpretable Deep Neural Networks

Deep learning applied to single-cell RNA sequencing (scRNA-seq) enables the identification of therapeutic targets by capturing complex gene expression patterns. However, deep neural networks (DNNs) are inherently opaque, limiting their interpretability for informed decision-making in the early drug discovery. Existing post hoc methods, such as attention mechanisms, offer limited biological relevance as they do not constrain model representations to align with known biological concepts. To address this challenge, we propose to design and implement biologically interpretable DNNs that integrate prior knowledge directly into the model. We enforce structure in the latent space through biologically informed priors, regularization terms, and architectural constraints derived from curated knowledge databases and ontologies. These constraints reflect gene-gene interactions, protein networks, and signaling pathways, ensuring that learned representations correspond to biologically meaningful features. By explicitly shaping the latent space, our approach enables direct interpretation of pathway perturbations, differential activation patterns, and cellular state transitions. This framework improves mechanistic understanding of disease-associated transcriptional deregulations and drug-induced perturbations, enhancing the biological relevance of model predictions. By bridging the gap between deep learning and biological interpretability, our approach strengthens the identification of actionable therapeutic targets, providing a more transparent and biologically grounded alternative to conventional black-box models.

Leveraging Brain-Derived Extracellular Vesicles as Biomarkers for Advancing Neurology Disease Research

Diagnosing and monitoring the effectiveness of therapies for neurological diseases remains challenging due to the scarcity of reliable circulating biomarkers. Current methods rely primarily on neuroimaging and neuropsychiatric assessments, which are costly, invasive, and often limited by overlapping symptoms among disorders. Among circulating biomarkers, extracellular vesicles (EVs)—small membrane-bound particles secreted by cells into the extracellular environment—are present in all biofluids, including blood, cerebrospinal fluid (CSF), urine, and saliva. EVs play a crucial role in cell-to-cell communication by carrying molecular cargo rich in proteins, lipids, and RNA, which reflect the physiological state of their cells of origin. Notably, brain-derived EVs (BDEVs)—originating from astrocytes, oligodendrocytes, and neurons—can cross the blood-brain barrier (BBB), making them promising candidates for the diagnosis and therapeutic monitoring of neurological diseases. Through the development of an immunocapture-based method to selectively isolate BDEVs from human plasma and CSF samples, our approach aims to comprehensively characterize their cargo using multi-omic techniques. Overcoming the technical challenges associated with BDEV isolation and analysis will pave the way for their clinical application as minimally invasive biomarkers, ultimately improving early diagnosis and monitoring of therapeutic strategies for neurological disorders.

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NEW MEMBER'S SPOTLIGHT

Mario Favre-Moiron
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Deep Mendelian Randomization: explaining causality between traits at genome-wide scale

Mendelian Randomization (MR) is a method that infers the causality between risk factors and diseases using genetic variants as instrumental variables. It has the potential to mimic drug target effects observed in clinical trials, paving the way for new therapeutic target discovery. However, MR faces biases such as pleiotropy, where a single variant influences multiple traits.

To address these limitations, we propose an innovative approach that leverages artificial intelligence with the aim to 1) include a larger number of exposures and variants 2) incorporate a greater variability of omics data, and 3) integrate these data with a Double Machine Learning pipeline. We expect that this strategy will allow us to take advantage of the prediction capacities of ML algorithms to process the large amount of data in order to disentangle the pleiotropic effects of variants and therefore provide more accurate causal effect estimators.

Our method is currently being tested in extensive simulation scenarios and will subsequently be applied to uncover intricate relationships between the immune system and cancer. The primary data in our pipeline are GWAS data, which are the basis of Mendelian Randomization analysis. A particular focus is placed on protein quantitative trait loci (pQTL) and expression quantitative trait loci (eQTL) data, given their significant potential for discovering therapeutic targets.

Characterization of a novel in vitro Human Blood Brain Barrier model for drug development and screening

The blood-brain barrier (BBB) is a complex structure that protects the brain by regulating the passage of substances from the bloodstream. While crucial for cerebral homeostasis, it presents a significant challenge for drug development. Most therapeutic compounds cannot cross it and reach their targets in the brain, and even when they do, they may induce neurotoxicity, limiting their clinical efficacy.

To date, no in vitro BBB model has fully replicated the structural and functional complexity of the in vivo BBB. At the CEA Saclay, Aloise Mabondzo's lab has developed a simple and effective model using the Transwell system, involving a co-culture of endothelial cells derived from induced pluripotent stem cells (iPSCs) and primary rat astrocytes. This model successfully mimics several key aspects of the in vivo BBB. However, it lacks the shear stress exerted by blood flow, a factor known to enhance endothelial maturation. Therefore, our collaborative project with Pr Mabondzo aims to integrate shear stress into this model, using PhysioMimix, an organ-on-a-chip (OOC) platform developed by CNBio. The impact of shear stress on the BBB properties will be assessed by measuring transendothelial electrical resistance (TEER) and analyzing biomarker expression. Additionally, the expression of efflux and uptake transporters will be evaluated and the permeability of compounds known to cross the BBB will be analyzed and compared with in vivo data. This model will also facilitate the design of future combination models, such as BBB-Liver, or BBB-Tumoroid models, to assess liver-derived metabolites permeability across the BBB and drug accessibility to brain tumor targets.

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SERVIER

MEMBERS' RESOURCES_DID YOU KNOW

The Spartners incubator at Servier is a true hub of innovation where promising startups come together, each bringing unique value to the ecosystem. The proximity between these emerging companies and Servier creates an environment conducive to the exchange of ideas and co-creation. This collaborative spirit fosters powerful synergies and stimulates creativity, thus accelerating the development of innovative solutions in the healthcare field.

This dynamic network encourages the sharing of knowledge, pooling of skills, and collaboration on ambitious projects. Spartners incubator welcoming innovative start-ups across a broad range of therapeutic areas — from cancer, neurology to life science technology. Every year, Spartner is opening a Golden Ticket to offer a startup a bench and a lab in the Spartner incubator. Choosing a winner is a difficult decision, especially as the shortlisted startups are all aligned with Servier's strategic focus—namely neurology, oncology, or technology platforms. Ultimately, only one startup is selected.

AGS Therapeutics (04.2023)

They develop medicines for devastating human diseases (e.g. ophthalmology, bowel diseases, CNS disorders and respiratory diseases) based on microalgae extracellular vesicles (EVs) to deliver human therapeutics, vaccines and gene therapies.
The power of the EVs is multiple; they can overcome stringent biological barriers and deliver specifically bioactive genes.

Sparing Vision (09.2023)

SparingVision is a biopharmaceutical company specializing in the development of innovative therapies for inherited retinal diseases. It focuses on R&D regarding the vision' preservation of patients with rare degenerative retinal conditions, such as retinitis pigmentosa. SparingVision employs gene therapy approaches to target photoreceptor cells and protect them from degeneration.

.omics (02.2024)

At .omics, AI takes an important place to revolutionize plant biology, by furnishing innovative solutions to food security and sustainability.

AlgenScribe (01.2024)

Genome editing technology is the cornerstone of this company. To treat diseases, they modify the genes' expression in target cells (by deactivating a nocive gene or inserting a therapeutic gene).
They apply this technology to therapeutics, bioproduction, diagnosis and research.

Diampark (02.2024)

Diampark is a neurothech company dedicated to Parkinson's disease. Innovation is based on the capture, measurement and analysis of digital neuromarkers specific to Parkinsons's disease.

DeltaWave (04.2024)

Deltawave aims to accelerate scientific discovery by developing softwares based on AI and machine learning.

OncoNex Remunity (10.2024)

They develop next-generation immunotherapies that aim to boost anti-tumor immune response. They also focus on overcoming resistance to current treatments.

GEG_Geneteci Engineering Technologies_ Tech (04.2024)

The biotechnology company is specialized in the development and application of gene editing technologies.
GEG platform adresses several areas:

- Cancer immunotherapy (CAR-T and other CAR cells, RNA cells pre-engineering…)
- mRNA vaccination (proprietary platform)
- Gene therapy applications leveraged by RNA/DNA vectorization systems
- R&D tools (custom advanced RNA/DNA vectors)

Cementic (10.2024)

Cementic is dedicated to revolutionizing dental care and bone regeneration through their advanced root canal sealer that permits eradicating bacteria, enhancing healing and preventing complications.

Ispiron (03.2025)

This company is specialized in R&D and biomanufacturing of therapeutic molecules.

Papilio.bio (04.2025)

They develop HPV screening to reduce the number of cervical cancers.

FloBiotech (03.2025)

FloBiotech uses advanced human brain cell models to develop disease-modifying therapeutic and diagnostic candidates to cure Alzheimer's disease.

Owl Life Sciences (04.2025)

Owl Life Sciences is a biotechnology company dedicated to advancing healthcare through systems & synthetic biology approaches such as in vitro vascularised assembloids and biohybrid computing. They also exploit AI to target otherwise unreachable advanced therapies for central nervous system conditions and dysfunctions.

BEHIND THE SCENE

Next issue

We are excited to announce that the upcoming issue of the SUNDARI Journal will feature a special edition focused on the Department of Chemistry. This edition will offer an in-depth exploration of cutting-edge research, innovative breakthroughs, and collaborative initiatives that shape the future of the field. It will include exclusive interviews with leading experts, thoughtful analyses of emerging trends and advancements within the chemistry community. Thanks to the opportunity opened by Dr Andras Telek, we are thrilled to bring SUNDARI to Hungary in this upcoming issue. Stay tuned for this rich edition!

Lisa and Audrey joined and are now actively involved in the SHINEDocs community as well as in the support of the Sundari journal.

Lisa Racine
R&D External Innovation project manager

Chemist engineer by training, with a PhD in drug formulation from CEA Leti Grenoble, Lisa joined Servier in 2018. In addition to her role of SHINEDocs community manager, Lisa is leading competitive intelligence activities for External Innivation needs withing the R&D External Innovation team.

Audrey Artinian
HR Business Partner

After earning a Master's in Marketing and Communication from ISC Paris, I spent five years in a Parisian communication agency specializing in mass retail. I joined Servier in 2021, supporting HR communication for the move to Saclay (DDAYs, videos, HR interviews). In 2023, I trained to become an HRBP. I am now HR for SPEED and DDAI, with a referent role for the SHINEDocs.

The Sundari Journal
Editorial Board

Meet the SUNDARI Journal's Editorial Board, a team of experts who steer our publication. They're responsible for maintaining the journal's high standards, curating innovative and insightful content, and fostering scientific exchange. Their commitment ensures the SUNDARI Journal remains a reliable source of knowledge, innovation, and collaboration.

SUNDARI Journal's Editorial Board (from left to right) : Hélène Lê, Julie Le Naour, Sergio Gonzalez Duque, Charlotte Brun, Nell Hirt.

Hélène Lê
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Julie Le Naour
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Sergio Gonzalez Duque
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Contact us and submissions:

We encourage contributions from our community. If you have research findings, insights, or stories to share, please reach out to us. The Editorial Board welcomes submissions that align with our commitment to advancing science and knowledge. For guidelines and submission details, or to discuss potential contributions, please contact us at sundarijournal@servier.com
We look forward to your valuable input and collaboration in shaping the future issues of the SUNDARI Journal.

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