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# PSL Chemical Biology Symposia Third Edition: A Branch of Science in its Explosive Phase

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**Abstract:** Chemical Biology, the science of building molecular systems to investigate biology, delivers otherwise inaccessible knowledge and provides the means to control cellular processes with unique spatiotemporal resolution and efficacy.

## Introduction

This symposium is the third PSL (Paris Sciences & Lettres) Chemical Biology meeting (2016, 2019, 2023) held at Institut Curie. This initiative originally started at Institut de Chimie des Substances Naturelles (ICSN) in Gif-sur-Yvette (2013, 2014), under the directorship of Professor Max Malacria, with a strong focus on chemistry. It was then continued at Institut Curie (2015) covering a larger scope, before becoming the official PSL Chemical Biology meeting. This latest edition was postponed twice for the reasons that we know. This has given us the opportunity to invite additional speakers of great standing. This year, Institut Curie hosted around 300 participants, including 220

on site and over 80 online. The pandemic has had, at least, the virtue of promoting online meetings, which we came to realize is not perfect but has its own merits. In particular, it enables those with restricted time and resources to take part in events and meetings, which can now accommodate unlimited participants. We apologize to all those who could not attend in person this time due to space limitation at Institut Curie.

As detailed below, the topics covered this year included the study and selective targeting of nucleic acids structures, mechanisms of innate immunity, new technologies to delineate protein functions in cells, the development of sensors for quantitative and spatial analyses of biochemical processes in living cells, the *de novo* design of proteins with new functions, the molecular basis of cell death involving oxidized lipids, the recent developments in the field of epitranscriptomics, a previously uncharted role of glycans in the signaling of anti-cancer immunity and the use of small molecules to investigate the underlying causes of human diseases, with a fresh perspective on 'molecular glues' and their rising profile. Perhaps wider than a pure biological focus, Jean-

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Marie Lehn discussed new concepts in supramolecular chemistry stating that ‘*if order can happen, order will happen*’, which in some ways reflects key features of the biology of the cell, notably membrane lipid assembly for belayer formation, cell compartmentalization and genome organization...and so life happened! Jack Szostak, on the other hand, provided a compelling vision of why life may have started with RNA, the results of several decades of thinking and repeated painstaking experiments. We have been honored by the ventures of so many deep thinkers, and ‘*giants in the field*’ said Bridget Wagner. Stuart Schreiber concluded the symposium by stating that ‘*the lectures had been mind-boggling and electrifying in many dimensions*’ and that the ‘*field was in an explosive phase*’. A clear message for the younger generations that stood out is that there is no success without taking risks and going through repeated failures. One of the secrets to success is to fail quickly, said Sir Shankar. There is no passion to be found playing small, in settling for a life that is less than the one you are capable of living, once stated Nelson Mandela. And so our mantra is: ease is a greater threat to progress than hardship. Hard work works!



Figure 1. Invited speakers

### Shankar Balasubramanian: Structure and function of DNA G-quadruplexes

Balasubramanian invented next-generation sequencing together with Klenerman, Mayer and few others. The Balasubramanian lab spent the past twenty years focusing on a non-Watson-Crick type of nucleic acid structure termed G-quadruplex (G4). This 3D structure is formed by the assembly of up to four DNA strands containing specific guanine rich motifs. His team is interested in understanding where these motifs form in genomes and whether they do exhibit a function. Using computational approaches, they discovered that in addition to the telomeres, G4s could also form in the promoter region of some genes, and therefore influence transcription<sup>[1]</sup>. He also presented how his team was able to visualize G4 DNA structures in human cells using an engineered antibody developed by phage display, which exhibits a high affinity for G4 structures<sup>[2][3]</sup>. With immunostaining, they showed that cancer cells contain a particularly high density of G4s. Balasubramanian then presented how next generation sequencing was exploited to identify these structures using ChIP-seq methods<sup>[4]</sup>. With his team, they found that the structure of G4 is closely associated with open chromatin. Finally, he presented the chemical profiling of a DNA G4-interacting protein. In fact, G4 structures in chromatin might act as hubs for the recruitment of

transcription factors. By mutating sequences of G4s in the MYC promoter and rescuing their structures, his team highlighted that transcription factors bind to DNA by recognizing G4 structures and not its unfolded sequence. A modified structure alters protein recruitment<sup>[5]</sup>: a killer experiment!

### Yamuna Krishnan: Quantitative chemical imaging in live cells

Yamuna Krishnan is a true pioneer in the field of nucleic acid-based nanotechnologies to probe living cells. “If the human body is a cell, then organelles are like its organs”. This was the opening statement of Krishnan. She went on describing the infinite complexity of the human cell and the role for compartmentalization in the functioning of cells. She asked the question of how we can access organelles in cells with precision, in particular to measure ion concentrations accurately in a controlled manner, one of the areas of focus of her laboratory. For this purpose, they have developed nucleic acid-based nanodevices carrying carefully selected fluorophores as organelle-specific ratiometric fluorescent reporters. Among them, Voltair is a fluorescent DNA nanodevice that can measure membrane potentials of different organelles *in situ* in live cells thanks to an integrated mV sensor<sup>[6]</sup>. This biochemical tool led to the discovery that organelles have different membrane potentials and ion permeabilities from each other and from the plasma membrane. This also permitted them to quantify the contribution of proton transport to the membrane potential of each organelle. Krishnan described a newly developed reporter called *pHlicKer*, which acts as a pH reporter for K<sup>+</sup> in organelles, which, based on the targeting module displayed, could be localized to early endosomes<sup>[7]</sup>, the trans Golgi network<sup>[8]</sup> or to recycling endosomes<sup>[6]</sup>. By calculating the ratio of the different fluorescent signals emitted by *pHlicKer*, it is possible to get a K<sup>+</sup> and pH heatmap of the organelle. This technology can also be adapted for other ions such as H<sup>+</sup> and Cl<sup>-</sup> and is called two-ion measurements<sup>[9]</sup>. Krishnan then discussed how *pHlicKer* could be applied to study the well-known cell surface potassium channel K<sub>v</sub>11.1, which moves K<sup>+</sup> ions across the plasma membrane. Using *pHlicKer*, she and her research group showed that K<sub>v</sub>11.1 is active not just at the plasma membrane, as previously thought, but also at membranes of organelles. She ended her talk by suggesting new roles for cell-surface K<sup>+</sup> channels in organelles, the potential existence of channel modulators that could change channel trafficking and localization to organelles, and that the open/close states of channels could vary in organelles.

### Andrea Ablasser: Intracellular DNA sensing in health and disease

Andrea Ablasser’s impactful research on the cGAS-STING pathway has given a new life to the field of innate immunity. She explained how sensing DNA can be a danger signal inside cells eliciting a signaling response of host defense. Prior work on the immune response showed that viruses communicate with immune cells. Viral nucleic acids bind to cell receptors and induce signal cascades, which triggers an immune response by the secretion of cytokines such as type I interferon (IFN). Thus, it is crucial to decipher DNA interactions with proteins and DNA sensing inside the cell. The work of Ablasser depicted the various actors and steps of the cGAS-STING pathway from DNA to the impact on type I IFN release, while evoking potential therapeutic outcomes. In this pathway, the ligand DNA binds to a first receptor: the cGAS enzyme, containing specific binding domains for DNA. The binding triggers a conformational change that provides a catalytic site, which creates a second messenger cGAMP binding to a second receptor called STING, a membrane protein of the endoplasmic reticulum. STING is then transported to the Golgi, where either the lysosomal degradation (TBK1 through CTT, with AP1 and clathrin) or the use of NF-κB to increase IFN transcription and translation (TBK1 through CTT and

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IRF1-3) are triggered. It was also demonstrated that the cGAS enzyme itself translocates to the nucleus and binds to chromatin.<sup>[10]</sup> It is interesting to note that in both cytosolic and nuclear compartments processes are tightly regulated, through DNA accessibility and DNase activity.<sup>[11]</sup> The cGAS–STING pathway is key to understanding inflammatory processes, but also different pathologies, in particular dysregulations in aging and neurodegeneration. Some potential therapies arise from these understandings, opening up avenues for new therapeutic approaches.<sup>[12]</sup>

### Laura Kiessling: Glycans in immunity

Laura Kiessling could be referred to as *'the queen of glycobiology'*. Glycans are present at the cell surface and therefore can be recognized by immune cells through specific surface receptors, called lectins. Kiessling's endeavors are focused on understanding how glycan recognition can be exploited to enhance immunity. Synthetic probes have been developed to mimic glycans and bind lectins to modulate immune responses<sup>[13]</sup>. Kiessling has been working on the activation of dendritic cells (DCs) by glycan recognition. DCs are the most powerful antigen-presenting cells that give instructions to T cells and induce their differentiation. Therefore, controlling DC activation can be a way to modulate immune response in patients, for instance to develop vaccines against cancer. Prophylactic vaccines rely on antibodies (T<sub>H</sub>2 immunity) and are efficient in preventing infections by pathogens but not to treat cancers. Kiessling's method consists of promoting anti-tumor responses via virus-like particles (VLPs) to deliver tumor antigen to DCs. Because these VLPs are decorated with synthetic mannositides, they are efficiently recognized, taken up by DCs, and signal via the C-type lectin DC-SIGN. A key finding is that the synthetic mannoside can collaborate with other immune receptors (e.g., the Toll-like receptors) to alter T cell differentiation. Only those particles decorated with the synthetic mannose derivative induce the secretion of proinflammatory cytokines characteristic of a T helper type 1 (T<sub>H</sub>1)-like immune response<sup>[14]</sup>, which is more adapted than a T<sub>H</sub>2-like response for an anti-cancer immunotherapy. This combinatorial signaling platform provides a blueprint to optimize the immune responses against cancer or other diseases.

### Chuan He: RNA methylation in gene expression regulation

Chuan He, a pioneer in the field of epitranscriptomics, works on how RNA methylation impacts on gene expression using chemical and biological approaches. His team showed that m<sup>6</sup>A, one of the most abundant mRNA modifications in eukaryotes, is regulated by a set of proteins that install, recognize and remove this modification. m<sup>6</sup>A was shown to be critical to cell differentiation and development. He reported that the biological function of m<sup>6</sup>A is mediated by a set of proteins that act as writers, readers and erasers. For example, METTL3/METTL14 methyltransferase complex and an accessory factor WTAP install m<sup>6</sup>A onto mRNA, while iron-dependent demethylases FTO and ALKBH5 act as "erasers" to reverse this process<sup>[15]</sup>. In addition, his team characterized the YTH protein family, the m<sup>6</sup>A reader proteins, involved in cellular mRNA homeostasis. For example, YTHDF2 binds to m<sup>6</sup>A in mRNA and mediates decay of transcripts during developmental events. YTHD1, YTHD3 and eLF3 promote translation of methylated mRNA<sup>[16]</sup>. Next, He showed that the m<sup>6</sup>A of chromatin-associated regulatory RNA can fine-tune chromatin states and transcription<sup>[17]</sup>. Finally, he presented his recent discovery on the role of FTO-mediated m<sup>6</sup>A demethylation of long-interspersed element-1 (LINE1) RNA in mouse embryonic stem cells. He showed that LINE1 RNA m<sup>6</sup>A demethylation regulates LINE1 RNA abundance and the local chromatin state during development<sup>[18]</sup>.

### Matthew Disney: Sequence-based design of small molecules targeting RNA structures to manipulate and study disease biology

Matthew Disney presented small molecule approaches to degrade RNA structures that play crucial roles in diseases, an alternative to the use of anti-sense oligonucleotides<sup>[19]</sup>. Through high throughput screening of the Repurposing, Focused Rescue, and Accelerated Medchem (ReFRAME) library<sup>[20]</sup>, his team identified a small molecule susceptible to target an intronic RNA repeat r(G4C2)<sup>exp</sup> whose retention in the C9orf72 gene causes amyotrophic lateral sclerosis (ALS) and frontotemporal dementia. Central Nervous System Multiparameter Optimization (CNS-MPO) desirability scores, which are primarily meant for protein-focused small molecules, were applied to the pool of hit compounds to obtain brain barrier penetrant RNA-specific targeting lead compounds that alleviate disease-associated defects in c9ALS patient-derived induced pluripotent stem cells (iPSCs) and in two c9ALS/FTD mouse models. Further investigation revealed the mode of action of the compound, whereby its binding to r(G4C2)<sup>exp</sup> diminishes intron retention and allows the liberated intron to nuclear exosomal decay without affecting its degradation.

### David Baker: Protein design using deep learning

David Baker is a pioneer in the field of protein structure prediction and *de novo* protein design. He presented two approaches that his team developed and used to model new proteins with optimized structures and functions. The first one is the Rosetta model based on previously established physical parameters, which computes amino acid sequences of targeted protein structures that are predicted to have the minimal global free energy<sup>[21]</sup>. The second approach is based on deep learning, i.e. training a model to understand the chemical propensities and environments with desired properties<sup>[22]</sup>. Using these methods, Baker and his team were able to design new binders that target a specific site on a surface protein by using only the 3D structure of the target<sup>[23]</sup>. Baker showed how these new technologies are leading towards a plethora of new possibilities for therapeutic intervention and possible treatments. For instance, his team developed miniprotein inhibitors that interfere with the binding of SARS-CoV-2 to the ACE2 receptor with high affinity, therefore blocking viral infection<sup>[24]</sup>.

### Jack Szostak: Why did biology begin with RNA and not something else?

Jack Szostak is known for his contribution to our understanding of how chromosomes are protected by telomeres and the enzyme telomerase, for which he was awarded the 2009 Nobel Prize in Physiology. His research team currently focuses on understanding the chemical and physical processes underlying the origin of life. He presented their recent findings on mechanism of non-enzymatic ribonucleic acid (RNA) copying in prebiotic systems. His research shows that replacement of the methyl group of 2-methylimidazole activated nucleotides with an amino group results in improved yields of nonenzymatic RNA template copying by primer extension<sup>[25]</sup>. Crystallographic studies of this process revealed that the formation of an imidazolium-bridged dinucleotide intermediate provides structural pre-organization that enables easy attack of the incoming nucleotide<sup>[26]</sup>. Deep sequencing of nonenzymatic RNA primer extension products shows that the bridged dinucleotide enhances the fidelity of this RNA copying mechanism<sup>[27]</sup>. Furthermore, his team found that monomers bridged to oligos are better substrates for nonenzymatic RNA replication<sup>[28]</sup>. He provided insights explaining why life may have started from RNA and how modern RNA emerged from a heterogenous prebiotic chemical pool. His research explains that the activated ribonucleotides are more efficient in the nonenzymatic primer extension, when compared to

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other nucleotides such as arabinonucleotides<sup>[29]</sup> and threonucleotides<sup>[30]</sup>. His team, therefore, proposes the hypothesis that heterogeneous oligonucleotides formed initially in the prebiotic chemical pool. Template copying chemistry then favored RNA synthesis, which after multiple rounds of replication enriched the RNA oligomer pool that may have led to the emergence of modern RNA.

### Chris Schofield: Oxygenase catalyzed protein modifications

“Chemistry of biology is indefinitely complicated, and science makes mathematical models to interpret experimental data”. With this Jack Baldwin-like thought-provoking statement, Chris Schofield started his lecture. He gave an introduction on 2-oxoglutarate (2OG)-dependent oxygenases, which are enzymes containing a Fe(II) at their catalytic center. Interestingly, although some substrate specificity has been reported for this type of enzymes, they have a rather promiscuous profile. In the presence of O<sub>2</sub> and 2OG, these enzymes oxidize the substrate and form CO<sub>2</sub> and succinate as co-products. Therefore, 2OG oxygenases are sensible to their physiological environment and participate in the general metabolism of the cell. 60-70 human 2OG oxygenases are involved in DNA repair, chromatin oxidation, histone modifying enzymes, RNA modifications and lipid metabolism among others. Although these enzymes have been shown to perform certain chemical reactions *in vitro*, it remains challenging to assign a specific substrate specificity in cells. Schofield argued that their promiscuity might make the interpretation of biological *in cellulo* data challenging. He continued arguing that because 2OG oxygenases need O<sub>2</sub> as a co-substrate, they are potential hypoxia sensing enzymes. For instance, HIF- $\alpha$  can be oxidized by the Prolyl Hydroxylase Domain (PHD) enzyme, leading to its degradation by the proteasome and thus turning down the hypoxic response. On the contrary, if O<sub>2</sub> levels become limiting, HIF- $\alpha$  levels rise and turn on the hypoxic response. Schofield described the structure of an enzymatic complex at the Fe(II) catalytic center and the consensus mechanism of the catalytic cycle<sup>[31]</sup>. He also discussed the value of using inhibitors to decipher the mechanism of specific 2OG oxygenases like HIF or FIH (factor inhibiting HIF) in the transcriptional regulation of their target genes, or to potentially treat some diseases such as anemia, renal cell carcinoma or van Hippel-Landau disease. In this respect, the design of specific inhibitors is challenging, not just because of substrate promiscuity but also because of different contexts between biological systems. He ended his talk by concluding that 2OG oxygenases are involved in all stages of protein synthesis and metabolism but there is still much to be discovered about other hypoxia sensors and their mechanisms<sup>[32]</sup>, and he advocated that we need new analytical methods to quantify physiologically relevant chemistry of biology.

### Maja Köhn: Modulator development and proteomics approaches to manipulate and study protein phosphatases

Maja Köhn's remarkable ability to delve into challenging research problems, such as deciphering phosphatase-substrate networks in cells, has earned her many accolades from the scientific community. She presented her laboratory's approach to activate specifically a serine/threonine-specific protein phosphatase, responsible for the majority of the dephosphorylation reactions, with a synthetic peptide. Protein phosphatase-1 (PP1) and 2A (PP2A) work on specific substrates during many cellular processes and are regulated by diverse holoenzymes, whose dysregulation contributes to diseases such as cancer, diabetes, and heart failure<sup>[33]</sup>. Her approach to control this protein-protein interaction is different from the common small-molecule pan-inhibitor as it involves highly specific, optimized, and cell-permeable PP1-disrupting peptides (PDPs), which disinherit PP1 in cells<sup>[34]</sup>. They then studied whether this mechanism of action

could help rescue the sarcoplasmic reticulum (SR) calcium leak in human patient tissues suffering from cardiomyopathy or cardiac hypertrophy. Inside the cardiac muscle, calcium ions mediate the contraction and relaxation of the heart, which is dependent on the phosphorylation of calcium channels. PDPs enable two serine residues of the calcium channel RyR2 to be dephosphorylated, leading to a 75% decrease in the total calculated SR calcium-leak. Their dephosphorylation assay on an 11,000 phospho-peptide-containing library followed by a proteomic approach highlighted that the catalytic subunit of PP1 contributes to substrate selectivity unlike that of PP2A, which requires holoenzymes. She concluded her seminar with their recent discovery that PDP-bound PP1 is more likely to recognize substrates containing basic p-loop motifs<sup>[35]</sup> and their update to the human DEPhosphorylation Database (DEPOD)<sup>[36]</sup>.

### Kathrin Lang: Expanding the genetic code – new chemistries for biology

Kathrin Lang reshuffles the cards in the competitive field of expanding the genetic code, with unprecedented applications. Her research group harnesses the power of chemical reactions and site-specific incorporation of non-canonical amino acids into proteins to develop tools for imaging proteins, studying protein-protein interactions and reengineering proteins to hijack molecular networks and biological pathways such as ubiquitylation in living cells. She described biorthogonal labeling of proteins in cells using chemoselective reactions with the incorporated non-canonical amino acid<sup>[37]</sup>. She illustrated the use of light-induced inverse electron-demand Diels–Alder cycloaddition (iEDDAC) reactions between tetrazine-tagged proteins and strained alkene/alkyne fluorophores to visualize proteins in living *E. coli*<sup>[38]</sup>. By site-specific incorporation of amino acids bearing diazirine moieties or leaving groups such as bromine into the protein of interest, her team covalently crosslinked the interacting proteins to profile substrates and study protein-protein interactions<sup>[39]</sup>. She presented her group's recent work on the use of genetic code expansion, bio-orthogonal Staudinger reduction and sortase-mediated transpeptidation to site-specifically ubiquitylate and small-ubiquitin-like modifier (SUMO)ylate target proteins *in vitro* and *in cellulo*<sup>[40]</sup>. Furthermore, by using orthogonal sortases, the generation of bi-, multi-, and branched-ubiquitylated and SUMOylated target proteins was achieved<sup>[41]</sup>. Recently, her team also developed a complementary chemoenzymatic approach to generate ubiquitylated protein conjugates using asparaginyl endopeptidases<sup>[42]</sup>.

### Jean-Marie Lehn: Constitutional dynamic chemistry and soft matter self-organization

Jean-Marie Lehn received the 1987 Nobel Prize in Chemistry for his pioneering work in the field of supramolecular chemistry. At the meeting, he presented some of his work on covalent and non-covalent dynamic combinatorial chemistry, where the molecular composition of a complex mixture evolves in response to physical or chemical stimuli. Lehn explained that solvents can act as modulators of the self-organization of supramolecules by giving the example of water, which promotes hydrophobic intermolecular interactions between organic molecules, and thus increases the selectivity to generate supramolecules as helical rigid polymers<sup>[43]</sup>. Lehn then pointed out that surface absorption at a solid/liquid interface can drive covalent reactions but also selectivity towards reactions in solution between multiple reagents. In addition, he explained that in a [2 x 2] or [3 x 3] network, where reactive molecules are agonists or antagonists of each other, different factors can modulate product selectivity<sup>[44]</sup>. Metals can modulate the selectivity by chelation from specific reagents to promote the synthesis of agonist molecules. Another driving force highlighted by Lehn is the selectivity of covalent reactions by gel formation. If one molecule of the system can form a gel below a specific temperature, the agonist compounds would be selectively

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amplified. Thus, amplification of the fittest promotes amplification of the unfit. Finally, Lehn illustrated the gel organization on two types of dynamic covalent chemical reactions: C=N/C=N amine exchange process and C=C/C=N organo-metathesis reaction to emphasize that modulation of order in molecular and supramolecular chemistry is possible<sup>[45]</sup>. To conclude he stated that *'when organization is possible, organization happens'*. This raises several questions: Is there a cosmic imperative to drive to organization? Does the organization constitute an intrinsic property of visible matter in our universe?

### **Jin Zhang: Illuminating the biochemical activity architecture of the cell**

Jin Zhang, the archetype of a creative mind, has pioneered many new technologies to study living cells in space and time with unprecedented resolution. She develops genetically encoded fluorescent biosensors to probe signaling enzymes in their cellular context and to characterize their changes in diseases including cancer. Their aim is to understand the environmental changes and orchestration of specific responses from multiple inputs that control various processes within cells. This provides insights on molecular mechanisms underlying these processes in the spatial and temporal framework of the cell<sup>[46]</sup>. Disease states reflect the reorganization or restructuring of this biochemical activity architecture. Their FRET-based kinase activity reporter (KAR), enabling an energy transfer upon phosphorylation-induced proximity between two fluorophores, helped decipher protein kinase A (PKA), AMP-dependent protein kinase (AMPK) and other mechanism of action of kinases and phosphatases<sup>[47]</sup>, cAMP nanodomains in the cAMP/PKA signaling pathway<sup>[48]</sup>, and spatiotemporal regulation of phosphoinositides and Akt in the PI3K/Akt/mTORC1 pathway or to quantify Ras activity in the Ras/ERK signaling pathway<sup>[49]</sup>. Ultrasensitive and super-resolution imaging technologies are also being developed, such as engineered novel ExRai biosensors and Halo-KAR or the FLINC methodology, where the red fluorophore blinks upon phosphorylation of the substrate within the FLINC-KAR by the kinase of interest<sup>[50]</sup>. Their technology enabled to clarify an ongoing debate about GPCR-mediated ERK signaling. They demonstrated that this activity originates at the endosome and propagates into the nucleus requiring ligand-stimulated GPCR endocytosis and relying on active G $\alpha$ <sub>s</sub> at the endosome<sup>[51]</sup>. This then leads to selective upregulation of cMyc expression, thus enhancing cell proliferation.

### **Bridget Wagner: Phenotypic screening and mechanism of action studies in diabetes**

Bridget Wagner is a world leader in the field of elucidating mechanisms of action of small molecules and their use to probe biology. This time, she presented her work on diabetes, which still represents a major health burden throughout the world. Type 2 diabetes (T2D) is orchestrated by dysregulation and degeneration of pancreatic beta cells. Small molecules such as sulfonylureas were discovered to stimulate production of beta cells, but side effects including hypoglycemia remain a major drawback for patients. One of the axes of Wagner's team is to promote insulin secretion by means of small molecule intervention. To identify potent molecules, she designed a luminescence assay by inserting *Gaussia* luciferase into the C-peptide portion of proinsulin. This assay replaces the previous ELISA assay which is more time consuming and more expensive. To identify small molecules able to protect beta cells, they adapted this assay to high-throughput screening of 384K compounds. This led to the discovery of a molecule named BRD5653 which resulted in high luciferase activity in T2D human islets even when glucose concentrations are high<sup>[54]</sup>. However, the mechanism of action studies did not reveal the target of BRD5653. To identify its target, a genome-wide CRISPR screen revealed several receptors as being involved in glucose blood concentration. Wagner's team

demonstrated that BRD5653 induces glucose-dependent insulin secretion by activating a completely new target in diabetes, which opens unexplored clinical prospects in diabetic research.

### **Marcus Conrad: Ferroptosis – from basic mechanisms to therapeutic opportunities**

Marcus Conrad, a true pioneer in the field of ferroptosis, discussed his most recent findings and views in the field. In early findings published back in 2008, they showed that inactivation of a selenocysteine enzyme named glutathione peroxidase 4 (GPX4) causes a non-apoptotic form of cell death, later called ferroptosis<sup>[55]</sup>. Ferroptosis is described as a vulnerability of cells to iron-mediated lipid peroxidation, which has now been identified in several diseases including cancer. GPX4 is the major enzyme balancing the redox potential of cells by inhibiting lipid peroxidation caused by the reaction of lipids with reactive oxygen species (ROS), and therefore plays a crucial role in the ferroptotic response. His laboratory discovered that the ferroptotic suppressor protein-1 (FSP1) enzyme inhibits ferroptosis by reducing extramitochondrial ubiquinone (CoQ<sub>10</sub>) to ubiquinol, which prevents lipid peroxidation<sup>[56]</sup>. Following this work, Conrad and his laboratory recently described that vitamin K is a naturally occurring anti-ferroptotic compound, protecting cells against lipid peroxidation<sup>[57]</sup>. Recent work from Conrad and colleagues revealed that FSP1 drives a non-canonical vitamin K cycle, which constitutes a novel mechanism to inhibit ferroptosis. Therefore, these data link ferroptosis research and vitamin K biology. Other work in the field described dihydroorotate dehydrogenase (DHODH) as a regulator of ferroptosis<sup>[58]</sup>. However, Conrad's latest findings challenged this view, showing that inhibitors of DHODH actually inhibit FSP1.

### **Stuart Schreiber: The rise of molecular glues and bifunctional compounds**

Stuart Schreiber is one of the fathers of modern chemical biology with the discovery of mTOR, HDACs and the development of small molecule proximity inducers among other major achievements. In the early 90s, Schreiber and co-workers had shown that small molecules and natural products can promote proximity between two proteins that would not normally interact with one another, thereby leading to *de novo* functions. He coined such small molecules "molecular glue" (discovered in 1991<sup>[59]</sup>) or bifunctional compounds (discovered in 1993<sup>[60]</sup>). Molecular glues can be defined as small molecules, which upon binding to a hotspot of a protein change its interactome and biophysical properties. This can for instance mimic missense mutations and lead to the recruitment of new substrates. This new modality of small molecule drugs consisting of a small molecule-protein conjugate was exemplified with Schreiber's groundbreaking work on cyclosporin and FK506, which bind to cyclophilin or FKBP12, respectively, therefore allowing cooperative binding to the calcineurin protein<sup>[61]</sup>. Molecular glues can also bind to exo-sites of a protein enabling substrate-specific entry to the active site, as illustrated with the example of rapamycin, which binds to FKBP12 and targets mTOR. Molecular glues can also exert their activity intramolecularly, thereby conferring a conformation to the protein that inactivates or restores its activity. The difference between the two types of chemical inducers of proximity is cooperativity ( $\alpha$ ). The complementary interface created by the ligand between the dimerization partners increases the ternary complex stability ( $\alpha > 1$ ) in the case of a molecular glue while it simply forces proximity ( $\alpha \sim 1$ ) for the bifunctional compound. Uncooperative systems present a destabilizing interface between the two proteins ( $\alpha < 1$ ), therefore greatly reducing the chances of interactions. A recent example of bifunctional compounds that stirred massive interest is the group of PROteolysis Targeting Chimeras (PROTACs)<sup>[62]</sup>, hijacking on one side an E3 ligase complex and recruiting on the other side a protein of interest that will be ubiquitinated through induced proximity and degraded through the Ubiquitin-

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Proteasome System (UPS). This system enables control of cellular processes, not via gene fusion, but through native proteins and chemicals<sup>[63]</sup>. According to Schreiber, we are currently only seeing the tip of the iceberg of this concept concerning bifunctional TARgeting Chimeras (TACs) with the latest LYTACs<sup>[64]</sup> (using the lysosome degradation pathway), AbTACs<sup>[65]</sup> (using genetically encoded bispecific IgG antibody scaffolds to mediate membrane protein degradation), or (de)phosphorylation agents such as PhoRCs<sup>[66]</sup> or PHICs<sup>[67]</sup>. Recent efforts to accelerate the screening for binders uses the combination of diversity-oriented synthesis (DOS) and DNA-encoded library (DEL) approaches to generate safe and effective therapeutics (library DOSEDO)<sup>[68]</sup> with tissue and substrate selectivity, representing new avenues for the development of next generation therapeutics.

## Conclusion

We were thrilled to host editors from several publishers, which gave to students and postdocs the opportunity to showcase their work and to be challenged during the poster sessions. Eleven prizes were awarded out of 103 poster presentations. These include two poster prizes from Oncodesign Services awarded to Sophie SHI (Institut Pasteur, France) and Isabelle TOUBIA (University of Rouen, France), a poster prize from the SCT awarded to Erik JUNG (University of Zurich, Switzerland), three poster prizes from Wiley awarded to Dante ANDERSEN (Aarhus University Denmark), Madoka HAZEMI (University of Cambridge, UK) and Ziwen JIANG (UCSF, USA), five poster prizes from the ACS (Journal of Medicinal Chemistry, ACS Chemical Biology, ACS Medicinal Chemistry Letters, ACS Organic & Inorganic Au, ACS Bio & Med Chem Au) awarded to Khoa CHUNG (Oxford University, UK), Lina EL HAJJI (Sorbonne University, France), Sophie MICHELIS (Ecole Normale Supérieure de Paris, France), Laurie PEVERINI (Institut Pasteur, France) and Jenna ROBINSON (Imperial College London, UK). Congratulations to the winners.

Social events were marked by an evening cocktail at Chimie ParisTech, the school of chemistry across the street established in 1896 by Charles Friedel, where the Friedel-Crafts reaction first saw the light of day, and where fluorine was discovered by Henri Moissan. Our speakers had, we hope, the great fortune of dining in Parisian Brasseries. We heard rumors that some participants enjoyed French wines from the 50s. Is that true? Overall, it was wonderful to catch up with old friends and to enjoy incredible science. With any luck, the next series will take place in January 2025. As a teaser, we understood that Ben Cravatt, Chris Chang and Nicolas Winssinger would be with us next time. Thank you all.

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## Conflict of Interest

The authors declare no conflict of interest.

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## Graphical Abstract:

