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Conference Report

Unlocking New Frontiers in Cell Signaling and Communication and Fostering New Collaborative Interactions and Scientific Initiatives: Lessons Learned from the International Cellular Communication Network Society (ICCNS) Workshop †

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Abstract: The International CCN Society has been organizing workshops and conferences for the past two decades to advance our understanding of the biology and pathophysiology of the cellular communication network (CCN) proteins. The 12th CCN Workshop broadened the scope of discussions, introducing topics like CCN-dependent and -independent signaling networks involved in brain development, cellular senescence, efferocytosis, neurobiology, and the application of DNA-fabricated origami structures. This expansion proved fruitful and should continue in future events. Fostering collaborations across various fields has created a dynamic environment for innovative ideas, driving substantial progress to tackle both basic scientific questions and clinically relevant challenges. Three standout presentations sparked significant discussions and highlighted key advancements in these areas. These include the work of Li-Jen Lee (Neurobiology and Cognitive Science Center, National Taiwan University) on the involvement of the CCN2 protein in depressive and aggressive behaviors in mice; the studies of Anna Zampetaki (King's College London British Heart Foundation Centre, School of Cardiovascular & Metabolic Medicine and Sciences) and Brahim Chaqour (University of Pennsylvania, Perelman School of Medicine, Dept of Molecular Ophthalmology) on the metabolome and mechanosensing in iPSC-derived human blood vessel organoids and in the microvasculature of genetically modified mice, and the talk of Björn Högberg (Karolinska Institutet, Department of Medical Biochemistry and Biophysics) on the promises of DNA origami. We believe that these examples illustrate better future directions, as they offer an opportune moment to pursue initiatives that broaden the focus of the CCN Workshops and other projects like ARBIOCOM (website link included below) that support collaboration among research societies, educational institutions, and private biomedical industries, all working together to further our understanding of biosignaling and cellular communication networks for the development of new drug discovery methods and disease treatments.

Keywords: CCN; networking; ARBIOCOM; cellular signaling

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1. Introduction

Over the past two decades, the International CCN Society has organized workshops and conferences aimed at advancing our understanding of the biology and pathophysiology of the cellular communication network (CCN) family of proteins [1]. These events have played a pivotal role in fostering communication among researchers from both the public and private sectors working in related fields of cell communication and signaling. Our efforts to broaden these interactions culminated in the 12th workshop in Oslo, where we introduced a more expansive model of collaboration [2]. The outcomes were highly satisfactory and merit further expansion in future meetings.

By bringing together leaders from both basic and translational research, the CCN Workshops and conferences have proven to be a unique platform for promoting collaboration across various disciplines. They bridge foundational science, preclinical findings, and clinical applications, with the goal of uncovering therapeutic possibilities for a wide range of human pathologies, including fibrosis, diabetes, cardiovascular disease, aging, and cancer.

The 12th CCN Workshop marked a significant expansion of its scope, moving beyond the CCN proteins to include presentations on signaling networks involved in brain development, circadian secretome profiling, microRNA-based therapies, and cellular senescence [2]. This workshop also represented a pivotal shift towards integrating emerging research areas, such as cell death and efferocytosis, neurobiology, cardiovascular biology, and the application of DNA-fabricated origami structures [2,3]. The dynamic, interdisciplinary collaborations fostered during these sessions created a rich environment for progress, novel insights, and creative solutions to both basic and clinically relevant research topics.

The cross-pollination of ideas is critical for addressing fundamental scientific questions and tackling pressing clinical issues, pushing the boundaries of what is possible in the study of intra- and extracellular communication.

The scientific community values platforms that enable active discussions and the exchange of diverse perspectives on both basic and clinically significant topics. This interdisciplinary synergy not only deepens the scope of research but also accelerates the discovery of new therapeutic strategies for currently incurable diseases. Such collaborations are essential for advancing scientific knowledge and expanding the frontiers of cellular communication research.

We have chosen to highlight below three presentations that showcased significant scientific advancements, sparking extensive and thought-provoking discussions among attendees with diverse research backgrounds and expertise.

2. A Genetic Approach to Understanding the Biological Functions of Brain CCN Proteins

In the talk “Elevated reactive aggression in forebrain-specific Ccn2 knockout mice”, Dr. Li-Jen Lee from National Taiwan University presented findings from his investigation into the function of CCN2 in the brains of rodents.

The CCN family (CCN1–6) is a group of cysteine-rich matricellular proteins, originally named after the first three members identified, Cyr61 (CCN1), CTGF (CCN2), and NOV (CCN3). Other members include WISP-1 (CCN4), WISP-2 (CCN5), and WISP-3 (CCN6) [4]. The nomenclature of these proteins was later adopted by the HUGO Gene Nomenclature Committee upon request of the International Cellular Communication Society (ICCS) Scientific Committee to cellular communication network factors 1–6 [5]. This group consists of secreted, cysteine-rich, integrin-binding regulatory proteins known to modulate cell growth, differentiation, adhesion, migration and extracellular matrix protein synthesis. The CCN proteins are produced by a variety of cells, including fibroblasts, endothelial cells, pericytes, epithelial cells, immune cells, and certain cancer cells, playing critical roles in processes such as angiogenesis, wound healing, and tumorigenesis. CCN2 is prominently synthesized not only by differentiated cells, such as chondrocytes, fibroblasts, endothelial cells, and vascular smooth muscle cells, but also by stem and mesenchymal cells highlighting its functions in skeletal development, fibrosis, and vasculogenesis.

Lee's presentation focused on the role of CCN2 in depressive and aggressive behaviors in mice. In the central nervous system, the basolateral amygdala, which includes the basomedial nucleus, is crucial for rapid escape behavior in response to imminent stress. It also aids in the formation of memories for contextual fear, a mechanism conserved across rodents and humans [6]. CCN2, one of the six Cellular Communication Network factors that make up the CCN family of proteins, is not expressed in the normal mouse amygdala but can be detected in the olfactory bulb, anterior olfactory nucleus, endopiriform nucleus, and cortical layer [7].

The forebrain-specific CCN2 conditional knockout mouse model is a unique tool to precisely explore its biological significance in the brain. Previous results obtained with this model suggested that CCN2 is involved in the maturation and functions of nearby oligodendrocytes throughout their life time [8]. Li-Jen Lee noted that while blocking olfactory inputs affects emotional state, sociability, and aggression [9,10], the deletion of CCN2 does not impact sociability in mutant mice. However, conditional deletion of CCN2 in the forebrain increases reactive aggression and heightened anxiety, which was closely linked to olfactory perception and emotional control regions [7]. Hyperactivity of the c-fos pattern in the medial and central amygdala escalated aggressive behavior in CCN2-deficient mice.

The key finding here is that the deletion of CCN2 in mice did not impair social behaviors but resulted in signs of anxiety and elevated aggression, as assessed using a resident–intruder task, which is a standardized method to measure offensive aggression, defensive behavior, and social stress in a semi-natural setting. Lee's findings revived the idea that CCN proteins potentially play a role in neurological development and the co-occurrence of anxiety and elevated aggression. These findings exemplify how rigorous data can uncover novel research directions across various domains of cell signaling and intercellular communication, which will certainly support potential biomedical applications.

Since CCN2 expression levels appear to be pro-depressant [11], and genetic deletion of CCN2 resulted in higher levels of anxiety and aggression only in *Ccn2*$^{-/-}$ males [12]. It will be interesting to investigate whether an intra-cerebroventricular injection of CCN2 could counteract the effects of *Ccn2* genetic deletion. More studies are needed to explore the causes of this gender-specific aggressive behavior and the importance of *Ccn2* expression or lack thereof in it.

This concept is reminiscent of some of the properties of CCN3, a protein closely related to CCN2 [13,14]. CCN3-positive neurons are widely distributed in the cerebral cortex, especially in the auditory area and in the piriform cortex of the olfactory bulb. Its localization in the basomedial amygdaloid nucleus suggests a functional role for CCN3 in regulating the fear response. The distribution of CCN3 RNA and CCN3 protein in the central nervous system of adult rodents and developing human embryos is similar. Interestingly, increased expression of CCN3 paralleled increased memory and learning ability in developing rats, as shown by the acquisition and retention of active and passive avoidance [14].

In one of their recent manuscripts [7], Li-Jen Lee et al. highlight the "yin-yang" divergent effects of CCN2 and CCN3 in the brain. The "yin-yang" concept was originally proposed based on their opposing roles and concurrent expression in human mesangial cells and was subsequently validated during chondrocyte proliferation and differentiation [15,16]. The observations of Li-Jen Lee et al. extend this concept to the regulation of CCN2 functioning as a suppressor and CCN3 as a promoter of oligodendrocyte differentiation. Oligodendrocytes are specialized cells in the central nervous system responsible for producing the myelin sheath that insulates neuronal axons. By regulating the speed and efficiency of electrical signal transmission, they help maintain proper communication between brain regions. This finely tuned connectivity can impact cognitive functions, emotional regulation, and even social behaviors. Emerging research suggests that disruptions in oligodendrocyte function may be linked to certain neurological and psychiatric conditions, underscoring the pivotal role these cells play in shaping behavior [17,18]. Undoubtedly, comparative expression analyses in rodents could help confirm or exclude any synergistic or antagonistic interactions.

In conclusion, the research presented by Li-Jen Lee on the biological roles of CCN2 in anxiety and depression, combined with existing data on CCN3 in the brain, establishes a strong foundation for interdisciplinary collaboration among molecular biologists, neurobiologists, and psychiatrists. The ICCNS could serve as a valuable platform for advancing neurological studies and assessing their potential therapeutic applications in treating neuropsychiatric disorders.

3. Towards a Better Understanding of the Biological Activities of CCN2 and Its Influence on the Metabolome and Connectome in Vascular Cells

With the talks “The role of CCN2 in microvascular integrity” by Anna Zampetaki and “Regulation of microvascular stiffness by CCN2: Implications in microvascular diseases” by Brahim Chaqour, the audience was offered two outstanding presentations on their latest findings regarding the role and mechanisms by which the CCN2 protein affects the metabolism and mechanical properties of the microvasculature and the potential subsequent effects of CCN2 expression—or its absence—on microvascular diseases. The iPSC-derived human blood vessel organoids (BVOs) have garnered increasing attention because of their ability to develop functional structures with histological and morphological features similar to human vessels and microvessels [19]. The BVO model was shown to recapitulate structural and functional features of the human microvasculature, including the presence of endothelial, mural, and hematopoietic cells and their reliance on glycolysis for energy production. Inhibition of glycolysis or exposure to hypoxia triggered profound remodeling and restructuring of BVOs characterized by reduced vessel density and length as well as loss of mural cells (i.e., pericytes). Under these conditions, CCN2 was identified as the most downregulated component in the BVO secretome [20]. These studies raised the following important questions: (i) How do these CCN2 activities relate to metabolism and energy production in microvascular cells? (ii) Are these findings in BVOs reflective of in vivo biological activities of CCN2 during microvascular development, and what particular role do they have in the pathogenesis of microvascular diseases? (iii) Are the effects of CCN2 on metabolic changes in the cells amenable to pharmacological manipulation in pathological conditions? (iv) Can these CCN2 activities be dissociated from other known CCN2 activities on blood vessel wall rigidity/compliance?

There are four major metabolic pathways involved in the energy-producing process: glycolysis, oxidative phosphorylation, glutamine metabolism, and fatty acid oxidation [21]. Glycolysis is essential for tip endothelial cell differentiation during angiogenesis, while both glycolysis and mitochondrial respiration are active in non-tip cell (i.e., stalk endothelial cell) proliferation [22]. Endothelial cells experience numerous mechanical cues during their differentiation and throughout their lifetime [23,24]. They counteract these external forces by fortifying their cytoskeletal networks and anchoring to the underlying substratum, such as the basement membrane. This reinforcement is energetically costly. Differential levels of shear stress exposure of tip and stalk endothelial cells could be the determining factor of the metabolic status of endothelial cells allowing tip and stalk cells to overtake each other in sprouting or becoming quiescent. Although shear stress may indirectly regulate endothelial glycolysis through nitric oxide production, this presentation suggests that the activity of CCN2, encoded by a mechanosensitive gene, could be the driving factor for the metabolic changes described in endothelial cells.

The studies presented by Chaqour on the regulation and function of CCN2 in the microvasculature in the mouse model of retinal vessel development and pathology lend credence to the interplay between CCN2 and mechanosensing mechanisms that potentially promote metabolic changes. Through conditional endothelial-specific deletion of CCN2 in mice, the group has identified numerous morphological and functional changes in endothelial cells, including impaired vascular cell growth and morphogenesis, as well as blood–brain barrier breakdown [25,26]. These changes were associated with transcriptional alterations of cytoskeletal and extracellular matrix proteins, growth factors, and transcriptional co-regulator genes, such as yes-associated protein (YAP) [27]. Proteomic analyses in the BVO model revealed that transcription factors and co-factors such as YAP, which regulate the expression of CCN2, were also sensitive to metabolic changes. The communication presented by Chaqour at the Oslo meeting further provided novel data showing that CCN2 provides a unique microenvironment in the wall of the microvasculature that fine-tunes angiogenesis and ensures blood–brain barrier integrity. Chaqour's studies established that CCN2 overexpression in endothelial cells was sufficient to increase the mechanical rigidity of the retinal microvasculature by altering the expression of cytoskeletal and nuclear matrix proteins and mimic pathological angiogenesis.

Future studies using transmission electron microscopy or two-photon microscopy are needed to further examine retinal vessel micromorphology and assess potential loss of endothelial cell contiguity. It is also important to investigate the ultrastructural changes in endothelial junctional complexes and correlate these changes with the metabolic status, behavior, and function of the cells. Additionally, there is a need to explore the link between CCN2 (and/or other CCN proteins) and different metabolic processes/genes in various cell types and under different conditions. It is essential to identify the specific intermediates that connect CCNs to metabolic activities in order to understand the mechanisms behind the adaptive and maladaptive responses of cells and tissues.

Based on these two exemplary studies, coordinated efforts among different groups would be extremely fruitful and rewarding in providing new information about the previously unknown mechanobiological activities of CCN2 and its influence on the metabolome and connectome in vascular cells.

4. The DNA Origami Promises

In the talk titled "Origami DNA and Signaling", Björn Högberg from the Karolinska Institutet in Stockholm presented research highlights from his recently published paper titled "Soluble and multivalent Jag1 DNA origami nanopatterns activate Notch without pulling force".

DNA origami is a technique in nanotechnology that uses the unique base-pairing properties of DNA to construct precise, three-dimensional structures. Researchers can fold long single-stranded DNA molecules into pre-defined shapes, like boxes or complex geometric patterns, by designing specific sequences and using short "staple" strands to maintain the structure together. This method enables highly accurate nanoscale construction and has promising applications in drug delivery, biosensing, and molecular computing [28,29].

A recent work by Högberg and others in DNA origami has demonstrated a shift from static shapes to dynamic functionalities. These advancements have been achieved through methods such as toehold-mediated strand displacement, which enables controlled movement within structures. Enzymatic reactions are also used, allowing enzymes to be integrated into designs to dynamically respond to specific conditions. Additionally, base-stacking interactions serve as another method, where environmental changes (e.g., pH changes) can induce conformational shifts within assembled structures. These capabilities open up opportunities for applications such as drug delivery systems, where stimuli-responsive mechanisms facilitate customized controlled release profiles to meet therapeutic requirements.

The biomedical field is an area where DNA origami shows immense promise. Encapsulating DNA origami into lipid-based nanoparticles has successfully targeted organ-specific gene expression [30]. In a recent study, cellular spheroids were designed with DNA origami, enabling the mass production of tissue complexes and standardized 3D models without the need for complex equipment. This provides a low-cost, efficient drug screening platform [31]. Others have utilized the DNA origami technique to engineer a modular and compartmentalized construct with multi-catalytic functions capable of segregating, unfolding, and proteolytically digesting specific substrates [32]. Similarly, Doxorubicin-loaded DNA origami nanostructures have been shown to be well-tolerated in vitro, indicating promise for drug delivery applications [33].

Drug delivery systems have been engineered to carry nanoparticles capable of releasing their payloads upon encountering specific cellular markers or environmental triggers [34]. Vaccine development has seen innovative approaches involving attaching viral antigens onto virus-shaped DNA particles designed to elicit immune responses or target pathogens like HIV, Ebola, or SARS-CoV-2 [35,36]. Cellular targeting mechanisms include programmable T-cell engagers developed using coated DNA origami, facilitating targeted destruction of cancer cells by enhancing immune system recognition processes. Sensing technologies benefit from enhanced sensitivity achieved through dynamic changes within molecular constructs positioning them favorably for biosensing applications, detecting biomolecules relevant in diagnostics.

As research continues on this innovative technology, several promising trajectories are emerging. Enhanced design algorithms will streamline design processes, reducing errors while increasing complexity. Integration with other nanomaterials could lead to hybrid systems capable of novel functionalities beyond current limitations. Clinical translation efforts are exciting frontiers worth pursuing diligently as more studies demonstrate efficacy across diverse applications. From drug delivery mechanisms targeting tumors effectively to advanced vaccine formulations, the transition from laboratory success to clinical implementation is becoming increasingly feasible.

The study by the Högberg group demonstrates that origami nanotechnology is an innovative technique for creating complex DNA nanostructures with high precision. Furthermore, Högberg's work has explored potential applications of DNA origami in diagnostics and therapeutics, allowing researchers to design custom scaffolds tailored to study specific protein interactions or cellular processes. Högberg's interdisciplinary approach fosters collaboration across fields, such as nanotechnology, molecular biology, and biochemistry, which is essential for advancing our understanding of complex biological systems. Beyond his research contributions, he is also dedicated to educating the next generation of scientists about the potential of DNA nanotechnology. During the Oslo meeting by sharing knowledge and fostering interest in this area, his work helped to cultivate a new wave of researchers who may further explore the applications of DNA origami. It is reasonable to expect that origami will open up new avenues for therapeutic interventions and diagnostic tools based on these innovative nanostructures.

In this context, it should be noted that DNA origami technology has already led to several important preclinical findings. Luo and colleagues recently showed that a two-dimensional planar material with a rectangular DNA origami nanostructure improved liver and renal function in db/db mice with diabetic sepsis [37]. Similarly, DNA nanostructures are being explored as advanced cancer immunotherapies or for targeting cell-surface receptors in tumor tissues [38,39].

In summary, DNA origami technology has the potential to revolutionize research in various areas. It can enable targeted delivery systems, facilitate studies on protein interactions and signaling pathways, mimic extracellular environments, develop innovative biosensors, and investigate disease mechanisms more effectively. As this field continues to progress, it may lead to new therapeutic approaches in biomedical applications. To effectively advance progress in these areas, collaborations should be coordinated through existing platforms (e.g., ICCNS) or novel platforms that aim to promote the exchange of knowledge and resources among different disciplines.

5. Conclusions

The 12th CCN Workshop showcased a diverse range of presentations focusing on intra- and extracellular signaling in different biological models and clinical settings (see Supplementary Materials). These presentations not only enhanced our understanding of CCN protein regulation and function but also expanded the workshop's scope to include cutting-edge advancements in protein and DNA biology, along with innovative signaling modeling approaches. Each presentation sparked lively discussion among participants, and we have selected three key presentations to demonstrate the breadth of the research topics covered. Overall, the CCN Workshop provided a dynamic platform for the exchange of ideas among investigators in various and sometimes unrelated research fields. This collaborative approach is essential for addressing fundamental scientific inquiries and tackling urgent clinical challenges, pushing the boundaries of what is achievable in the study of intra- and extracellular communication. In this context, the CCN Workshop's scope is expanding to encompass innovative concepts like ARBIOCOM (https://arbiocom.wordpress.com, accessed on 31 March 2025). The ARBIOCOM initiative offers a unique opportunity to unite the efforts of researchers from diverse settings, societies, and organizations to collectively develop novel, comprehensive approaches within a supportive environment to accelerate research progress in all areas of cell communication and signaling. Under this framework, each participating member, society, or organization maintains its unique identity but collaborates with all other ARBIOCOM members to facilitate the integration of scientific knowledge acquired from exploring the variability in biological communication within and between cells and organs. Ultimately, this initiative aims to foster collaboration among various research societies, educational institutions, and private biomedical industries interested in advancing their understanding of biosignaling and cellular communication networks for new applications in drug discovery and disease treatment.

Supplementary Materials: The program of the 12th CCN Workshop can be found at https://www.mdpi.com/article/10.3390/proceedings2025115001/s1.

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Abbreviations

The following abbreviations are used in this manuscript:

BVO(s)	Blood vessel organoid(s)
CCN	Cellular communication network

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