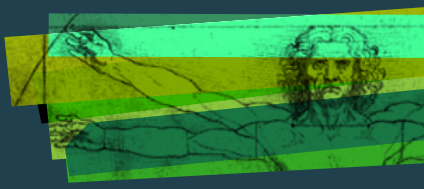
LE STUDIUM

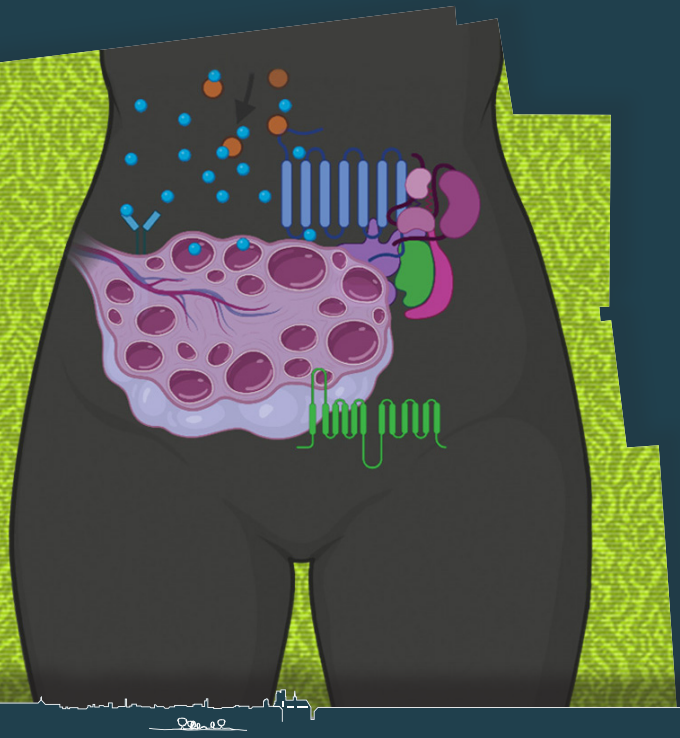
CONFERENCES

VIRTUAL MEETING | 2022



14-15 September 2022

Gonadotropins in the Physiopathology: Current advances in the Mechanisms of Action



LOCATION

VIRTUAL MEETING

CONVENORS

Prof. Rita Singh

LE STUDIUM VISITING RESEARCHER

FROM University of Delhi - IN

IN RESIDENCE AT Physiology of Reproduction and Behaviour (PRC) / Centre INRAe Val de Loire, CNRS, University of Tours, IFCE - FR

Dr Pascale Crépieux

Physiology of Reproduction and Behaviour (PRC) / Centre INRAe Val de Loire, CNRS, University of Tours, IFCE - FR

LE STUDIUM Loire Valley Institute for Advanced Studies

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VIRTUAL MEETING | 14-15 SEPTEMBER 2022

ABSTRACTS

Gonadotropins in the Physiopathology: Current advances in the Mechanisms of Action

CONVENORS

Prof. Rita Singh
LE STUDIUM VISITING RESEARCHER
FROM: Division of Molecular Endocrinology and Reproduction, Department of Zoology, Faculty of Science, University of Delhi - IN
IN RESIDENCE AT: Physiology of Reproduction and Behaviour (PRC) / Centre INRAe Val de Loire, CNRS, University of Tours, IFCE - FR

Dr Pascale Crépieux
Physiology of Reproduction and Behaviour (PRC) / Centre INRAe Val de Loire, CNRS, University of Tours, IFCE - FR

ORGANIZING COMMITTEE

Sophie Gabillet, General Secretary

Dr Aurélien Montagu, Scientific Manager

Maurine Villiers, Communication & Events Manager

LE STUDIUM Loire Valley Institute for Advanced Studies • Région Centre-Val de Loire • FR

EDITO

Created in 1996 on the CNRS campus in Orleans La Source, LE STUDIUM has evolved to become the multidisciplinary Loire Valley Institute for Advanced Studies (IAS), operating in the Centre-Val de Loire region of France. LE STUDIUM has its headquarters in the city centre of Orleans in a newly renovated 17th century building. The amazing facilities are shared with the University of Orleans. In 2014 new developments and programmes linked to the smart specialisation of the Centre-Val de Loire region came to strengthen existing IAS collaborative relationships with the local and the international community of researchers, developers and innovators.

LE STUDIUM IAS offers to internationally competitive senior research scientists the opportunity to discover and work in one of the IAS's affiliate laboratories from the University of Tours, the University of Orleans, National Institute of Applied Sciences (INSA) Centre Val de Loire and ESAD Orléans, as well as of nationally accredited research institutions located in the region Centre-Val de Loire (BRGM, CEA, CNRS, INSERM, INRAE). Our goal is to develop and nurture trans-disciplinary approaches as innovative tools for addressing some of the key scientific, socio-economic and cultural questions of the 21st century. We also encourage researchers' interactions with industry via the IAS's links with Poles of Competitiveness, Clusters, Technopoles, and Chambers of Commerce etc.

LE STUDIUM has attracted near two hundred and fifty experienced researchers coming from 47 countries for long-term residencies. In addition to their contribution in their host laboratories, researchers participate in the scientific life of the IAS through attendance at monthly interdisciplinary meetings called LE STUDIUM THURSDAYS. Their presentations and debates enrich the regional scientific community at large (researchers of public and private laboratories, PhD students, research stakeholders' representatives, etc...)

For the period 2015-2021, LE STUDIUM has operated with an award from the European Commission, a programme supporting the mobility of international researchers, the Marie Skłodowska-Curie Actions (MSCA) COFUND programme. For the period 2022-2025, LE STUDIUM has joined the FIAS Programme (French Institute for Advanced Study) along side five other institutes in France, also supported by the MSCA Actions. Since 2013, LE STUDIUM is also an official partner of the Ambition Research and Development programmes initiated by the Centre-Val de Loire Regional Council to support the smart specialisation strategy (S3) around priority domains: biopharmaceuticals, renewable energies, cosmetics, environmental metrology, digital twins, materials, forestry and natural and cultural heritage. Furthermore our current collaboration with the ATHENA European University Consortium allows us to welcome fellows from ten European partners universities. New programmes are currently designed to include all major societal challenges.

Researchers are also invited and supported by the IAS to organise, during their residency and in collaboration with their host laboratory, a two-day LE STUDIUM CONFERENCE. It provides them with the opportunity to invite internationally renowned researchers to a cross-disciplinary conference, on a topical issue, to examine progress, discuss future studies and strategies to stimulate advances and practical applications in the chosen field. The invited participants are expected to attend for the duration of the conference and contribute to the intellectual exchange. Past experience has shown that these conditions facilitate the development or extension of existing collaborations and enable the creation of productive new research networks.

The present LE STUDIUM CONFERENCE named "*Gonadotropins in the Physiopathology: Current advances in the Mechanisms of Action*" is the 121st in a series started at the end of 2010 listed at the end of this booklet.

We thank you for your participation and wish you an interesting and intellectually stimulating conference. Also, we hope that scientific exchanges and interactions taking place during this conference will bring opportunities to start a productive professional relationship with presenting research laboratories and LE STUDIUM Loire Valley Institute for Advanced Studies.

Yves-Michel GINOT

Chairman
LE STUDIUM

INTRODUCTION

Human reproductive health and fertility is dependent on gonadotropins (FSH &LH), which act through their specific G protein-coupled receptors (GPCR) and regulate the reproductive functions. Gonadotropin hormone imbalance may contribute to the development of sub-fertility or infertility such as seen in women with polycystic ovary syndrome (PCOS), the most common endocrinopathy and a threat to human reproduction. The usage of ART/IVF has increased all over the world to restore sub-fertility in young women.

With the emerging role of gonadotropins (FSH and LH), It is important to understand the mechanisms of gonadotropin signaling, especially for delineating the metabolic defects due to their imbalance (high LH:FSH ratio) in women with PCOS, menopause and gynaecological cancers. It is further imperative to increase the positive outcome of IVF protocols to deal with the sub-fertility in young women due to PCOS or other environmental factors.

This interdisciplinary conference will discuss the current challenges in the targeting of GPCRs and finding novel pathways to optimize not only reproduction but also metabolism, and to discuss their role as non-gonadal ligands.

This international conference is organised in the framework of the ARD CVL BIOPHARMACEUTICALS Programme.

PROGRAMME

WEDNESDAY SEPTEMBER 14TH, 2022 (PARIS TIME, GMT +2)

12:00 Welcome address: **Prof. Rita Singh**
12:10 **Dr Aurélien Montagu**, Scientific Manager of Le Studium
12:15 Remarks by **Dr Yves-Michel Ginot**, President of Le Studium

SESSION I: METABOLISM AND REPRODUCTION

12:30 **Prof. Steve Franks -** Metabolic regulation of gonadotropin action in polycystic ovary syndrome (PCOS)

13:15 **Prof. Rita Singh -** Cross-talk between FSH and LH: Implications for metabolic disorder in women with PCOS

14:00 **Dr Joëlle Dupont -** Involvement of chemerin and CMKLR1 in the progesterone decrease by PCOS granulosa cells

14:45 **Dr Antara Banerjee -** Functional Characterization of two naturally occurring mutations $V^{221}G$ and $T^{449}N$ in the follicle stimulating hormone receptor

14:55 **Dr Romain Yvinec -** Kinetic biased signaling: towards a system biology definition of drugs selectivity. Illustration on the Follicle Stimulating Hormone Receptor

15:05 **Dr Anjali Geethadevi -** Impaired crosstalk between FSH and IRS-2 alters glucose metabolism in granulosa cells- Implications in PCOS pathogenesis.

15:15 **Dr Emilia Przygrodzka -** LH-responsive metabolic pathways essential for luteal steroidogenesis

15:30 *Coffee break*

SESSION II: GONADOTROPIN IN PHYSIOPATHOLOGY

16:00 **Prof. Jerry Strauss -** A novel signal transduction pathway directs increased thecal cell androgen production in polycystic ovary syndrome

16:45 **Dr Kim Jonas -** Towards understanding the role of gonadotrophin receptor oligomerisation in reproductive health and disease

17:30 **Prof. Rajendra Kumar -** Genetic and pharmacological approaches to study FSH action in the male

18:15 *Quick round up of the day*

THURSDAY SEPTEMBER 15TH, 2022 (PARIS TIME, GMT +2)

12:15 Welcome address

SESSION III: FUNCTIONAL AND PHYSICAL GONADOTROPIN RECEPTOR INTERACTION

12:30 **Dr Aylin Hanyaloglu -** Spatial control of gonadotrophin hormone receptor signaling; mechanisms and applications

13:15 **Prof. Pascale Crépieux -** Regulation of the translatome by FSH, in Sertoli cells

14:00 **Prof. Livio Casarini -** Crosstalk between G protein-coupled estrogen and gonadotropin receptors

14:45 **Juliette Gourdon -** Role of cellular compartmentation of gonadotropin receptors' signalling in reproductive physiology

14:55 **Dr Clara Lazzaretti -** Effects of human luteinizing hormone/ choriogonadotropin receptor (LHCGR) and G protein-coupled estrogen receptor (GPER) heteromers *in vitro*

15:05 **Dr Elisa Mascolo -** Impact of two differently glycosylated recombinant FSH on signal transduction

15:15 **Dr Elia Paradiso -** Luteinizing hormone (LH)- and choriogonadotropin (hCG)-induced internalization of the receptor (LHCGR) is responsible for hormone-specific signaling

15:30 *Coffee break*

SESSION IV: REGULATION OF GONADOTROPIN ACTION

16:00 **Prof. George Bousfield -** Estradiol and progesterone effects on transfected rat somatotroph GH3 cell N-glycosylation of recombinant hFSH.

16:45 **Prof. Alfredo Ulloa-Aguirre -** Mutations in gonadotropin receptors that impact receptor trafficking and reproductive function. Functional rescue by pharmacological chaperones

17:30 **Prof. John S. Davis-** Hypo-glycosylated hFSH has greater bioactivity than fully-glycosylated hFSH enabling greater follicular health and growth

18:15 **Prof. Pascale Crépieux -** Concluding remarks on the Conference

18:30 **Prof. Rita Singh -** Declaration of Awards - Vote of Thanks

ARD CVL PROGRAMME
BIOPHARMACEUTICALS

A drug is any substance or composition presented as having properties for treating, preventing or diagnosing disease in humans or animals. Biopharmaceuticals in the strict sense of the term are molecules that have the characteristic of being produced from living organisms or their cellular components. These molecules are intermediate between chemical drugs and organisms' intrinsic biologics. By definition, a biopharmaceutical is any drug whose active substance is a therapeutic macromolecule produced by living organisms. Biopharmaceuticals are overwhelmingly protein-based, mainly represented by non-living vaccines, therapeutic antibodies, enzymes, protein hormones and growth factors. Being proteins, they currently have to be administered by injection. The proportion of biopharmaceuticals in the drug market has dramatically increased over the past decade. The Centre-Val de Loire region is at the cutting edge of research in the pharmaceutical sector with strong capabilities of multidisciplinary regional research teams. Since 2013, the development of biopharmaceuticals is a regional priority with effective budget lines to support research and to facilitate innovative inter-sectorial industrial development and partnerships for socioeconomic development.

The Biopharmaceuticals programme aims to:

- Develop a flagship research and development pole on biopharmaceuticals.
- Configure the biopharmaceuticals field by inter-sectorial development and innovation in the pharmacy/health sectors through start-ups, SMEs including established local and regional based multinational companies.
- Promote the transfer of technologies/competences to existing and new businesses.
- Support the development of new competences for the sector.

The Biopharmaceuticals Programme is driven by the University of Tours and mobilises actors in the pharmaceutical sector, from fundamental research to production, in order to develop tomorrow's biopharmaceutical treatments and production centres in the Centre-Val de Loire region. A number of innovative projects including academic and industrial partnerships covering a wide spectrum of biological molecules and domains receive funding to bring immediate outcomes: vaccines, therapeutic antibodies, nucleic acids, lipoproteins, bio- production of medicines...

BIOPHARMACEUTICALS
Innovation Dynamics in Health
IN REGION CENTRE-VAL DE LOIRE

TABLE OF CONTENTS

CONVENORS

SPEAKERS

CONVENORS

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Rita Singh is professor at Faculty of Science, University of Delhi, India. She has collaboration with INRA, France as Le Studium Fellow, with Medical Schools in USA: VCU as Indo-US-grant PI, & UPENN as CREST awardee, Department of Biotechnology. She was academic-visitor at Medical School, NUS. She received LS Ramaswami award & gold medal for outstanding work in Reproductive health from Indian society for study of Reproduction & Fertility; Young Scientist award from Ministry of S &T, India. Her research contributions are i) genomic differences in gonadotropin responses in women with & without insulin resistance, ii) a novel signaling mechanism which establishes different roles of FSH & LH in glucose metabolism in human granulosa cells & a role of high LH in metabolic disorder in women with PCOS.

Cross-talk between FSH and LH: Implications for metabolic disorder in women with PCOS

Polycystic ovary syndrome (PCOS) is a complex endocrine disorder with multifactorial changes in the metabolism of glucose and fat with serious implications for fertility. Most women with clinical evidence of PCOS have elevated luteinizing hormone (LH) levels and an increased expression of LH receptors early in the follicular phase. Interestingly, tissue-specific differences in insulin resistance have been reported in women with PCOS however, they represent a large group of women at risk for developing early-onset type II diabetes mellitus (T2D). The quality of oocytes, the development of embryos and the rate of genetic abnormalities (such as aneuploidy) in women with PCOS are not different from those in normal women. However, there is a significantly high rate of pregnancy loss in lean as well as obese women with PCOS. Recently, we have reported that high LH or LHR activity not only alters the steroidogenesis in theca and granulosa cells but also adversely impacts the sensitivity of granulosa cells to FSH and insulin with respect to their regulation of glucose uptake and storage as glycogen, leading to metabolite imbalance within the ovary. Abnormalities in the metabolic pathways in ovarian follicles are the potential reason for follicular growth arrest in women with PCOS. A discussion on the altered mechanisms of action of FSHR and LHR in the presence of different ratios of LH and FSH, such as in PCOS conditions, will be discussed in this presentation.

Dr Pascale Crépieux

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Dr Pascale Crépieux is a CNRS research director at the Laboratory of Physiology of Reproduction and Behaviors in Nouzilly. She obtained her PhD in Molecular Oncology at the Pasteur Institute, France, then spent 3 years at McGill University, Canada, as a post-doc. Her research has revealed a developmental regulation of signalling processes during gonadal post-natal development, and have highlighted the importance of translational regulations in the trophic role of FSH in these cells. Her studies now aim at deciphering new signalling mechanisms whereby the FSHR controls localized mRNA translation in Sertoli cells of the male gonad, integrating spatial and temporal constraints.

Regulation of the translatome by FSH in Sertoli cells

Follicle-Stimulating Hormone (FSH) binding to the Follicle-Stimulating Hormone Receptor (FSHR) targets mRNA-specific translation to fine-tune Sertoli cell protein content in the male gonad. The FSHR is a G protein-coupled receptor (GPCR). Through a complex signaling network, GPCRs indirectly regulate gene transcription, but little is known about their role in mRNA translation. Here, we used polysome profiling and RNA sequencing to identify the FSHR-regulated translatome in rat primary Sertoli cells. In 90 minutes, ~ 100 genes were found to be regulated at the transcriptional level, while more than two thousand mRNA were regulated at the translational level. The translation of many of them into a protein was validated by parallel label-free mass spectrometry. Several well-known testis markers were identified in these translated mRNAs. Importantly, network inference based on the translatome dataset suggested that many components belonging to the major FSHR-dependent regulatory pathways (PDE, Gαs, cAMP) may be co-translated in response to FSH. Independent sets of experiments have confirmed this point.

In conclusion, by reporting one of a few GPCR-dependent translatomes analyzed at the systems level, our data highlight a potential feedback loop of FSH-dependent signaling component at the level of translation. We expect that this translatome will eventually provide insights onto the molecular mechanisms whereby this class of receptor physiologically controls cell phenotype.

SPEAKERS

Dr Antara Banerjee

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Dr Antara Banerjee, is working as a Scientist in the Cellular and Structural Biology Division of National Institute for Research in Reproductive and Child Health, Indian Council of Medical Research, Mumbai, India. Her doctoral work was on the human follicle stimulating hormone receptor (FSHR), a G-protein coupled receptor that plays a central role in mammalian reproduction. She identified certain residues in extracellular loops 2 and 3 of FSHR that are crucial for FSH mediated internalization of FSHR and downstream signaling events. She has also carried out functional characterization of some naturally occurring mutations in FSHR, that are responsible for affecting its function, thus resulting in reproductive pathologies.

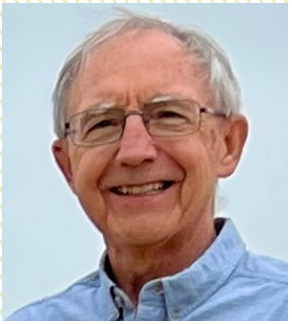
Functional Characterization of two naturally occurring mutations $V^{221}G$ and $T^{449}N$ in the follicle stimulating hormone receptor

Co-authors : Antara A. Banerjee[a], Swati K. Achrekar[b], Shaini Joseph[b], Bhakti R. Pathak[a], Smita D. Mahale[a,b]

[a] Division of Cellular and Structural Biology, National Institute for Research in Reproductive and Child Health (Indian Council of Medical Research)

[b] ICMR Biomedical Informatics Centre, National Institute for Research in Reproductive and Child Health (Indian Council of Medical Research)

Follicle stimulating hormone receptor (FSHR) is a GPCR belonging to the subfamily of glycoprotein hormone receptors (GPHRs) which includes luteinizing hormone/choriogonadotropin receptor (LH/CGR) and thyroid stimulating hormone receptor. Structurally, it contains a large extracellular domain (ECD) consisting of leucine rich repeats at the N-terminal end and a hinge region at the C-terminal that connects the ECD to the membrane spanning transmembrane domain (TMD). The TMD comprises of seven α-helices that are connected to each other by means of three extracellular loops and three intracellular loops and ends in a short cytoplasmic tail. The binding of FSH to FSHR triggers folliculogenesis in females and spermatogenesis in males. Hence, the residues involved in this hormone-receptor interaction need to be mapped. In this study, we characterized two naturally occurring mutations, V221G and T449N, in the ECD and TMD, of FSHR, respectively. The diminished receptor function in terms of FSH binding and signaling seems to be responsible for primary amenorrhea in the woman harbouring the V221G mutation. An enhancement in the FSHR function in terms of hormone binding and hormone induced signaling response in case of the T449N mutation corroborated with the clinical manifestation of spontaneous ovarian hyperstimulation syndrome. Thus the study of the naturally occurring mutations in FSHR enabled us to establish a genotype-phenotype correlation.



Prof. George Bousfield

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George Bousfield graduated from Saginaw Valley State College in 1974 with B.S. degress in chemistry and biology. He received an A.M. degree in Zoology from Indiana University in 1976 and a Ph.D. in Zoology also from Indiana University in 1981. He was a postdoctoral fellow, research associate, and research assistant professor at MD Anderson Cancer Center 1981-1990 in the laboratory of Darrell N. Ward. In 1991, he moved to Wichita State University as a visiting assistant professor in the Department of Biological Sciences. He was appointed assistant professor in 1992, promoted to associate professor in 1997, to full professor in 2005, and became the Dr. L.M. Jones Distinguished Professor in 2010. His research interests revolve around carbohydrate modulation of gonadotropin function.

Estradiol and progesterone effects on transfected rat somatotroph GH3 cell N-glycosylation of recombinant hFSH

Follicle-stimulating hormone (FSH) glycosylation is very heterogeneous. Oligosaccharyl transferase skips either one or both Asn7 or Asn24 N-glcosylation sites in the hormone-specific FSHbeta subunit. The resulting hypo-glycosylated FSH glycoforms, FSH18 and FSH21, respectively, exhibit greater FSHR occupancy and no lag in engaging the receptor, as compared with fully-glycosylated FSH24. Microheterogeneity resulting from differences in oligosaccharide branch initiation, extension, and termination with sialic acid is more difficult to study, as charge-based separated fractions possess very similar glycan populations. The three physiologically relevant FSH variants resulting from macroheterogeneity appeared more tractable for structure-function studies. Nevertheless, microheterogeneity should not be completely overlooked as differences between pituitary FSH glycoforms possessing largely tri-antennary glycans appear to be more reproducible than those between recombinant FSH glycoforms, which possess largely bi-antennary glycans. While we expected FSH glycoforms to differentially activate target cell signal pathways, significant differences in FSHR binding were observed. Partially glycosylated FSH glycoforms immediately bind FSHR, while fully glycosylated FSH binding is slow for the first 30-60 min. Partially glycosylated FSH glycoforms occupy more FSHRs than fully glycosylated FSH. Although an age-related change in FSH glycoform abundance has been observed in female pituitary glands, the mechanism is unknown. As sites missing N-glycans possess the encoded Asn residues rather than PNGase-catalyzed conversion to Asp, oligosaccharide was not attached at these sites. Moreover, PNGaseF cannot remove oligosaccharides from either FSH beta-subunit N-glycosylation site. Evaluating oligosaccharyl transferase is challenging because the enzyme isoforms are complexes of 7-8 subunits expressed by 12 genes. We evaluated OST expression in a rat somatotrope GH3 cell line that had been transfected with FSH alpha- and beta-subunit expression vectors, which were known to partially glycosylate ~50% of FSH beta-subunits. Preliminary RNA-seq studies confirmed expression of all 12 OST subunit genes as well as Esr1 and Pgr. The latter suggested the impact of steroids could be evaluated. Early and late-passage GH3 cells used to express recombinant hFSH over a _-year period showed a difference in efficiency of FSH glycosylation in that FSHbeta glycosylation increased while FSHalpha glycosylation decreased in the presence of serum. Evaluation of OST subunit expression revealed no significant change in either of the two catalytic subunit genes

Prof. Livio Casarini

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Livio Casarini is associate professor of Molecular and Translational Endocrinology at the University of Modena and Reggio Emilia. He is team leader of a research group working in the field of basic and translational endocrinology, with special focus on endocrine regulation of human reproduction, glycoprotein and sex steroid hormones and their receptors. Main scientific achievements account for studies of gonadotropin-mediated signaling and physiology, GPCR mode of action.

Crosstalk between G protein-coupled estrogen and gonadotropin receptors

Gonadotropins are glycoprotein hormones modulating reproductive functions through the action exerted via class A G protein-coupled receptors. These molecules are used also as drugs to induce the ovarian multi-follicular maturation in assisted reproduction. This talk will provide new insights into the follicle-stimulating (FSH) mode of action, and how membrane partners physically interacting with the receptor (FSHR) act as a switch between gonadotropin-mediated life and death signals.

Prof. John S. Davis

University of Nebraska Medical Center & Omaha VA Medical Center

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John S. Davis is Director of Research and Development at the Olson Center for Women's Health at the University of Nebraska Medical Center (UNMC). His research in ovarian physiology, particularly on molecular and cellular signaling mechanisms, has provided new information on the mechanisms of action of the gonadotropins LH and FSH, prostaglandins and growth factors involved in follicular development and the formation and regression of the corpus luteum. He is a strong supporter of collaborative research and mentoring students and junior investigators. His research is supported by the NIH, the DVA and NIFA (USDA), as well as local and private sources. Dr. Davis served as President of the Society for the Study of Reproduction (SSR) in 2018 and was appointed a Fellow of the SSR in 2021.

Hypo-glycosylated hFSH has greater bioactivity than fully-glycosylated hFSH enabling greater follicular health and growth

Glycosylation of FSH is necessary for FSH to effectively activate the FSHR and promote formation of antral follicles. *In vitro* studies demonstrate that compared to fully-glycosylated recombinant human FSH (hFSH24), hypo-glycosylated FSH (hFSH18/21) has greater activity in receptor binding studies, and more effectively stimulates the PKA pathway and steroidogenesis in human granulosa cells. Commercially prepared recombinant hFSH used for ovarian stimulation in human assisted reproductive technology (ART) is fully-glycosylated FSH. Using a mouse model, our findings indicate that hypo-glycosylated hFSH has greater bioactivity enabling greater follicular health and growth without exaggerated estradiol production *in vivo*, which may benefit clinical ART outcomes. In agreement with in vitro studies using granulosa cells, we observed that hypo-glycosylated hFSH has greater bioactivity in vivo than the fully glycosylated hFSH glycoform. The results indicate that FSH18/21 has greater ability to drive expression of early response genes (AP-1 transcription factor complex, EGR1/2, NR4A1/2) correlated with follicular development and differentiation. *In vivo* and *in vitro* studies indicated that hypo-glycosylated hFSH more effectively stimulates activation of multiple RTKs, PI3K/AKT and MAPK/ERK signaling, which are required for optimal follicular development. Taken together, our findings demonstrate the potential for development of hypo-glycosylated hFSH for application in human ART.

Dr Joëlle Dupont

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Joëlle Dupont, Director of Research at UMR PRC INRAE Centre Val Loire, Nouzilly, is an expert on the the molecular mechanisms of adipokines in reproductive functions. She received her M.S., Ph.D., and HDR in France in 1999 and she spent two years at NIDDK, NIH, Bethesda, in USA for her Post-doc. She is internationally recognized in the links between metabolism and reproductive functions in human and domestic animal models. Her lab has reported main advances in major recognised reproductive journals such as Human Reproduction, Reproduction and Biology of Reproduction. Joëlle authored more than 200 papers in international journals, 250 abstracts and 5 book chapters and was PI of several National and European projects. Her work has been cited 11500 times and she trained more than 30 young scientists (M.S and Ph.D students).

Involvement of chemerin and CMKLR1 in the progesterone decrease by PCOS granulosa cells

Polycystic ovarian syndrome (PCOS) is frequently associated with reduced progesterone (Pg) production by human luteinised granulosa cells (hlGCs). However, the mechanisms involved in these steroidogenesis alterations in PCOS patients are unclear. In a dihydrotestosterone-induced PCOS mouse model, steroid production is maintained in the setting of chemokine-like receptor 1 (Cmklr1) knockout. Thus, chemerin and chemerin receptors in terms of expression and progesterone regulation could be different in control (CT) and PCOS hlGCs. We confirmed that Pg levels in both plasma and follicular fluid (FF) were significantly reduced in PCOS normal weight women compared to CT women. These data were associated with a lower StAR mRNA expression in both in vivo and in vitro hlGCs from PCOS women. Chemerin FF levels and RARRES2 and CMKLR1 mRNA levels in GCs were higher in PCOS normal weight patients. Treatment of hlGCs with a specific nanobody (the VHH CA4910) targeting and inhibiting the human receptor for CMKLR1 leading to its inactivation abolished chemerin-induced Pg inhibition, suggesting the involvement of CMKLR1 in this process. Furthermore, the inhibition of Pg secretion induced by chemerin was two-fold higher in PCOS hlGCs. Moreover, the VHH CA4910 reinstated a normal Pg secretion with lower concentrations in PCOS hlGCs, suggesting a different chemerin sensitivity between PCOS and CT hlGCs. Thus, chemerin, through CMKLR1, could be involved in the steroidogenesis alterations in PCOS hlGCs.

Prof. Stephen Franks

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Stephen Franks is professor of reproductive endocrinology at Imperial College London, Faculty of Medicine He is a former chairman of the Society for Endocrinology (UK). He is a fellow of the Academy of Medical Sciences and holds an honorary doctorate from the University of Uppsala, Sweden. His research is in the field of normal and disordered function of the hypothalamic-pituitary-ovarian axis with a major interest in polycystic ovary syndrome (PCOS), a common endocrine disorder with both reproductive and metabolic effects. His research focuses on the interaction between genetic and environmental factors in aetiology of the syndrome.

Metabolic regulation of gonadotropin action in polycystic ovary syndrome (PCOS)

PCOS is characterised by hyperandrogenism and anovulation, associated with elevated serum levels of LH which play a significant role in aberrant function of both theca and granulosa cells. Metabolic signals are well recognised to have an impact on gonadotropin regulation but there is also evidence that such signals modify action of both LH and FSH on the ovary. In particular, the hyperinsulinaemia associated with PCOS can amplify the effects of LH on theca and contribute to elevated androgen levels. Adipokines (adipose-derived cytokines, the secretion of which is abnormal in PCOS) can also influence LH action and androgen production. This presentation will include discussion of the possible mechanism(s) by which insulin and adipokines interact with gonadotropins.

Dr Anjali Geethadevi

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Anjali Geethadevi is a Postdoctoral Fellow in the Department of Obstetrics and Gynecology/Cancer Center at Medical College of Wisconsin, USA. Anjali completed her Ph.D. in Zoology from University of Delhi under the mentorship of Prof. Rita Singh. Her research focus has always been on women's health such as understanding the molecular mechanisms of PCOS, ovarian and breast cancer pathogenesis. Anjali has published several first and co-authored papers in high-impact factor journals such as Cancer Research, Cell Reports, Advanced Sciences etc. Anjali is also serving as an editorial board member of several peer reviewed journals as reviewer and guest/associate editor. Besides this, Anjali is an active fundraiser for Ovarian Cancer awareness and research and enjoys cooking and photography.

Impaired crosstalk between FSH and IRS-2 alters glucose metabolism in granulosa cells- Implications in PCOS pathogenesis.

Follicle stimulating hormone (FSH) plays a central role in the growth and differentiation of ovarian follicles to preovulatory phenotype. Previous studies have reported that infertile polycystic ovarian syndrome (PCOS) patients tend to exhibit defects in glucose metabolism, defective FSH-stimulated follicle development and oocyte maturation, and alterations in insulin receptor substrate-2 (IRS-2). In this study we have explored the mechanism of crosstalk between FSH and IRS-2 that regulates glucose metabolism in preovulatory granulosa cells (GCs) which is pivotal for successful ovarian follicle development, oocyte maturation and ovulation. Any defect in this mechanism may cause defective follicular maturation such as in PCOS. We found that FSH upregulates the expression of IRS-2 in human and rat GCs by cAMP-dependent translocation of a transcription factor-SP1 into nucleus. SP1 further binds to IRS-2 promoter to increase its transcription. We also found that FSH-stimulated glucose uptake and GLUT-4 translocation are mediated via IRS-2-PI3K-AKT pathway. However, in GCs from PCOS patients and RU-486 PCOS rat model, we observed a reduced glucose uptake and IRS-2 expression indicating a selective defect in the FSH-induced IRS-2 expression in the PCOS GCs. Taken together, our findings indicate an impairment of FSH responsiveness in terms of decreased IRS-2 expression which could be an important factor for defective metabolism, growth, and differentiation of GCs in PCOS women.

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After studying Molecular and Cellular Biology (Sorbonne Université) and Reproductive Biology (Université de Tours), I joined the GPCR Signalling Systems Biology team (INRAe, CNRS ; Nouzilly, France) as a PhD student in October 2021, under the supervision of Dr Eric REITER and Dr Frédéric JEAN-ALPHONSE. My work aims at deciphering the spatiotemporal dynamics of gonadotropin receptors trafficking and signalling, and at understanding the link between signalling compartmentation at organelles scale and reproductive physiology. To better understand the molecular mechanisms underlying these phenomena, I use and develop different approaches (compartmentalized sensors, biased ligands, ...), to both correlate cellular signalling mechanisms with gonads activity and modulate this activity *in vivo*.

Role of cellular compartmentation of gonadotropin receptors' signalling in reproductive physiology

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Gonadotropins (FSH and LH) regulate reproductive functions through binding their G protein-coupled receptors (GPCRs), FSHR and LHR, at gonadal cell surface. Activation of the receptors by their ligands engenders a complex signalling network controlling steroidogenesis, spermatogenesis (in male), follicular growth and ovulation (in female). A key regulator of this signalling network is the second messenger cAMP. Long known to be produced at plasma membrane, cAMP has more recently been identified to be also produced from endosomes after receptor internalisation, for gonadotropin receptors and other GPCRs. cAMP is involved in the control of broad range of cellular functions. Despite the suggested importance of LHR-dependent sustained endosomal cAMP for oocyte meiosis, very little is known about the mechanisms by which cAMP signalling is achieving functional specificity to regulate gonadal activity. Our data support that gonadotropin receptors endocytosis and endosomal cAMP signalling are both essential to regulate biological processes such as gene transcription, MAPK signalling and progesterone production. As for other GPCRs, spatial and temporal organisation of gonadotropin receptors' cAMP signalling may represent a key mechanism to regulate gonadal function and reproductive physiology.

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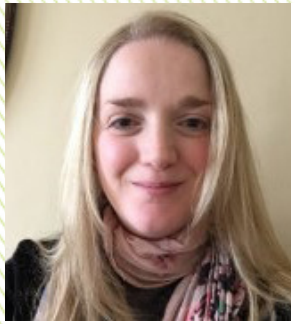
Prof. Hanyaloglu has been a Group Leader at Imperial College London since 2007. She received her BSc in Human Biology from King's College London, and her Ph.D. in Molecular Endocrinology from the University of Western Australia. Prof. Hanyaloglu undertook her postdoctoral training at the University of California, San Francisco. Her research focuses on identifying fundamental mechanisms regulating GPCR activity, including spatial control of GPCR signalling and receptor crosstalk, and applying these mechanisms in diverse physiological and pathophysiological systems. Her work is currently funded by Biotechnology and Biological Sciences Research Council, Wellcome Trust, and the Medical Research Council.

Spatial control of gonadotrophin hormone receptor signalling; mechanisms and applications

Our models of GPCR signaling have rapidly evolved from single receptors activating distinct G protein pathways at the plasma membrane, to one that exhibits high signal diversity, and whose properties are exquisitely regulated at both a spatial and temporal level. The gonadotrophin hormone receptors have contributed to this rewriting of our GPCR 'signalling atlas' and thus offer new interpretations of faulty GPCR activity in disease and provide novel therapeutic strategies to target receptor signalling. We have recently demonstrated that gonadotrophin hormone receptors are organized into distinct intracellular endosomal compartments from other GPCRs following internalization, and this tight spatial control is critical for regulation of Gs/cAMP/PKA signalling. However, the gonadotrophin hormone receptors activate multiple G protein pathways, with distinct functions in vivo. Here I will describe how pleiotropic GPCR signalling can be differentially regulated at a spatial level as a mechanism for reprogramming LH/FSH activity to specific pathways, including in disease contexts, and efforts within our group to further understand this poorly understood endosomal compartment at a proteomics level. Furthermore, the possibility of reprogramming the spatial fate of gonadotrophin hormone receptors at a pharmacological level could represent a novel therapeutic avenue to modulate gonadotrophin hormone receptor function.



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Dr Kim Jonas is a Senior Lecturer in Reproductive at KCL. Kim undertook her PhD in ovarian physiology at University College London and completed postdoctoral research at the Royal Veterinary College and Imperial College London, where she elucidated physiological, cellular, and single molecule aspects of receptor-mediated control of the hypothalamic-pituitary-ovarian axis. Kim's research programs, funded by UKRI, NIH and Merck Serono, utilise convergent approaches to understand the role(s) of G protein-coupled receptors in controlling ovarian ageing and infertility. She is the convenor of the Reproductive Endocrinology and Physiology Network (Society for Endocrinology), editor of The Endocrinologist magazine, and a member of Society for Reproduction and Fertility council.

Towards understanding the role of gonadotrophin receptor oligomerisation in reproductive health

The coordinated actions of the gonadotrophin hormone receptors are essential for reproduction, with dysfunction leading to infertility and premature ovarian ageing. As G protein-coupled receptors (GPCRs), an increasingly recognised mechanism for regulating the type, duration and strength of intracellular signals activated, and the functional responses, thereafter, is via GPCRs associating with the same (homomers) or other (heteromers) GPCRs. This talk will describe our work, primarily in heterologous cell models and moving to physiological models using primary cells and ovarian follicles to begin to understand the role of gonadotrophin receptor homomers and heteromers in the control of reproductive functions and ovarian ageing.

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Professor Kumar is The Makowski Family Endowed Chair and the Director of the Women's Reproductive Health Research, Department of Ob & Gyn, University of Colorado Anschutz Medical Campus, USA. He published very high-impact papers, book chapters and reviews on genetics and physiology of gonadotropin synthesis, secretion and action. He gave seminars at several symposia and institutes all over the world. He received the Biomedical Research Excellence Faculty Scholar Award, Faculty Investigator Research Award and The Thomas Noffsinger Investigator Award - all from University of Kansas Medical Center. He is the recipient of the 2021 Neena Schwartz Memorial Keynote Lecture Award, 2021 Janice E. Bahr Keynote Lectureship Award in Reproductive Biology and 2021 David Yawn Commemorative Lecture Award.

Genetic and Pharmacological Approaches to Study FSH Action in the Male

FSH binds to FSHRs expressed on Sertoli cells and regulates their proliferation and differentiation, the two events critical for optimal male reproductive function. FSH actions in the male are species-specific and remain controversial. Male mice lacking either FSH beta subunit- or FSHR- encoding gene demonstrate decreased testis size as a result of reduced Sertoli cell proliferation. Although male germ cell-carrying capacity is compromised, these mutant mice display normal fertility. In contrast, mutations in the corresponding human genes result in more severe reproductive phenotypes in men. To further understand the species- specific variations in FSH action in the male, we have taken two approaches. In a genetic approach, we generated novel mutant mice in which FSH action via both the FSH ligand and receptor is abolished from birth. Despite lacking both FSH/FSHR from birth, these double male mutants phenocopy the single mutants. In an independent approach, in collaboration with Dr. Mone Zaidi, we have pharmacologically abolished FSH binding to FSH receptors in adult mice by a well-characterized polyclonal FSH-neutralizing antibody. Blocking FSH action in adult mice, unlike that from birth as in the genetic approach also resulted in normal fertility without any overt male reproductive phenotypes. Together, our genetic and pharmacological data reinforce that FSH action in the male is species-specific and yet unknown mechanisms may compensate for loss of FSH action in male mice.

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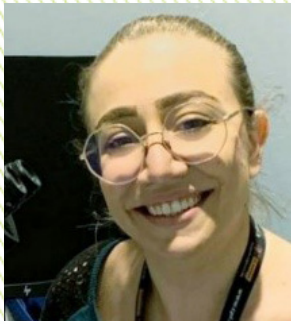
I am a post-doctoral research fellow with a PhD in Clinical and Experimental Medicine (CEM) and I am actually carrying out my research at Professor Simoni's laboratory at the Unit of Endocrinology of the University of Modena and Reggio Emilia. My studies are focused on molecular mechanisms linked to gonadotropins activity exerted *via* GPCRs, as master regulators of endocrine reproductive functions. Currently, my research is focusing on the heterodimerization of follicle-stimulating and luteinizing hormone receptors (FSHR; LHCGR) with other GPCRs and on their involvement in ovarian physiology and gametogenesis. I am a member of the "European Society of Endocrinology" (ESE).

Effects of human luteinizing hormone/choriogonadotropin receptor (LHCGR) and G protein-coupled estrogen receptor (GPER) heteromers *in vitro*

Human luteinizing hormone (LH)/choriogonadotropin (hCG) receptor (LHCGR) and the G protein-coupled estrogen receptor (GPER) are co-expressed in the ovary, where they are regulators of fertility. We previously demonstrated that GPER may form heteromers with the follicle-stimulating hormone (FSH) receptor, structurally similar to LHCGR, shifting FSH-induced signals to survival pathways. Here, we evaluated whether GPER interacts with LHCGR modulating the LH/hCG-dependent intracellular signalling in transiently transfected HEK293 cells, using energy transfer-based methods and photo-activated localization microscopy, revealing the presence of heteromeric structures on the cell surface. Interestingly, GPER-LHCGR complex did not affect the LH/hCG-induced cAMP production nor the activation of the cAMP/protein kinase A (PKA) pathway. Instead, GPER displaced the LHCGR/Gαq coupling, causing the failure of the LH/hCG- induced intracellular Ca^{2}+ increase, the inositol monophosphate (IP1) accumulation. A reporter system revealed GPER-dependent inhibition of downstream IP1/Ca^{2}+ target gene transcription.

In conclusion, GPER interacts with the ovarian receptor LHCGR in the cell surface, selectively inhibiting the intracellular Gαq-mediated activity and suggesting a possible role in regulating female gonadal physiology.



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My name is Elisa Mascolo. My academic junior preparation comes from the Sapienza University of Rome, where I obtained the Ph.D. in Genetics and Molecular Biology. During this period, I evaluated how human genetic variants impact diabetes, as well as their predictive potential of cancer risk. Currently, I am a Junior post-Doc at the Unit of Endocrinology (University of Modena and Reggio Emilia), where I had the opportunity to work in basic and translational research in reproductive endocrinology and physiology, under the supervision of Prof. Livio Casarini. My studies focus on human reproduction, pharmacogenetics of sex hormones and their receptors, as well as other aspects such as thyroid pathophysiology.

Impact of two differently glycosylated recombinant FSH on signal transduction

Different follicle-stimulatin hormone (FSH) glycoforms are available for assisted reproduction, where they are administered to women to induce multifollicular growth. The aim of this study *in vitro* is to compare the intracellular signaling pattern mediated by two differently glycosylated, recombinant FSH. Gonal-f® (Merck KGaA) is produced using a modified chinese hamster ovary (CHO) cell line and it is assumed to be the reference hormone, while Rekovelle® (Ferring Pharmaceuticals) is produced by the human fetal retinal PER.C6® cell line. Transfected HEK293 cells overexpressing the FSH receptor (FSHR) were treated by increasing FSH doses (0.0-1.0 µM range). Intracellular cAMP and Ca^{2+} increase, IP1 production, as well as FSHR homomers formation were evaluated by energy transfer-based methods, while pCREB and pERK1/2 activation by Western blotting. Results were compared by two-way ANOVA and Bonferroni post-test ($P<0.05$). While Gonal-F produced higher concentrations of intracellular cAMP (n=7) and intracellular Ca^{2+} release (n=2) than Rekovelle, the latter was more potent in inducing FSHR homomer formation (n=7) and CREB phosphorylation (n=2). No different IP1 and pERK1/2 activation were detected (n=2). Recombinant FSH used in clinical practice may impact differently intracellular signaling cascades *in vitro*.

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I'm a post-doctoral research fellow at the Unit of Endocrinology, Dept. Biomedical, Metabolic and Neural Sciences, of the University of Modena and Reggio Emilia. My basic research is supervised by Prof. Livio Casarini and is focused on the pathophysiology of gonadotropins and their receptors. My main achievements consist in the differentiation between LH and hCG action, the formation of G protein-coupled receptor heteromers and the role of sphingosine-1-phosphate in the ovary. I'm a member of "European Society of Endocrinology" (ESE).

Luteinizing hormone (LH)- and choriogonadotropin (hCG)-induced internalization of the receptor (LHCGR) is responsible for hormone-specific signaling

Luteinizing hormone (LH) and human choriogonadotropin (hCG) regulate reproduction through binding the same receptor (LHCGR). They act via activation of G protein and ß-arrestin-dependent signals, resulting in ligand-specific pattern of signaling cascades and LHCGR internalization into endosomal vesicles. We compared the role of LHCGR internalization in determining LH- and hCG-specific signals in transfected HEK293 cells. LH/hCG-induced LHCGR trafficking was evaluated by specific bioluminescence resonance energy transfer (BRET) biosensors, in the presence and in the absence of internalization blockade by Dynasore. hCG induced Gs, Gq and ß-arrestin 2 coupling to LHCGR, cAMP activation and intracellular Ca^{2+} increase, as well as LHCGR-Rab5 interaction, a marker of internalization of early endosome, more effectively than LH. Conversely, LH induced preferential Gi coupling, ERK1/2 activation and LHCGR-Rab11 interaction, the latter involved in recycling of the receptor in the cell membrane. Although no hormone-specific LHCGR-Rab7 interaction was found, Dynasore treatment increased LH-induced the recruitment of Rab7, indicating ligand-specific routing through the degradation pathway. We conclude that LHCGR internalization is fundamental to modulate LH- and hCG specific signals, impacting the downstream signaling cascades.

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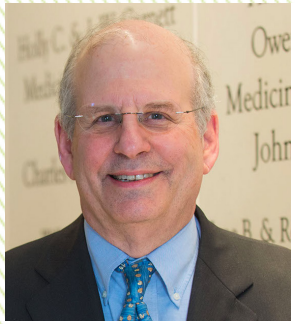
I work as Instructor in Dr. John S. Davis lab, OBGYN Department, *University of Nebraska Medical* Center (UNMC). I gathered PhD degree from the Institute of *Animal Reproduction and Food Research* (IARFR) of the *Polish Academy of Sciences* (PAS), Olsztyn, Poland. During my PhD studies I identified cascade of events occurring at molecular and hormonal level in the porcine corpus luteum during the estrous cycle and early pregnancy. In 2018, I joined Dr. John Davis lab, where I started to work on metabolic events and pathways regulating luteal formation, development, and regression. I am especially interested in identification of metabolic events and pathways driven by luteotrophic and luteolytic factors in the corpus luteum and determine metabolic pathways crucial for progesterone production.

LH-responsive metabolic pathways essential for luteal steroidogenesis

Co-authors : John S. Davis

Luteinizing hormone (LH) is essential for the formation and function of the corpus luteum, an endocrine gland important for establishment and maintenance of pregnancy. We evaluated metabolomic changes in response to LH (0-4 h) in highly steroidogenic bovine small luteal cells (SLC) using GC/MS and LC/MS/MS, NMR, and Seahorse platforms. LH provoked rapid reductions in glucose and other carbohydrates, delayed reductions in glutamine and glutamate, and simultaneously elevated lactate, metabolites of the pentose phosphate pathway (PPP) and lysophospholipids. ^{13}C- glucose labeling studies confirmed LH-induced changes in the glycolytic pathway, *de novo* lipogenesis, PPP, hexosamine biosynthesis pathway, and glutathione production. Seahorse analysis confirmed enhanced oxygen consumption rate, glycolytic capacity, and increased ATP production, which were coupled with mitochondria elongation in response to LH. LH stimulated phosphorylation of ATP citrate lyase (ACLY), which converts citrate to Acyl-CoA, a precursor for lipid synthesis. Inhibition of either ACLY or fatty acid transport to the mitochondria reduced LH-stimulated ATP production by 80% and progesterone synthesis. Small molecule inhibition of pyruvate metabolism reduced the extracellular acidification rate and progesterone synthesis. Thus, LH rapidly mobilizes metabolic pathways involved glucose metabolism, the TCA cycle, and fatty acid synthesis, which contribute to the acute effects of LH on progesterone production.



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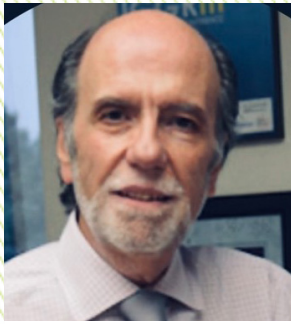
Dr. Strauss served as Associate Chair of the Department of Obstetrics and Gynecology and Associate Dean at Penn before joining Virginia Commonwealth University as Executive VP for Medical Affairs & Dean of Medicine. His research resulted in the discovery of genes involved in polycystic ovary syndrome, lipid and steroid metabolism, preterm birth and preeclampsia. He is a member of the National Academy of Medicine, National Academy of Inventors, received the Arnaldo Bruno International Prize in Gynecology of the Accademia Nazionale dei Lincei, Research Award of the Society for the Study of Reproduction, Transatlantic Medal of the British Endocrine Society, President's Achievement Award, Distinguished Scientist Award, and Mentorship Award of the Society for Reproductive Investigation.

A Novel Signal Transduction Pathway Directs Increased Thecal Cell Androgen Production in Polycystic Ovary Syndrome

Polycystic ovary syndrome (PCOS), characterized by hyperandrogenemia of ovarian origin and follicular growth arrest leading to anovulation and infertility, affects up to 15% of reproductive-age women. Family studies, twin-based studies, and genome-wide association studies (GWAS) have provided compelling evidence that PCOS is a polygenic disorder. However, the specific genes, the ways by which they promote PCOS phenotypes, and the genetic variants that have causal roles in PCOS remain to be identified. We propose that two strong PCOS GWAS regulatory gene candidates, DENND1A and ZNF217, are involved in the pathogenesis of PCOS. DENND1A.V2, a splice variant of DENND1A, which has been identified in multiple GWAS and association studies, augments thecal cell expression of CYP17A1 and androgen production, a cardinal feature of PCOS. Based on our discovery that V2 traffics to the nucleus and increases CYP17A1 promoter activity, we propose that DENND1A.V2 is a novel signal transducer involved in determining the theca cell PCOS phenotypes. We have elucidated the role of another transcription factor, ZNF217, whose expression is inversely correlated with DENND1A.V2. The abundance of the microRNA, miR-130b-3p, which targets DENND1A.V2 transcripts, is correlated with ZNF217 expression. Knockdown of ZNF217 or miR-130b-3p in normal theca cells increases DENND1A.V2 and induces a PCOS phenotype. Our studies have disclosed new potential diagnostics and novel therapeutic targets for PCOS.



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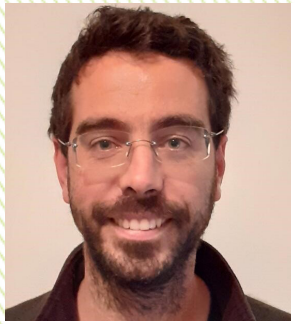
Alfredo Ulloa-Aguirre M.D., D.Sc., obtained his academic degrees from the National University of Mexico (UNAM). In 1980-1982 and 1986-1988 he was postdoctoral research fellow at the University of Pennsylvania, USA, where he worked with Scott C. Chappel and Jerome F. Strauss III. In 1996 and 2003 he was Visiting Scientist at the Oregon National Primate Research Center, USA, working in the laboratory of the late P. Michael Conn, and in 2009-2010 he was invited as LE STUDIUM Scientist Fellow at the INRA, Centre de Tours-Nouzilly, where he worked with Eric Reiter. He currently leads the Core Facility (Red de Apoyo a la Investigación) of the UNAM-National Institutes of Health in Mexico. His research is focused on the study of the structure-function relationship of gonadotropins and their receptors, areas in which he has published prolifically, being currently an internationally recognized leader.

Mutations in Gonadotropin Receptors that Impact Receptor Trafficking and Reproductive Function. Functional Rescue by Pharmacological Chaperones

In eukariotes, proteins are synthesized in a cellular organelle called endoplasmic reticulum, where they fold to reach a 3-dimensional configuration. If protein folding fails as a result of a mutation in its corresponding sequence, the misfolded conformer is degraded and thereby unable to express and act at its site of action in the cell. Molecular chaperones are essential components of the complex quality control system (QCS) of the cell; QCS monitors that newly synthesized proteins are folded properly before continuing their intracellular trafficking to their final destination. In the case of cell surface membrane proteins (such as membrane receptors and ion channels) that act as mediators of extracellular signals, their absence due to misrouting leads to an array of diseases. A new strategy to overcome the misfolding problem is by the so-called pharmacological chaperones or pharmacoperones, which are small, synthetic molecules that act as molecular frameworks to assist misfolded proteins to fold properly and adopt a more stable, minimal free-energy conformation to pass the scrutiny of the cell's QCS, thereby correcting misrouting. In this presentation, I will briefly describe the molecular basis of pharmacoperone action as a potential and useful therapeutic approach to rescue gonadotropin receptor mutants, which are essential for reproductive function.



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Romain Yvinec (INRAE Tours) co-leads the interdisciplinary team Biology of GPCR Signaling Systems (BIOS) at the Physiology of Reproduction and Behavior laboratory (PRC, INRAE UMR85, CNRS UMR7247, Université de Tours, IFCE). He is a permanent member of the joint project-team (EPC) Musca (INRIA-INRAE-CNRS).
Romain Yvinec has a strong expertise in biomathematical modeling, using population dynamics and chemical reaction network to understand physiological processes.

Kinetic biased signaling: towards a system biology definition of drugs selectivity. Illustration on the Follicle Stimulating Hormone Receptor

An active area of research in pharmacology and drug discovery applies to functional selectivity: the ability of a ligand to selectively activate some signal transduction pathways as compared to the native ligand acting at the same receptor.

At the theoretical level, biased signaling is supported by the concept of conformational selectivity: a given receptor may adopt several conformations, that can be stabilized by its interaction with a ligand, and each of these conformations potentially activates the downstream signaling pathways with different efficacies.

At the practical level, experimentalists seek to quantify ligand bias in order to classify ligands according to their selectivity. One popular method uses the so-called operational model to fit dose-response curves.

Our objective is then to design a method that fully take into account the kinetic nature of signaling pathways and as well as their possible cross-talks. I will explain how one can exploit kinetic data and dynamical reaction network modeling with suitable statistical framework to provide a complete "bias map" of a ligand, compared to the native ligand, that successfully answer to our objective.

The methodology is illustrated with kinetic BRET measurements of effectors of the FSHR, stimulated by either the FSH or low molecular weight allosteric ligands.

References:

Pharmacological characterization of low molecular weight biased agonists at the follicle stimulating hormone receptor

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24 - 25 September 2020

Dr Emilio Maria Sanfilippo & Xavier Rodier
FAIR Heritage: Digital Methods, Scholarly Editing and Tools for Cultural and Natural Heritage
17-18 June 2020

Dr Margriet Hoogvliet & Prof. Chiara Lastraioli
Spatial Humanities and Urban Experiences During the Long Fifteenth Century
11 Mai 2020

Dr Thimmalapura Marulappa Vishwanatha & Dr Vincent Aucagne
Challenges and prospects in chemoselectuve ligations: from protein synthesis to site-specific conjugation
27-29 January 2020

Dr Arunabh Ghosh & Prof. Fouad Ghamouss
Towards Futuristic Energy Storage; paving its way through Supercapacitors, Li-ion batteries and beyond
22-24 January 2020

2019

Dr Yuri Dancik & Dr Franck Bonnier
Skin Models in Cosmetic Science: Bridging Established Methods and Novel Technologies
2 - 4 December 2019

Dr Eric Robert, Dr Jean-Michel Pouvesle & Dr Catherine Grillon
International Meeting on Plasma Cosmetic Science
25-27 November 2019

Prof. Richard Freedman & Prof. Philippe Vendrix
Counterpoints: Renaissance Music and Scholarly Debate in the Digital Domain
14-16 November 2019

Prof. Manuela Simoni, Dr Frédéric Jean-Alphonse, Dr Pascale Crépieux & Dr Eric Reiter
Targeting GPCR to generate life, preserve the environment and improve animal breeding: technological and pharmaco logical challenges
16-18 October 2019

Prof. Akkihebbal Ravishankara & Dr Abdelwahid Mellouki
Climate, air quality and health: long-term goals and near-term actions
28 June 2019

Dr Wolfram Kloppmann
N and P cycling in catchments: How can isotopes guide water resources management?
18 June 2019

Dr Carmen Díaz Orozco & Dr Brigitte Natanson
Forging glances.
Images and visual cultures in XIXth century Latin America
28-29 May 2019

DrTijen & Dr Gülçin Erdi
Rebel streets : urban space, art, and social movements
28 - 29 May 2019

Dr Marcelo Lorenzo & Prof. Claudio Lazzari
New avenues for the behavioral manipulation of disease vectors
21-23 May 2019

Dr Agnieszka Synowiec & Dr Christophe Hano
Biological Activities of Essential Oils
13-15 May 2019

Prof. Yiming Chen & Prof. Driss Boutat
2019 International Conference on Fractional Calculus Theory and Applications (ICFCTA 2019)
25-26 April 2019

Prof. Temenuga Trifonova & Prof. Raphaële Bertho
On the Ruins and Margins of European Identity in Cinema: European Identity in the Era of Mass Migration
2-3 April 2019

Dr Patrizia Carmassi & Prof. Jean-Patrice Boudet
Time and Science in the Liber Floridus of Lambert of Saint-Omer
27-28 March 2019

Dr Guillermina Dalla-Salda & Dr Philippe Rozenberg
Adapting forest ecosystems and wood products to biotic and abiotic stress
12-15 March 2019

Dr Vincent Courdavault & Prof. Nathalie Guivarc'h
Refactoring Monoterpenoid Indole Alkaloid Biosynthesis in Microbial Cell Factories (MIAMi)
5-6 February 2019

Dr Denis Reis de Assis & Prof. Hélène Blasco
Induced Pluripotent Stem Cells (iPSCs): From Disease Models to Mini-Organs
28-30 January 2019

2018

Prof. Igor Lima Maldonado & Prof. Christophe Destrieux
Frontiers in Connectivity: Exploring and Dissecting the Cerebral White Matter
5-6 December 2018

Dr Marius Secula, Prof. Christine Vautrin-Ul & Dr Benoît Cagnon
Water micropollutants: from detection to removal
26-28 November 2018

Prof. Guoxian Chen & Prof. Magali Ribot
Balance laws in fluid mechanics, geophysics, biology (theory, computation, and application)
19-21 November 2018

Dr Volodymyr Sukach & Prof. Isabelle Gillaizeau
Progress in Organofluorine Chemistry
15-17 October 2018

Jens Christian Moesgaard, Prof. Marc Bompaire, Bruno Foucray & Dr Guillaume Sarah
Coins and currency in the 10th and 11th centuries: issuing authorities, political powers, economic influences
11-12 October 2018

Dr Norinne Lacerda-Queiroz & Dr Valérie Quesniaux
Malaria - Current status and challenges
27-28 September 2018

Dr Renaud Adam & Prof. Chiara Lastraioli
Lost in Renaissance
20-21 September 2018

Prof. Abdelwahid Mellouki & Dr Véronique Daële
The 6th Sino-French Joint Workshop on Atmospheric Environment
10-12 September 2018

Prof. Emre Erdem & Dr Guylaine Poulin-Vittrant
Frontiers in Nanomaterials for Energy Harvesting and Storage
27-29 August 2018

Prof. Graeme Boone & Prof. Philippe Vendrix
Affective horizons of 'song' in the long fifteenth century
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Prof. Bilal Haider Abbasi, Prof. Nathalie Guivarc'h & Dr Christophe Hano
Modern aspects of Plant in Vitro Technology
27 June 2018

Prof. Marek Łos & Dr Catherine Grillon
Stem cells & cancer stem cells: Regenerative medicine and cancer
11-13 June 2018

Dr Ewa Łukaszyk & Prof. Marie-Luce Demonet
Transcultural Mediterranean: in search of non-orthodox and non-hegemonic universalism(s)
30-31 May 2018

Prof. Vladimir Shishov & Dr Philippe Rozenberg
Wood formation and tree adaptation to climate
23-25 May 2018

Dr Ján Žabka & Dr Christelle Briois
Advances in Space Mass Spectronometry for the Search of Extraterrestrial Signs of Life
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Dr Massimiliano Traversino Di Cristo & Prof. Paul-Alexis Mellet
From Wittenberg to Rome, and Beyond
Giordano Bruno: Will, Power, and Being
Law, Philosophy, and Theology in the Early Modern Era
26-27 April 2018

Dr William Horsnell & Dr Bernhard Ryffel
Neurotransmitters: non-neuronal functions and therapeutic opportunities
26-28 March 2018

Prof. Eric Goles & Prof. Nicolas Ollinger
Discrete Models of Complex Systems
19-21 March 2018

2017

Dr Kristina Djanashvili & Dr Éva Jakab Tóth
Is Multimodal Imaging an Invention with a Future? The Input of Chemistry
11-13 December 2017

Dr Emmanuel Saridakis & Dr Marc Boudvillain
Structural biology and biophysics of RNA-protein complexes
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The Runaway Word. Languages and Religious Exile in the Renaissance
7-8 November 2017

Prof. Michiel Postema & Dr Ayache Bouakaz
Acoustic bubbles in therapy: recent advances with medical microbubbles, clouds and harmonic antibubbles
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Dr Mauro Simonato & Dr Jérôme Rousselet
Species spread in a warmer and globalized world
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1968 and the boundaries of childhood
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Prof. Mihai Mutascu & Prof. Camelia Turcu
Globalization and growth in eurozone: new challenges
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Dr Mauro Manno & Prof. Richard Daniellou
The role of glycosylation on serpin biology and conformational disease
27-29 September 2017

Prof. Salvatore Magazù, Prof. Francesco Piazza, Dr Sivakumar Ponnurengam Malliappan, Dr Emilie Munnier
Recent advances in basic and applied science in cosmetics
3-5 July 2017

Dr Maria Clotilde Camboni & Prof. Chiara Lastraioli
The dynamics of the relationship with the more recent past in early modern Europe: between rejection and acknowledgement
20-22 June 2017

Dr Sohail Akhter & Prof. Chantal Pichon
Messenger RNA therapeutics: advances and perspectives
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Prof. Gary Gibbons & Prof. Sergey Solodukhin
GARYFEST: Gravitation, Solitons and Symmetries
22-24 March 2017

2016

Dr Mohammed Ayoub & Dr Eric Reiter
Antibodies Targeting GPCRs, Recent Advances and Therapeutic Challenges
24-25 November 2016

Prof. David Koester, Dr Bernard Buron & Dr Jean-Philippe Fouquet
Practical Engagements and the Social-Spatial Dimensions of the Post-Petroleum Future
7-9 November 2016

Dr Jorge Gutierrez & Dr Philippe Frank
Lipids, Nanotechnology and Cancer
10-12 October 2016

Dr Ferenc Kàlmàn & Dr Éva Jakab Tóth
Being Smart In Coordination Chemistry: Medical Applications
26-28 September 2016

Jean-Philippe Bouillon, Mourad Elhabiri, Jiri Kozelka, Laurent Plasseraud, Michèle Salmain & Eva Tóth, Roman Bulánek, Radek Cibulka, Michal Otyepka, Jan Preisler, Vladimír Šindelář & Irena Valterová
7th French-Czech "Vltava" Chemistry Meeting
Advancing Chemistry through Bilateral Collaboration
5-6 September 2016

Dr Satyajit Phadke, Dr Chandrasekaran & Prof. Mériem Anouti
Future strategies in electrochemical technologies for efficient energy utilisation
7-9 September 2016

Prof. Peter Bennett & Prof. Philippe Vendrix
Sacred/secular intersections in early-modern European ceremonial: Text, music, image and power
11-13 July 2016

Prof. Leandros Skaltsounis & Prof. Claire Elfakir
Olive Bioactives: applications and prospects
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Dr Mikhail Zubkov & Dr Maxim Chernodub
Condensed matter physics meets relativistic quantum field theory
13-15 June 2016

Prof. Brown-Grant, Dr Carmassi, Prof. Drossbach, Prof. Hedeman, Dr Turner & Prof. Ventura
Inscribing Knowledge on the Page: Sciences, Tradition, Transmission and Subversion in the Medieval Book
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Classical and quantum black holes
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Dr Gyula Tircsó & Dr Éva Jakab Tóth
Medicinal flavor of metal complexes: diagnostic and therapeutic applications
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Prof. Erminia Ardissino & Dr Elise Boillet
Lay Readings of the Bible in Early Modern Europe
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Prof. Kathleen Campbell & Dr Frances Westall
Habitats and inhabitants on the early Earth and Mars
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Prof. Marion Harris & Dr David Giron
Insects, pathogens, and plant reprogramming: from effector molecules to ecology
5-7 October 2015

Dr Arayik Hambardzumyan & Dr Sylvie Bonnamy
Bioinspired molecular assemblies as protective and delivery systems
7-9 September 2015

Dr Peter Arensburger & Dr Yves Bigot
Analysis and Annotation of DNA Repeats and Dark Matter in Eukaryotic Genomes
8-10 July 2015

Prof. Scott Kroeker & Dr Pierre Florian
Nuclear Waste Disposal: Designing Materials For the End of Time
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Entanglement, Holography and Geometry
17 April 2015

Prof. Kari Astala & Dr Athanasios Batakis & Prof. Michel Zinsmeister
Conformal Methods in Analysis, Random Structures & Dynamics
12 April 2015

Prof. Kari Astala & Dr Athanasios Batakis
Loire Valley Workshop on Conformal Methods in Analysis, Random Structures & Dynamics
12-16 April 2015

2014

Dr Natalia Kirichenko & Dr Alain Roques
Insect invasions in a changing world
17-19 December 2014

Dr Alejandro Martinez & Dr Philippe Rozenberg
Natural and human-assisted adaptation of forests to climatic constraints: the relevance of interdisciplinary approaches
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Dr Magnus Williamson & Prof. Xavier Bisaro
Reconstructing Lost Spaces: acoustic, spatial, ceremonial contexts
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Dr C. Oshman & Dr G. Poulin-Vittrant
Piezoelectric micro and nano-structures and their applications
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Dr Eric Reiter
3rd International Congress on Gonadotropins & Receptors - ICGRIII
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Dr Robin Beech & Dr Cédric Neveu
NemaTours: bringing worms together
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Heterogeneous catalysis : recent advances in preparation and characterization
31 March - 1 April 2014

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Prof. Chandani Lokuge & Prof. Trevor Harris
Postcolonialism now
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Dr Fabrizio Gherardi & Dr Pascal Audigane
Geochemical reactivity in CO_2 geological storage sites, advances in optimizing injectivity, assessing storage capacity and minimizing environmental impacts
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Prof. Marcos Horacio Pereira & Prof. Claudio Lazzari
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Prof. Marc Hillmyer & Prof. Christophe Sinturel
Bottom-up approaches to Nanotechnology
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Dr Svetlana Eliseeva & Prof. Stéphane Petoud
Lanthanide-based compounds : from chemical design to applications
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Vision and image-making : constructing the visible and seeing as understanding
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Chronic inflammatory lung diseases : The next-generation therapeutic targets to consider
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Macromolecular crowding effects in cell biology : models and experiments
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Biology and mathematical inverse problems : a new wedded couple ?
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Dr Lidewij Tummers & Prof. Sylvette Denèfle
Co-housing : born out of need or new ways of living ?
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Prof. Clive Oppenheimer & Dr Bruno Scaillet
Mount erebus, antarctica : an exceptional laboratory volcano
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Prof. Friedrich Wellmer
Life and innovation cycles in the field of raw material supply and demand — a transdisciplinary approach
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Dr Gerard Klaver, Dr Emmanuelle Petelet & Dr Philippe Negrel
Rare earth elements in our environment from ores towards recycling through the continental cycle
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Prof. Rosalind Brown-Grant & Prof. Bernard Ribémont
Textual and visual representations of power and justice in medieval manuscript culture
5-6 July 2012

Dr Agata Matejuk & Prof. Claudine Kieda
Defeating Cancer Can non coding small RNAs be new players ?
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Prof. Nicola Fazzalari & Prof. Claude-Laurent Benhamou
Osteocyte Imaging
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Prof. Nikolay Nenovsky & Prof. Patrick Villieu
Europe and the Balkans : economic integration, challenges and solutions
3-4 February 2011

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Cosmetics and Pharmaceutics : New trends in Biophysical Approaches
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Inflammatory and infectious diseases
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Non commutative geometry, strings and gravity
25-27 May 2011

Prof. Jinglin You & Dr Patrick Simon
In situ Molecular Spectroscopic Technique and Application
20-21 June 2011

Prof. Valery Terwilliger & Dr Jérémy Jacob
Hydrogen isotopes as environmental recorders
15-16 September 2011

Prof. Philip Weller & Prof. Philippe Vendrix
Mystères des voix perdues – Polyphonies reconstituées, 1420-1520
24-30 October 2011

Prof. John Brady & Prof. Marie-Louise Saboungi
Water in biological systems
5-6 December 2011

2010

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Prof. Alfredo Ulloa Aguirre & Dr Eric Reiter
New directions in gonadotropin hormones and their receptors
3-4 June 2010

Dr Yossi Maurey & Dr Christine Bousquet-Labouérie
Sacred space, sacred memory : bishop saints and their cities
10-12 June 2010

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