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MEETING REPORT

Cellular Serpents and Dreaming Spires: New Frontiers in Arginine and Pyrimidine Biology

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The International Conference on Arginine and Pyrimidines (ICAP) had its origin as an arginine workshop organised by a group of microbiologists led by Werner Maas in 1972 (Rubio, 2003). The shared requirement of carbamoyl phosphate in both arginine and pyrimidine metabolism led to a natural association of researchers working in both fields. The 24th International Conference on Arginine and Pyrimidines (ICAP2014) was hosted on July 16th−19th, 2014 at St Anne's College, Oxford, the city of dreaming spires, and organised by Ji-Long Liu and colleagues (MRC Functional Genomics Unit at the University of Oxford) (Fig. 1). Fifty-four researchers from around the world presented a broad range of novel work and ideas on the genetics, cell biology, biochemistry, genomics, and structural biology of arginine, the urea cycle, and pyrimidines (Fig. 2). Thirty platform presentations were given over the four-day meeting as well as a well-attended interactive poster session. This meeting included a session on the emerging field of cytoophidia, evolutionarily conserved snake-shaped structures, which contain CTP synthase. Discussion on the past, present and future of the ICAPs extended from the lecture theatre and lobby to the pubs and dining hall.

The conference attendees were welcomed by Ji-Long Liu (University of Oxford), who recalled how an on-site vote in Bogota led to Oxford to be the host city for the ICAP2014 meeting. Elizabeth Carrey (formerly of Dundee University and University College London) gave a short overview of the changing perceptions of the multienzyme polypeptide, CAD, which catalyses the first three steps of pyrimidine biosynthesis; at first, a large protein derived from ancient gene fusions, and now a target for several protein kinases, demonstrating its central role in regulating the flux of nucleotides for use in the cell. She summarised the 42-year history of the ICAP conference and went on to mention the importance of small meetings such as ICAPs with focused group discussion, and the progress of pyrimidine research in recent history.

STRUCTURE AND FUNCTION: NEW FRONTIERS IN PYRIMIDINE BIOLOGY

Due to the fundamental role of pyrimidines in DNA and RNA synthesis, as well as lipid metabolism and cell signalling, understanding the biology of pyrimidines has been intensively studied for over half a century. This year's ICAP meeting demonstrated that this interest has not diminished, with around 20 talks given on various aspects of pyrimidine biology.

David Evans (Wayne State University) gave an introduction to the structure and function of the non-covalent complex of dihydroorotase and aspartate transcarbamoylase of *Aquifex aeolicus* and detailed the development of novel peptide inhibitors, which helped to facilitate insights into the regulation of the enzyme dynamics (Purcarea et al., 2002). Santiago Ramón-Maiques (Spanish National Cancer Research Centre, Spain) described the crystal structure and function of the DHOase and ATCase domains of human CAD using site directed mutagenesis in combination with MALS (multi-angle static light scattering) (Ruiz-Ramos et al., 2013; Grande-Garcia et al., 2014). Sergio de Cima and Carmen Díez Fernandez from Vicente Rubio's lab (Instituto de Biomedicina de Valencia) further enlightened us about CPS1 (carbamoyl phosphate synthetase I). Sergio de Cima walked us through the detailed X-ray structure of CPS1 and identified a potential channel for free ammonia intake. Carmen Díez Fernandez identified a domain of unknown function (UFSD) in CPS1 which contains many potentially pathological missense mutations. Finally, she concluded by suggesting that the UFSD may be involved in the cross talk between N-acetyl glutamate

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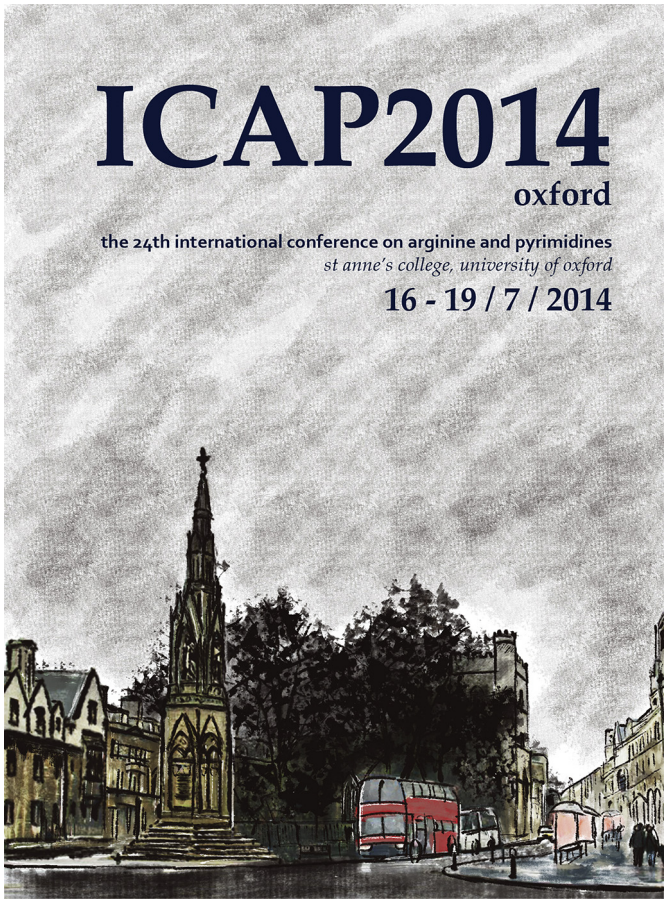

Fig. 1. The ICAP2014 meeting was hosted in Oxford, the city of dreaming spires (designed by Jing Zhang).

(NAG) and ATP binding sites (Diez-Fernandez et al., 2013; Diez-Fernandez et al., 2014).

Monika Löffler (Phillips University Marburg) reintroduced many facts regarding orotic acid and highlighted the differences in symptoms between mutations in the pyrimidine biosynthesis pathway, leading to speculation as to the function and fate of orotate in the cell beyond regulating UMP production. Wolfgang Knecht (Lund University) discussed the diversity of deoxyribonucleoside kinase pyrimidine salvage enzymes across evolution, summarising the different substrate specificities of isoforms in mammals compared to insects and plants (Clausen et al., 2012). He went on to talk about the potential exploitation of these genes in cancer suicide-gene therapy. Zee-Fen Chang (Yang-Ming University) gave an insightful talk about the relation between ribonucleotide reductase (RNR) and dUTPase and their roles in cancer progression, commenting on how the ratio between the two enzymes may be used as a prognostic indicator.

Following the talks regarding pyrimidine metabolism, Torsten Möhlmann (University of Kaiserslautern) offered a change of pace with his presentation regarding the intracellular transport of pyrimidines between cellular compartments in *Arabidopsis*, describing the structure and biochemical functions of the transmembrane plastidic nucleobase transporter, PLUTO (Witz et al., 2012). Dolores Gonzalez-Pacanowska (Higher Council for Scientific Research) went on to describe the role of deoxyuridine triphosphate nucleotidohydrolase (dUTPase) in maintaining genomic stability and cell viability in *Trypanosoma brucei*, through its role in preventing incorporation of dUTP into DNA. Patricia Kuwabara (University of Bristol) described how a genetic screen in *Caenorhabditis elegans* led to the identification of UMP synthase as a gene involved in radiation sensitivity, and discussed the involvement of this gene in mediating the coordination of metabolism with pyrimidine synthesis (Astin et al., 2008). Jun Yan (CAS-MPG Partner Institute for Computational Biology) gave an enlightening insight into the regulation of nucleotide biosynthesis genes by the circadian clock in zebrafish, and showed two independent roles for inosine monophosphate dehydrogenase (IMPDH) isoforms in eye development and circadian rhythmicity in zebrafish.

CTP SYNTHASE AND THE CYTOOPHIDIUM: AN EMERGING FIELD IN METABOLIC CELL BIOLOGY

Many speakers gave exciting talks regarding the relatively recent observation that CTP synthase (CTPsyn) is incorporated into a novel filamentous structure which has been termed as the cytoophidium (meaning cellular serpent in Greek), which is thought to regulate pyrimidine metabolism through as yet undefined mechanisms (Ingerson-Mahar et al., 2010; Liu, 2010; Noree et al., 2010; Chen et al., 2011). Lydia Hulme from Ji-Long Liu's lab (University of Oxford) presented data indicating that cytoophidia formation was prevalent in *Schizosaccharomyces pombe*, and discussed novel nutrient signalling pathways influencing filament assembly. Chia-Chun Chang, a PhD student from Li-Ying Sung's lab (Taiwan University), discussed the dynamic behaviour of cytoophidia during mammalian cell division and the interesting observation that CTPsyn structures may be present in the nucleus (Gou et al., 2014). Gerson Keppeke, a PhD student from Luis E.C. Andrade's lab (Federal University of Sao Paulo) described the relationship between CTPsyn and IMPDH using novel patient derived autoantibodies (Keppeke et al., 2012). Barbara Zimmerman (Universidad de los Andes) gave an introduction into the regulation of CTPsyn in the parasitic protozoan *Toxoplasma gondii* and described the changes occurring in CTPsyn-containing structures throughout its novel life-cycle. She finished by saying that CTP synthase can be a potential target for drug development against *T. gondii*, and how this might open doors for novel treatments for Toxoplasmosis.

Other researchers focused on the role of cytoophidia and CTPsyn in the context of regulating physiological processes in metazoan animal models. Ömür Tastan from Liu's lab in Oxford showed that CTPsyn has an important role specifically in the development of the *Drosophila* larval central nervous system. Gabriel Aughey from the same lab showed that CTPsyn compartmentalisation is involved in the switching of neuroblasts from quiescent to proliferative states, as well as adaptive metabolism *in vivo*. Li-Mei Pai (Chang Gung University) indicated that the E3 ubiquitin-protein ligase, cbl, is