

# COMPARE

CENTRE OF MEMBRANE PROTEINS AND RECEPTORS

## Newsletter

Edition 25 April 2020

### New Co-Directors of COMPARE

As you will be aware, Steve Hill and Steve Watson successfully led a bid for five years of funding for COMPARE from the Universities of Birmingham and Nottingham in 2016, and have been its co-Directors since its launch. Their intention was to lead the first five years of the Centre as co-Directors and to then step back, with others taking over leadership. To this end, we have recently undertaken a process to recruit their successors, and are pleased to announce that, from January 2021, the new co-Directors of COMPARE will be Professor Jeanette Woolard (Nottingham) and Professor Davide Calebiro (Birmingham) – congratulations to you both.

The Strategic Oversight Group that works with COMPARE on behalf of both universities' UEBs met with the International Advisory Group towards the end of last year to discuss the progress and future plans of COMPARE. The meeting and the report of the IAB were very complimentary and celebrated many of the successes of COMPARE since it was established. This is due to the hard work of everyone in COMPARE and we wanted to take this opportunity to recognise and thank all of you for your hard work in making COMPARE a success.

We would also like to formally thank Steve and Steve for their strong leadership of COMPARE to date, and we look forward to continuing to work with them in their current capacity as co-Directors until the end of the calendar year.

Jessica Corner,  
Pro-Vice-Chancellor, Research and Knowledge Exchange,  
University of Nottingham

Tim Softley,  
Pro-Vice-Chancellor for Research and Knowledge Transfer,  
University of Birmingham

### New Directors Vision

Dear all,

We would very much like to thank Steve Watson and Steve Hill for their leadership and development of COMPARE over the last several years. They have created a collaborative, successful signature institute with a world-leading reputation. We hope that together with your help, that success will continue well into the future.

As we navigate some difficult times ahead, not only for COMPARE but for our wider scientific community, your thoughts and perspectives are needed – perhaps more than ever. We look forward to hosting our first virtual meeting with COMPARE PIs on **Wednesday 24th June 2020**. Other initiatives dedicated to all COMPARE members will follow. The purpose of the June meeting will be to consider the challenges ahead and develop a strong vision that will ensure active engagement from all members of our team, as we progress into the next phase of COMPARE. Details will be communicated in due course.

In the meantime, stay safe and well.

Jeanette and Davide

### Key Dates

**Symposium—G protein-coupled receptor (GPCR) pharmacology and cell signalling**

**Teams—19th and 20th May 13:00-16:00**

<https://www.eventbrite.com/e/compare-ecr-gpcr-symposium-tickets-103906444974>

### External Events

**3I Marianas LightSheet Webinar -13th and 15th May 2020**

<https://www.intelligent-imaging.com/webinars>

[birmingham-nottingham.ac.uk/compare](http://birmingham-nottingham.ac.uk/compare)

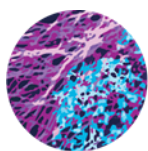
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If you have any items for the next newsletter please send to:

[compare@birmingham-nottingham.ac.uk](mailto:compare@birmingham-nottingham.ac.uk)

### IN PARTNERSHIP:

The Universities of Birmingham and Nottingham



# COMPARE

CENTRE OF MEMBRANE PROTEINS AND RECEPTORS

## Symposium—G protein-coupled receptor (GPCR) pharmacology and cell signalling 19th & 20th May 2020

COMPARE are delighted to be hosting an online satellite symposium which is focussed on **G protein-coupled receptor (GPCR) pharmacology and cell signalling**. We have an exciting programme of talks from early-career researcher from prestigious institutions, including Univ. Cambridge, Univ. Leipzig, and VU Amsterdam as well as members of COMPARE. This event is to celebrate the involvement of early-career researchers in the field and is free to attend.

As you may know, we were originally planning on holding this meeting in Nottingham earlier in April, however the covid-19 outbreak has dictated that we must pivot to an online format. We will be holding this meeting over two successive afternoons on **Tuesday 19th and Wednesday 20th May (13.00 – 16.00 GMT)**.

Registration will still take place via EventBrite (see link below). The meeting itself will be held on Microsoft Teams. After registration we will send out the details for the symposium so you can join on the day. The login details should work for both days once set up.

We still plan on holding a poster session. If you would like to display your poster on Teams during this session, please email your poster title to Mark (mark.soave@nottingham.ac.uk) or Laura (laura.kilpatrick@nottingham.ac.uk) in addition to filling in the details on the registration form.

We look forward to seeing you all online for this exciting symposium!

Registration link: <https://www.eventbrite.com/e/compare-ecr-gpcr-symposium-tickets-103906444974>

## Webinar—3i Marianas LightSheet 13th and 15th May 2020

### Marianas LightSheet: Selective Plane Illumination with Isotropic Resolution Webinar – May 13 & 15 2020

3i are hosting a series of webinars on the Marianas Light Sheet (diSPIM based system). This is a nice opportunity to learn more about a system we have in the COMPARE facility in Birmingham. This is a very versatile light sheet system that can be used in a dual view mode to image larger organisms or as a single sided system to image single cells. We have used the system to successfully image spheroids, zebrafish embryo, thrombi and single cells over prolonged periods of time. The microscope is fully equipped with temperature and humidity control. The webinar is hosted by Hella, who gives fantastic support to the facility and users of the Marianas Light Sheet.

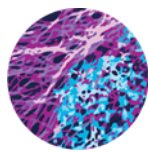
Marianas LightSheet™ merges the low phototoxicity and large specimen handling of dual inverted selective plane illumination (diSPIM) with the power and flexibility of a live-cell microscope system. diSPIM technology enables rapid 3D imaging of samples with isotropic resolution ranging from single cells to small organisms over the course of hours to days. Unlike capillary-based light sheet methods, diSPIM allows for standard specimen preparation in standard dishes in standard media. Combined with spinning disk confocal, TIRF, and photomanipulation, Marianas LightSheet is a powerful live-cell imaging workstation. SlideBook™ hardware and software integration seamlessly manages acquisition, alignment, deconvolution and rendering. Join this webinar to learn more about how Marianas LightSheet can be used in your experiments! For more information on the Marianas LightSheet, visit <https://www.intelligent-imaging.com/marianas-lightsheet>.

Link to register: <https://www.intelligent-imaging.com/webinars>

If you have any questions about the system following the webinar please contact Dee (D.M.Kavanagh@bham.ac.uk)

### IN PARTNERSHIP:

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## Research Focus—Cemre Tuzer



**TITLE:** Design, Synthesis and Development of Novel Fluorescently-Labelled Allosteric Probes for the Human  $\beta$ 2-Adrenoceptor

It is well-known that the success rate of traditional G protein-coupled receptors (GPCR)-based drug discovery is in decline related to difficulty in selectively targeting orthosteric binding site at receptors that display high sequence homology between subtypes. In last decade, small molecules that target topographically distinct allosteric sites on GPCRs have shown a great success and these drugs offer enormous potential in terms of achieving higher selectivity, fewer side effects and lower toxicity. Allosterism in drug discovery has therefore emerged as a promising strategy to develop efficient and safe therapeutics.

$\beta$  adrenergic receptors are G protein-coupled receptors with two well-known subtypes  $\beta$ 1AR and  $\beta$ 2AR. Drugs inhibiting  $\beta$ 1AR and  $\beta$ 2AR are known as beta-blockers which are extensively used for post-myocardial infarction (MI), heart failure, unstable angina arrhythmias, hypertension, and other cardiovascular diseases whereas  $\beta$ 2AR agonists are mainstays of asthma therapy. However, current beta blockers have poor selectivity for  $\beta$ 1AR over  $\beta$ 2AR and they are contraindicated for patients suffering from heart diseases together with asthma because of undesired  $\beta$ 2AR inhibition which is resulting in life-threatening bronchospasms. Thus, the major therapeutic aim of  $\beta$ -adrenoceptor blockage by antagonism of endogenous catecholamines acting at  $\beta$ 1AR in order to reduce cardiac workload has remained unmet. Hence, attaining selectivity via targeting allosteric binding pocket in  $\beta$ -adrenoceptor subtypes, can met this clinical need and can provide a safe profile of  $\beta$ -blockers. For this purpose, so far only one ligand, named as Cmpd-15 has been reported as a negative allosteric modulator of  $\beta$ 2AR.

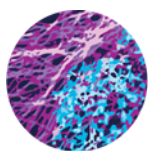
Our interest in allosteric modulation targeting beta adrenoceptors in terms of high selectivity for  $\beta$ 1AR over  $\beta$ 2AR, forms a promising basis for this project. Major aim of this study is generation of allosteric ligands which seek to determine and modify novel intracellular ligands for both  $\beta$ 1 and  $\beta$ 2 adrenoceptors. To investigate the topic of interest, we have synthesized Cmpd-15 and its fluorescent versions and conducted robust binding assays by using Bioluminescence resonance energy transfer (BRET) technology in order to investigate allosteric character of the ligands. Although N terminal-tagged receptors of interest have been studied before together with orthosteric fluorescent compounds, C terminal probes have not been investigated yet for the determination of allosteric modulation. Hence, we employed an intracellular sensor design using the BRET technique. The results revealed that Cmpd-15 has minimal negative allosteric modulation on the binding affinity of orthosteric agonists. However, intracellular BRET assay indicated the direct binding of the allosteric modulator to the intracellular site of the receptor, although the length of the linker between pharmacophore and the fluorophore, the low binding affinity/high lipophilicity of fluorescent Cmpd-15, and potential for Bystander BRET means that further studies are required to confirm the true nature of this interaction. More binding and functional assays will be conducted to fully characterize the allosteric nature of Cmpd-15 before moving on designing novel allosteric modulator by optimizing Cmpd-15 which can help to overcome selectivity problems in beta-blockers.

Email: cemre.tuzer@nottingham.ac.uk

## Congratulations

Congratulations to the following members of COMPARE at the University of Birmingham, **Iain Styles**, Deputy Director of COMPARE, has been promoted to Professor of Computer Sciences, **Dr Neil Morgan** has been promoted to Reader, **Dr Larissa Fabritz** to Professor and **Dr Davor Pavlovic** to Senior Lecturer.

Dr Rob Lane and Prof Meri Canals, University of Nottingham have been awarded a BBSRC grant, project title: *New tools for acute spatiotemporal control of GPCR signalling in vivo*.



# COMPARE

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## Team Science Grant Wording

Following discussions on Research Culture at the COMPARE Management Board it was agreed to develop a standard set of wording for PIs to add to independent grant applications in support of Team Science, allocating a small budget from grants to support team science activities.

### Team Science Justification of Resources

#### Guidance:

Standard level of contribution suggested £300 per ECR per year for a range of Team Sciences activities including an annual symposium and training courses.

Justification should be linked to career development / building a research culture.

Most grants give money for conferences etc. and so we need to make a strong case to have this additional funding.

#### Past events have included:

- An ECR symposium and away day.
- A communications workshop, which provided interactive training on how to disseminate research findings to a wider audience.
- Participation in a cross-institutional seminar speaker programme, giving ECRs the opportunity to present their work at the partner university.
- Collaborative cross-site grants and contribution towards conference attendance for ECRs to engage in discussions relating to cutting-edge research activities.

See website for more details:

<http://www.birmingham-nottingham.ac.uk/compare/team-science.aspx>

*Please note this text should be used as a guidance, tailored to your specific applications and adhere to all funder rules and requirements:*

The PI/Col [delete as appropriate] is a member of the Centre of Membrane Proteins and Receptors (COMPARE). This signature institute has developed a 'Team Science' ethos to tackling important biomedical research questions. Within this positive research culture, COMPARE has established key approaches, including training, team building and network events to support and develop novel career paths for our early career scientists and those outside the traditional 'PI track'. We would like to request £XXX to support these personal and career development opportunities for the colleagues included in this application [provide details e.g. one x postdoc and a technician].

## Publications

Fang Z, Chen S, Pickford P, Broichhagen J, Hodson DJ, Corrêa IR Jr, Kumar S, Görlitz F, Dunsby C, French PMW, Rutter GA, Tan T, Bloom SR, Tomas A, Jones B, (2020). The Influence of Peptide Context on Signaling and Trafficking of Glucagon-like Peptide-1 Receptor Biased Agonists. ACS Pharmacol Transl Sci. 3:345-360. doi: 10.1021/acsptsci.0c00022.

Siddig S, Aufmkolk S, Doose S, Jobin ML, Werner C, Sauer M, Calebiro D, (2020). Super-resolution imaging reveals the nanoscale organization of metabotropic glutamate receptors at presynaptic active zones. Science Advances. DOI: 10.1126/sciadv.aay7193

Chauhan A, Sheriff L, Hussain MT, Webb GJ, Patten DA, Shepherd EL, Shaw R, Weston CJ, Halder D, Bourke S, Bhandari R, Watson S, Adams DH, Watson SP, Lalor PF, (2020). The platelet receptor CLEC-2 blocks neutrophil mediated hepatic recovery in acetaminophen induced acute liver failure. Nat Commun. 11 : 1939. doi: 10.1038/s41467-020-15584-3

Pike JA, Simms VA, Smith CW, Morgan NV, Khan AO, Poulter NS, Styles IB, Thomas SG, (2020). An adaptable analysis workflow for characterization of platelet spreading and morphology. Platelets. 1-5. doi: 10.1080/09537104.2020.1748588. [Epub ahead of print]

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