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Towards a molecular understanding of PSGR activation

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► **To cite this version:**

Gwenaëlle André-Leroux, Adrien Acquistapace, Jean-Francois Gibrat, Guenhaël Sanz. Towards a molecular understanding of PSGR activation. 3. Annual Meeting of the CNRS GDR-3545 G Protein-coupled Receptors: from Physiology to Drugs (RCPG-Physio-Med), Oct 2014, Montpellier, France. pp.1-9, 2014. hal-02792285

HAL Id: hal-02792285

<https://hal.inrae.fr/hal-02792285v1>

Submitted on 5 Jun 2020

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Editorial

By RALF JOCKERS, director of GDR 3545 CNRS « RCPG-Physio-Med »



Dear GDR members,

Here we are for the 5th edition of the NEWSLETTER of our GDR with all the essential information on G protein-coupled receptors gathered by our fantastic editorial team composed of Julie,

Véronique, Angélique and Florence.

I am happy to announce that we recently established a partnership with the British Society of Pharmacology that will be expanded soon by exchanging young scientist speaking at our corresponding annual congresses. I am also happy to announce the 3rd edition of the joint Hybrigenics-GDR-3545 call for a free Two-Hybrid Screen, exclusively reserved to GDR members (please check our web site).

I am very much looking forward to see you all soon at our annual meeting in Montpellier, a privileged moment to talk about science with our academic and industrial partners. We have once again more than 200 participants and over 80 posters, which is an exceptional score!

Ralf

Newsletter... number 5!

This is the fifth issue of the GDR 3545 Newsletter. This will provide you the last information of the GDR before the third annual meeting in Montpellier from October 20th to 22nd 2014 and the 2nd workshop, October 22nd-23rd. We would like to take this opportunity to remind you the establishment of tool databases that would be beneficial for all GDR community. Do not hesitate to contact the indicated persons for your contribution.

For this issue, we have decided to interview a young scientist, Guillaume Lebon, in the "A minute with...".

We would also like to remind you that we are willing to take into account any comment or suggestion regarding the newsletter sections, to accept contributions from everybody and to hear any criticisms you might have to improve the quality of the newsletter. Furthermore, anyone from each of the participating teams of the GDR is more than welcome to contribute by using the address newsletter@gdr3545.com.

Florence, Angélique, Véronique et Julie

A minute with...

Guillaume Lebon,

CNRS Researcher (CR2) – ATIP-AVENIR team leader. He is the group leader of the "Structural biology of G protein coupled receptors: a focus on class C" team in the "Institut de Génomique Fonctionnelle" (IGF) at Montpellier. After a postdoctoral experience in UK where he solved the structure of A2A receptor by X ray-crystallography, he has established his own group thanks to the ATIP-AVENIR CNRS and INSERM program with the aim to determine high-resolution structure of G protein-coupled receptors (GPCRs) bound to their ligands and to their signaling complexes.



<http://www.igf.cnrs.fr/en/research/transverse-axis/gpcr-signaling>

What are your research interests?

My research interest is focused on understanding the structure-function relationship of the large family of highly medically relevant membrane proteins: the G Protein-Coupled Receptors. GPCRs are fascinating cellular machinery that receive a message and transmit this signal to the intracellular compartment of the cell, to finally activate intracellular signaling machineries, such as the trimeric G protein or arrestin. In the lab, we combine molecular pharmacology and biophysical techniques such as X-ray crystallography to decipher at the molecular level how the ligands bind to the receptor and induce conformational changes to activate the intracellular G protein. Finally, GPCRs are important and validated drug target and I like to think that the results of our academic research may help to develop or discover new medicine related to GPCRs.

What is your background?

I completed a Phd in biochemistry and Molecular biology in Nantes University, with Professor Vehary Sakanyan (2003-2006), working on the characterisation of RNA polymerase subunit for the conception of transcription inhibitor. In december 2006, I joined the Lab of Dr Ed Hulme, NIMR London, UK, in collaboration with GSK. There, I learned molecular pharmacology techniques for studying G protein-coupled receptors. In december 2007, I moved to the Laboratory of Molecular Biology (LMB), Cambridge, to join Chris Tate and Richard Henderson for a second post-doctoral experience in collaboration with Heptares Therapeutic. During this work, I learned protein crystallisation and X-ray structure determination and solved the 3D structure of the A2A receptor-bound to its

natural agonist adenosine. In September 2011, I joined the lab of J.P. Pin and L. Prézeau to start a program on structural studies of class C GPCRs and I was awarded of an ATIP-AVENIR Grant.

Who has initiated you to GPCRs' world?

Dr Ed Hulme, who is an expert of M1 muscarinic receptor. During my first post-doctoral position with Ed, we identified the binding site for the selective agonists of muscarinic M1 receptor and described their binding mode. This was for me the starting point of a fascinating research adventure to understand the ligand binding mode and activation mechanism of G protein-coupled receptor.

You have been doing your postdocs in UK, can you tell us about that period? What are the similarities and differences between British and French systems?

I had the chance to work for two high-standard units of Medical research Council in UK, the MRC-National Institute for Medical Research in London and the MRC-Laboratory of Molecular Biology in Cambridge. In France, I worked for the university during my PhD and the CNRS since I joined the IGF in Montpellier. They all have advantages. It is difficult to compare the two systems in a few lines but the most striking difference is probably the time dedicated to administrative work in France. In UK, at the MRC, I had only science to focus on.

What is the composition of your group?

We are 5 at the moment, 1 Inserm researcher, Gaetan Bellot, 2 post-doctoral scientists, Chady Nasrallah and Harshesh Bhatt, 1 research assistant (ingénieur d'étude) Karine Rottier and myself.

What were the challenges and difficulties that you encountered to establish your group?

The first challenge is of course to be successful with grant application, and we all know the science funding situation at the moment, which makes it not that easy. It is then important to keep doing experimental work whilst establishing the lab, hiring and integrating new young scientists to the group. All this requires lots of time and energy. Finally, to be fully established as a scientific group the challenge is to publish the results of your research activities and to stay active in your scientific community.

Was there a specific person in your experience that gave you advices to build your scientific career?

We can probably call them mentors. I mean by mentor, people who give you advices in order for you to successfully build your scientific career. Scientific career is difficult; the experience of a mentor is highly valuable. I had the chance to cross the road of absolutely excellent scientists but also very good mentor, Ed Hulme when I was in London, Chris Tate and Richard Henderson when I was in Cambridge.

Tell us about the ATIP-AVENIR program, what does it implies? Can you tell us about your own experience in applying to this program?

The program ATIP-AVENIR gives the opportunity to young scientists to create and lead a team within an established laboratory in France and this is under a partnership between INSERM and CNRS. In my case, when I joined the IGF in September 2011, I applied to the

ATIP-AVENIR call, my application was accepted and I was invited for an interview. I defended my proposal in front of a panel of international experts and it was actually a very challenging and scientifically stimulating interview. In July 2012, I got the final and positive answer from the ATIP-AVENIR program. I started the lab in January 2013 by receiving the first part of the funding money allocated to ATIP-AVENIR laureate. This program represents the first step to establish, independently, your own research program but also gives a reference to apply for other grants.

You are one of the few persons who have solved the structure of a GPCR, what kind of future to you envision of structural biology in this field?

More and more high-resolution structures of course!, high-resolution structure of receptors but also of signalling complexes. We also need to have a more dynamic view of this highly flexible membrane protein receptor family. Again, I really hope that all this structural information will also help to design and discover new therapeutic molecules.

Your post doctoral period is not so far, which advises or hopes could you give to a PhD student or post doctoral fellow?

As you said I was still a post-doc a few years ago, so I'm not sure if I am the best person to give advice to post-docs and PhD students. A scientific career is long and difficult and it is important for sure to be passionate and to be ready to spend lots of time in the lab.

And to finish, some short questions:

Beer or wine? Well, both!

Fish'n chips or tielle à la sétoise ? Fish'n chips with mushy peas

Rugby or football? Rowing. Rugby only on TV

See or Mountain? both

GDR information

Annual meeting 2014

The 3rd annual meeting of the CNRS GDR-3545 G Protein-coupled Receptors: from Physiology to Drugs (RCPG-Physio-Med) will be held in **Montpellier** at the Corum from **October 20th to 22nd 2014**.



Workshop 2014

A workshop will be held in **Montpellier, October 22nd-23th 2014 following the annual meeting**. Like last year, this workshop is aimed to inform GDR members on techniques available within the network.

Tool databases to be found on your "Member space"

As previously mentioned, a part of the GDR website is a private space open only to GDR members. This space is dedicated to upload validated tools and protocols to establish databases on viral vectors, antibodies, transgenic mouse lines and GPCR structures and ligands. A temporary password has been sent by administrationweb@gdr3545.com. Be aware that only the webmaster can create a new account. Newcomers and departure must be informed using the address newsletter@gdr3545.com. This will help us both to create and maintain the members account and to keep our member list and email address.

After login to the member's space, you can consult and complete the GPCRs, antibodies and mice lines databases. The persons responsible for the different tool lists are:
Transgenic mouse lines: Dominique Massotte
GPCR amino acid sequences with TM, ICL and ECL annotations: Didier Rognan
Antibodies against GPCRs, ligands and signaling proteins: Véronique Gigoux

Recruitment

Mohammed Akli Ayoub has been recruited in the group "**Biologie et Bioinformatique des Systèmes de Signalisation**" of the "Physiologie de la Reproduction et des Comportements" laboratory at **INRA Val de Loire center**, as part of the ARD2020 "Biomédicaments" project sponsored by Région Centre. Mohammed Akli Ayoub is the recipient of **LE STUDIUM® RESEARCH FELLOWSHIP – SMART LOIRE VALLEY** and is **the laureate of the international mobility program Agreenskills +**.

See more information at <http://www.val-de-loire.inra.fr/Toutes-les-actualites/Agreenskills-Inra-Val-de-Loire-un-chercheur-laureat>

Marion Espéli has been recruited in the group "**Chemokine SDF-1/CXCL12 and its receptors** » lead by Karl Balabanian at INSERM U996 Clamart. Marion is the laureate of the "Junior Team Leader starting package" awarded by the LabEx Lermite.

<http://www.labex-lermit.fr/fr/component/content/article/30-presentation-appels-a-projets/77-laureat-junior-team-2013>

New group

A new group named **DRuGS "Déficit de Récompense, GPCR et Sociabilité"** lead by **Jérôme Becker and Julie Le Merrer** has been created in the "Physiologie de la Reproduction et des Comportements" laboratory of the INRA Val de Loire Center.

PhD defenses

Amandine Dupuis has defended her PhD thesis prepared under the direction of Christine Rausch at the University of Auvergne on September 19th 2014 and entitled "**Le récepteur de la sérotonine 5-HT2A: une nouvelle cible**

thérapeutique pour le traitement de la douleur neuropathique. Approche physiopathologique et pharmacologique chez le rat neuropathique". Read the summary here :

<http://www.gdr3545.com/index.php/news/theses-abstracts/116-the-serotonin-receptor-5-ht2a-a-new-target-to-manage-neuropathic-pain-pathophysiological-and-pharmacological-approaches-in-neuropathic-rat>

Ivan Gushchin has defended his PhD thesis prepared under the direction of Valentin Gordeliy at the University of Grenoble on September 5th 2014 and entitled: "**Structural studies of microbial rhodopsins and other membrane proteins by means of X-ray crystallography and computer modeling**". Read the summary here :

<http://www.gdr3545.com/index.php/news/theses-abstracts/115-etudes-structurales-des-rhodopsines-microbiennes-et-des-autres-proteines-membranaires-au-moyen-de-la-cristallographie-aux-rayons-x-et-de-la-modelisation-informatique>

Alexandre Bignon has defended his PhD thesis prepared under the direction of Karl Balabanian at the University Paris Sud on September 30th 2014 and entitled: "**Dérégulation des récepteurs de chimiokine CCR1 et CXCR4 dans le lupus érythémateux disséminé et la lymphopénie T CD4+ idiopathique**". Read the summary here :

<http://www.gdr3545.com/index.php/news/theses-abstracts/114-deregulation-des-recepteurs-de-chimiokine-ccr1-et-cxcr4-dans-le-lupus-erythemateux-dissemine-et-la-lymphopenie-t-cd4-idiopathique>

Press review

A 'switchable' molecule to specifically detect G protein-coupled receptors; D Bonnet and AS Klymchenko. Researchers from the 'Laboratoire d'innovation thérapeutique' (CNRS / Université de Strasbourg) and the 'Laboratoire de biophotonique et pharmacologie' (CNRS / Université de Strasbourg) have set up an innovative method using fluorescent to visualize and quantify G protein-coupled receptors at the cell surface and more particularly the oxytocin receptor. This work has been published in ChemBioChem. See also En direct des laboratoires de l'institut de Chimie, 2014: http://www.cnrs.fr/inc/communication/direct_labos.htm.

A subtle relationship between cell proliferation and G protein-coupled receptors. Sandra Lecat and her co-workers from the 'laboratoire biotechnologie et signalisation cellulaire' (CNRS / Université de Strasbourg) showed that GPCRs are involved in regulating the activation of the mTORC1 complex, a central regulator of cell proliferation, by a new mechanism based on a modification of the intracellular localization of REDD1. This work has been published in Journal of Cell Science. See also En direct des laboratoires de l'institut de des Sciences Biologiques, 2014:

<http://www.cnrs.fr/insb/recherche/parutions/articles2014/s-lecat.html>.

Fernando Arenzana-Seisdedos leader of the Viral Pathogenesis Unit at Pasteur institute (Inserm U1108) was awarded the **George Jacques and Elias Canetti prize 2014** for his research on AIDS.

<http://www.pasteur.fr/fr/institut-pasteur/presse/documents-presse/pierre-arditi-remet-fernando-arenzana-l-institut-pasteur-le-prix-georges-jacques-et-elias-canetti-2014-pour-ses-recherches-sur-le-sida>

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Job offers

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(<http://gdr3545.com/index.php/news/job-offers>).

To add your job offer, contact Ralf Jockers (ralf.jockers@inserm.fr)

Local contacts

Important information? New publications? Recruitment of new persons? ... Local contacts are here to gather your communications.

Clamart campus: Christelle Freitas (christelle.freitas@u-psud.fr); **Clermont-Ferrand** campus: Jérôme Busserolles (jerome.busserolles@udamail.fr); **Grenoble** campus: Christophe Moreau (christophe.moreau@ibs.fr); **Illkirch ESBS** campus: Sandra Lecat (lecat@unistra.fr); **Montpellier** campus: Julie Kniazeff (julie.kniazeff@igf.cnrs.fr); **Paris** campus: Angélique Levoye (Angelique.levoye@inserm.fr) et Florence Gbahou (florence.gbahou@inserm.fr); **Paris Sud** campus: Jean-Philippe Guilloux (jean-philippe.guilloux@u-psud.fr); **Toulouse** campus: Véronique Gigoux (veronique.gigoux@inserm.fr) et Lionel Mouldéous (lionel.mouldéous@ipbs.fr); **Tours** campus: Nathalie Langonne (Nathalie.Langonne@tours.inra.fr); **Lyon** campus: Anass Jawhari (ajawhari@calixar.com)
We are still looking for some volunteers for the unrepresented campus (Lille, Illkirch Pharma...).

Industrial partners corner



HYBRIGENICS SERVICES, an industrial partner of the GDR-3545, has the pleasure to offer 1 full yeast two-hybrid screen per year (10 000€) to GDR members. Submission deadline for the next call is 8th December 2014. More information on selection process and time table at:

<http://www.gdr3545.com/index.php/news/partners-announcements/108-call-for-yeast-two-hybrid-screen-2014>



"Illuminations: A Cell Notes Publication", provides the latest more powerful and sensitive bioluminescent kits for cellular analysis: cell signaling, metabolism, kinase profiling, ... and drugs development. To get your "Illuminations" copy and read

an article about the new GloSensor technology, please follow this link :

<http://www.gdr3545.com/index.php/news/partners-announcements/111-illuminations-a-cell-notes-publication>



interchim presents the **Methoxy e-Coelenterazine** a substrate for Renilla luciferase (Rluc) with 13-fold higher luminescence than Coelenterazine 400a for **Luminescent Detection**. Interested in this product? More information on it and others popular coelenterazines here :

<http://www.gdr3545.com/index.php/news/partners-announcements/109-methoxy-e-coelenterazine-luminescent-detection-by-interchim>



Tecan's washers and plate readers offer the perfect combination to yield a high cell number during assay preparation and to maintain a perfect environment for long-term experiments.

For more information go to:

<http://www.gdr3545.com/index.php/news/partners-announcements/112-worried-about-consistent-results-from-your-cell-assay>



CALIXAR, company specialized in the native isolation of integral membrane protein targets, announced today the issue of a new generation of compounds able to extract and stabilize complex pharmaceutical targets.

For more information :

<http://www.gdr3545.com/index.php/news/partners-announcements/107-calixar-to-extend-its-portfolio-of-strategic-compounds-for-complex-pharmaceutical-target-isolation> and visit www.calixar.com or contact Dr Martine MOULY, Chief Communication Officer, mmouly@calixar.com



PerkinElmer presents EnSight™ his new multimodal microplate reader. In addition to the conventional technologies (Absorbance, Fluorescence, Luminescence, Alpha, TRF / TR-FRET) this modular and scalable microplate reader can be equipped with the Label-free and a cellular imaging system. To discover more about this new reader, follow this link : <http://www.gdr3545.com/index.php/news/partners-announcements/110-ensighttm-nouveau-lecteur-de-microplaques-multimodal-perkinelmer>

What's up in GPCR world ?

The article of the month

« Separation of on-target efficacy from adverse effects through rational design of a bitopic adenosine receptor agonist ».

Celine Valant, Lauren T May, Luigi Aurelio, Chung Hui Chuo, Paul J White, Jo-Anne Baltos, Patrick M. Sexton, Peter J. Scammells, and Arthur Christopoulos
Proc. Nat. Acad. Sci. USA 111, 4614-19 (2014)

In this article, the authors aimed at rationally design a novel ligand targeting the Adenosine 1 receptor (A1AR) with improved pharmacology to potentially opening new avenues for cardioprotection treatment. While classical orthosteric agonists of A1AR have limited beneficial effect for this application because they also induce major adverse effects like bradycardia, the rationally designed compound is aimed at promoting the known therapeutic effect of A1AR agonists, and simultaneously at silencing the adverse effects. To achieve that goal, the authors take advantage of the high dynamics of G protein-coupled receptors (GPCRs). Indeed, these proteins are fluctuating between different conformations, which are promoting a specific cellular response. When interacting with the receptor, ligands stabilize one of the receptor conformations which in turn model the cellular response. This phenomenon is often referred to as biased agonism. Although none of the orthosteric ligands of A1AR have been reported to be biased, the allosteric modulator VCP171 promotes bias in the prototypical R-PIA orthosteric agonist signaling. On this basis, the authors designed a so called bitopic ligand containing both the orthosteric moiety, adenosine, to confer high efficacy and the allosteric moiety, VCP171, to induce bias signaling, the two moieties being fused by linkers of different size. These ligands are thought to bind both to the orthosteric and allosteric sites of A1AR and to have a combined pharmacological profile as seen in Figure 1. If such ligand binds both to the orthosteric and allosteric binding sites, it would in turn display both competitive and non-competitive antagonism relative to the concentration of orthosteric ligand used.

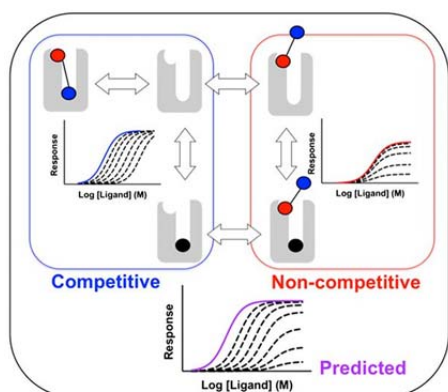


Figure 1: Theoretical behavior of a bitopic agonist. The black circle denotes the orthosteric antagonist (e.g. DPCPX), the blue circle denotes the orthosteric agonist and the red circle denotes the allosteric pharmacophore. The scheme on the left represents expectations for a simple competitive interaction, whereas the scheme on the right represents negative allosteric modulation by orthosteric antagonists of allosteric signaling efficacy.

The authors processed in analyzing the pharmacological and signaling properties of these ligands. First, all bitopic ligands were found to displace [3H]-DPCPX orthosteric antagonist in a binding assay with the compound VCP746 showing the highest affinity ($K_i \sim 60$ nM – about 100-fold higher than adenosine itself). In [35S]-GTP γ S binding assay, all the whole series of ligands was found to be full agonists but with different potencies. In this assay, VCP746 was also the more potent.

In a second step, the authors validated the bitopic binding of VCP746 by analyzing its functional interaction with DPCPX in an ERK1/2 phosphorylation assay. By comparing the experimental data obtained with those predicted by the theoretical model, VCP746 was confirmed to interact with A1AR in bitopic manner.

In addition of synthesizing a bitopic ligand, this study aims at identifying a biased agonist. Accordingly, modulation of forskolin-induced cAMP accumulation was measured for both classical and bitopic agonists and compared to ERK1/2 signaling. The first assay was chosen because it represents the canonical A1AR-Gi/o-adenylyl cyclase pathway while the later constitutes a downstream convergent pathway activated both in a G protein-dependent and -independent manner. Compared to prototypical orthosteric agonists, VCP746 showed a preferential coupling to cAMP pathway (about 30-fold preference).

At last, the authors tested the physiological relevance of VCP746. By using rat embryonic cardiomyoblasts (H9c2(2-1)) under ischemic conditions, VCP746 was more efficient in reducing cell death than other A1AR agonists (e.g. CPA). The effect of VCP746 was also assessed on rat atrial rate. Compared to orthosteric agonists, who dramatically reduced heart rate at high concentration, VCP746 did not have substantial effect even at concentration that showed maximal cardioprotective effect (Figure 2). Altogether, these data indicate that the bitopic VCP746 is a biased agonist of A1AR therapeutically relevant.

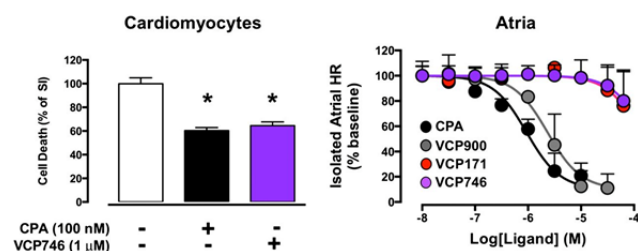


Figure 2: Left. Effects of the indicated compounds on cell death under ischemic conditions in native A1AR expressing rat neonatal ventricular cardiomyocytes. Right. Effects of the indicated compounds in rat atrial heart rate (HR).

This study shows that the rational design of bitopic ligand at GPCR may constitute an interesting alternative to classical agonists or allosteric modulator to promote biased agonism and decrease adverse effects linked with more classical ligands.



Very Important Publications

- Tang W, Strachan RT, Lefkowitz RJ, Rockman HA** (2014) Allosteric Modulation of β -Arrestin-Biased AT1R Signaling by Membrane Stretch. *J Biol Chem.* (in press)
- Bai B, Cai X, Jiang Y, Karteris E, Chen J** (2014) Heterodimerization of apelin receptor and neurotensin receptor 1 induces phosphorylation of ERK1/2 and cell proliferation via G α -mediated mechanism. *J Cell Mol Med.* (in press)
- Abrol R1, Trzaskowski B2, Goddard WA 3rd1, Nesterov A3, Olave I3, Irons C3** (2014) Ligand- and mutation-induced conformational selection in the CCR5 chemokine G protein-coupled receptor. *Proc Natl Acad Sci U S A.* 111(36):13040-5.
- Lane JR, Donthamsetti P, Shonberg J, Draper-Joyce CJ, Dentry S, Michino M, Shi L, López L, Scammells PJ, Capuano B, Sexton PM, Javitch JA, Christopoulos A** (2014) A new mechanism of allostery in a G protein-coupled receptor dimer. *Nat Chem Biol.* 10(9):745-52.
- Kendall RT, Lee MH, Pleasant DL, Robinson K, Kuppuswamy D, McDermott PJ, Luttrell LM** (2014) Arrestin-Dependent Angiotensin AT1 Receptor Signaling Regulates Akt and mTor-Mediated Protein Synthesis. *J Biol Chem.* 289(38):26155-66.
- Mohammad S, Patel RT, Bruno J, Panhwar MS, Wen J, McGraw TE** (2014) A naturally occurring GIP receptor variant undergoes enhanced agonist-induced desensitization, which impairs GIP control of adipose insulin sensitivity. *Mol Cell Biol.* 34(19):3618-29.
- Rose AS, Elgeti M, Zachariae U, Grubmüller H, Hofmann KP, Scheerer P, Hildebrand PW** (2014) Position of transmembrane helix 6 determines receptor g protein coupling specificity. *J Am Chem Soc.* 136(32):11244-7.
- Rodríguez D, Brea J, Loza MI, Carlsson J** (2014) Structure-Based Discovery of Selective Serotonin 5-HT1B Receptor Ligands. *Structure.* 22(8):1140-51.
- Shukla AK, Westfield GH, Xiao K, Reis RI, Huang LY, Tripathi-Shukla P, Qian J, Li S, Blanc A, Oleskie AN, Dosey AM, Su M, Liang CR, Gu LL, Shan JM, Chen X, Hanna R, Choi M, Yao XJ, Klink BU, Kahsai AW, Sidhu SS, Koide S, Penczek PA, Kossiakoff AA, Woods VL Jr, Kobilka BK, Skiniotis G, Lefkowitz RJ** (2014) Visualization of arrestin recruitment by a G-protein-coupled receptor. *Nature* 512(7513):218-22.
- Doré AS, Okrasa K, Patel JC, Serrano-Vega M, Bennett K, Cooke RM, Errey JC, Jazayeri A, Khan S, Tehan B, Weir M, Wiggin GR, Marshall FH** (2014) Structure of class C GPCR metabotropic glutamate receptor 5 transmembrane domain. *Nature* 511(7511):557-62. doi: 10.1038/nature13396. Epub 2014 Jul 6.
- Weichert D, Kruse AC, Manglik A, Hiller C, Zhang C, Hübner H, Kobilka BK, Gmeiner P** (2014) Covalent agonists for studying G protein-coupled receptor activation. *Proc Natl Acad Sci U S A.* 111(29):10744-8.
- Oh da Y, Walenta E, Akiyama TE, Lagakos WS, Lackey D, Pessentheiner AR, Sasik R, Hah N, Chi TJ, Cox JM, Powels MA, Di Salvo J, Sinz C, Watkins SM, Armando AM, Chung H, Evans RM, Quehenberger O, McNelis J,**

Bogner-Strauss JG, Olefsky JM (2014) A Gpr120-selective agonist improves insulin resistance and chronic inflammation in obese mice. *Nat Med.* 20(8):942-7

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Spyridaki K, Matsoukas MT, Cordini A, Gkoutelias K, Papadokostaki M, Mavromoustakos T, Logothetis DE, Margioris AN, Pardo L, Liapakis G (2014) Structural-Functional Analysis of the Third Transmembrane Domain of the Corticotropin-releasing Factor Type 1 Receptor: ROLE IN ACTIVATION AND ALLOSTERIC ANTAGONISM. *J Biol Chem.* 289(27):18966-77.

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Antonio LS, Stewart AP, Varanda WA, Edwardson JM (2014) Identification of P2X2/P2X4/P2X6 heterotrimeric receptors using atomic force microscopy (AFM) imaging. *FEBS Lett.* 588(12):2125-8.

Zhang J, Zhang K, Gao ZG, Paoletta S, Zhang D, Han GW, Li T, Ma L, Zhang W, Müller CE, Yang H, Jiang H, Cherezov V, Katritch V, Jacobson KA, Stevens RC, Wu B, Zhao Q (2014) Agonist-bound structure of the human P2Y12 receptor. *Nature.* 2014 509(7498):119-22.

Reviews:

Vilardaga JP1, Jean-Alphonse FG1, Gardella TJ2 (2014) Endosomal generation of cAMP in GPCR signaling. *Nat Chem Biol.* 10(9):700-6.

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Kusumi A1, Tsunoyama TA1, Hirose KM2, Kasai RS1, Fujiwara TK2. (2014) Tracking single molecules at work in living cells. *Nat Chem Biol.* 10(7):524-32.

Gonzalez A1, Cordini A, Matsoukas M, Zachmann J, Pardo L (2014) Modeling of G protein-coupled receptors using crystal structures: from monomers to signaling complexes. *Adv Exp Med Biol.* 796:15-33.

Book:

Current Opinion in Cell Biology, 2014, Vol 27 : special issue on GPCR (dimerization, signaling, endosome, arrestin, biased ligands, ubiquitination, trafficking..)

Conferences

GTBio2014 will be held from October 7th to 10th 2014 in Grenoble, France.

This meeting is organized by the 'Institut de Biologie Structurale' together with ESRF and the French Crystallography Association.

<http://gtbio2014.ibs.fr>

A symposium on "Biomembranes and membrane proteins" will be held from November 14th in Grenoble, France.

This symposium aims at sharing information regarding scientific projects, methods and instruments developed for membrane proteins and membranes.

PSBWorkshop2014@ibs.fr

Molecular Pharmacology (GRS). Gordon Research Seminar. New Frontiers in GPCR Signaling: From Biased Agonism to Disease Progression. January 31 - February 1, 2015 Ventura Beach Marriott, Ventura, CA

Chair: [Neil J. Grimsey](#)

Associate Chair: [Stephanie S. Dusaban](#)



3rd Annual Conference of the International Chemical Biology Society. Driving Biology with Chemistry

San-Francisco, November 17-19 2014

<http://www.chemical-biology.org>

11^{ème} Symposium national du Réseau INSERM de recherche sur la Douleur à Strasbourg – March 2015.

More details soon



12th Conference of the French Neuroscience Society – Montpellier – May 19-22 2015

<http://www.neurosciences.asso.fr/V2/colloques/SN15/>