CaSR Biomedicine Training Network

Marie Curie Actions European Training Network

NEWSLETTER ISSUE NO. 2

IN THIS ISSUE:

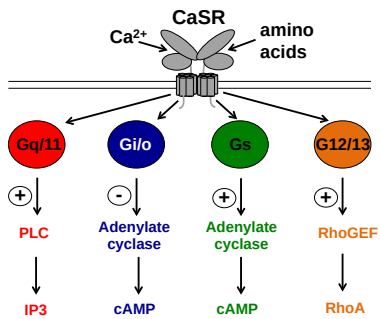
This issue focuses on the role of the CaSR in signal transduction

Introduction to the newsletter

Welcome to the 2nd issue of the Calcium-Sensing Receptor (CaSR) Biomedicine newsletter. We focus on academic beneficiaries from the CaSR Biomedicine European Training Network (ETN) Consortium who are investigating the role of the CaSR in intracellular signal transduction.

The CaSR and signal transduction

- The CaSR is a widely expressed cell-surface G-protein coupled receptor (GPCR) that transduces extracellular metabolic stimuli (e.g. Ca^{2+} and amino acids) through distinct intracellular pathways in a process known as ligand-biased signalling.
- The CaSR is a therapeutic target for major diseases such as asthma, diabetes, Alzheimer's disease and cancer.



Overview of CaSR mediated signal transduction

- Appropriate drug design requires an understanding of ligand- and tissue-specific CaSR-mediated signalling to maximize therapeutic efficacy and minimize off-target drug effects.

Aims of the CaSR-mediated signalling workpackage

The aims of the groups from the CaSR-mediated signalling workpackage are to identify major CaSR-mediated signalling routes and effector molecules, with the goal of establishing a comprehensive understanding of CaSR-dependent physiology. This workpackage is also elucidating the molecular mechanisms of biased signalling and conditional efficacy to aid to the development of next generation CaSR therapeutics.

Profiles of academic beneficiaries in workpackage 1

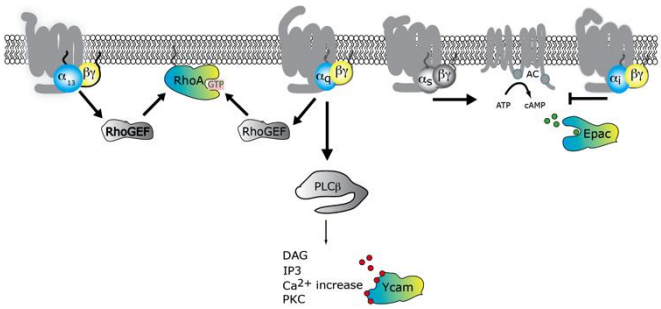
Vrije Universiteit Amsterdam; PI: Prof Frank Bruggeman

CONTACT DETAILS of PI:
Prof Dr Frank J Bruggeman
University Research Chair in Interdisciplinary Life Sciences, Systems Bioinformatics Section, Amsterdam Institute for Molecules, Medicine and Systems, VU University, Amsterdam, The Netherlands;
E-Mail: f.j.bruggeman@vu.nl

Research at the Bruggeman Lab:
We study the molecular networks inside cells that give rise to cell behaviour. We focus on the principles and general understanding of how those networks adapt in response to environmental and genetic changes. We combine mathematical modelling, theory, and experiments.

CONTACT DETAILS of CO-PI:
Dr Joachim Goedhart
Section of Molecular Cytology, Swammerdam Institute of Life Sciences, University of Amsterdam
Amsterdam, The Netherlands
@JoachimGoedhart
E-Mail: j.goedhart@uva.nl

Research at Molecular Cytology:
The central research theme is 'Self-organisation and signalling in living cells'. To study these processes we make use of a wide range of fluorescence microscopes of the van Leeuwenhoek Centre for Advanced Microscopy that is embedded in our section.



Cartoon image of the signaling events that are potentially activated downstream of the CaSR. The FRET-based biosensors used in our studies are highlighted in cyan & yellow

ETN research project: Ligand-biased G-protein activation by CaSR
Sergei Chavez Abiega (ESR)

The general aim of my project is to get a better understanding of cellular processes that are controlled by the CaSR. To this end, I use fluorescent sensors that can be introduced into cells. When the CaSR is activated these sensors respond with a colour-change, which can be recorded with a microscope. Our approach allows us to measure the colour-change in individual cells over time. These experiments provide valuable information on the early processes that are activated by the CaSR. On top of this, for a more complete view, I plan to use sensors that report on later signalling events. Finally, our approach will be used to study the effect of potential drugs that target the CaSR.

Roth, S. and Bruggeman, F.J. (2014) A conformation-equilibrium model captures ligand–ligand interactions and ligand-biased signalling by G-protein coupled receptors. *FEBS J.*, 281, 4659-4671.
Van Unen, J. et al. (2016) Quantitative Single-Cell Analysis of Signaling Pathways Activated Immediately Downstream of Histamine Receptor Subtypes. *Mol. Pharmacol.*, 90, 162-176.

Profiles of academic beneficiaries in workpackage 1

University of Manchester; PI: Dr Donald Ward

The University of Manchester

Nuclear physics was initiated in Manchester when Ernest Rutherford first split the atom. The world's first stored-program computer was developed here and Alan Turing pioneered artificial intelligence during his time at the University.
Manchester ranks in the world's top-40 best universities (ARWU, 2017) and in the top-10 in Europe.

The University of Manchester

The Ward lab

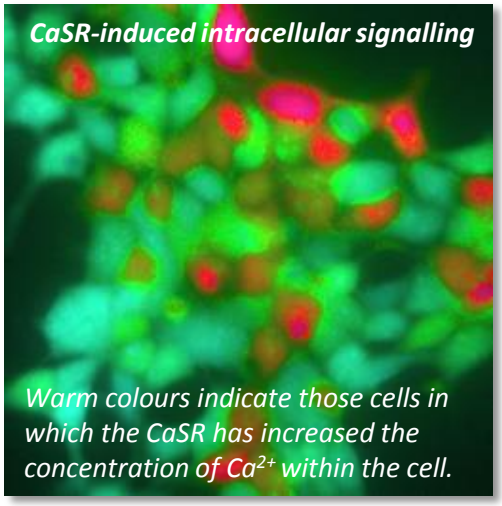
Our main interest is to understand how the parathyroid gland works and thus how it controls the secretion of parathyroid hormone in health but also in conditions such as kidney disease. The CaSR plays a critical role in this process.

Dr Donald Ward (PI) and Patricia Centeno (ESR)

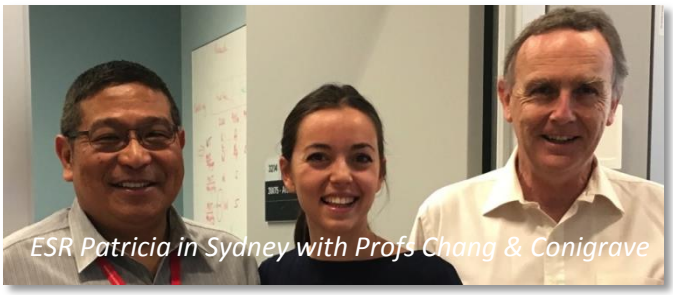
CONTACT DETAILS:
Dr Donald Ward,
Faculty of Biology,
Medicine and Health
University of Manchester
d.ward@manchester.ac.uk

ETN research project: *Cell-specific CaSR signalling*
Patricia Pacios Centeno (ESR)

Patricia is currently in Australia on secondment in the lab of Professor Arthur Conigrave (University of Sydney). Having received a Schachter Travel Award from the British Pharmacological Society, Patricia is learning how to perifuse freshly-isolated parathyroid cells (human and mouse). She is also performing collaborative experiments while there together with both Prof. Conigrave and Prof. Wenhan Chang (UCSF). Patricia is currently examining whether the conditions of kidney disease may affect how the CaSR functions.



Warm colours indicate those cells in which the CaSR has increased the concentration of Ca^{2+} within the cell.



ESR Patricia in Sydney with Profs Chang & Conigrave

Patricia Centena:

"The first 14 months of my project have taken me to Florence, Copenhagen, Oxford and now Sydney. I feel I have made very good progress so far and am now very excited about the rest of the project."

Campion KL, McCormick WD, Warwicker J, Bin Khayat ME, Atkinson-Dell R, Steward MC, Delbridge LW, Mun H-C, Conigrave AD, Ward DT. (2015) Pathophysiological Changes in Extracellular pH Modulate Parathyroid Calcium-Sensing Receptor Activity and Secretion via a Histidine-Independent Mechanism. *J Am Soc Nephrol.* 26, 2163-2171.

Profiles of academic beneficiaries in workpackage 1

University of Copenhagen; PI: Prof Hans Bräuner-Osborne

The University of Copenhagen was founded in 1479. With >30,000 students, >3,000 PhD students, >9,000 employees and an annual budget of >1,1 billion € it is one of the largest universities in Scandinavia.
It has consistently received high international rankings (e.g. 5th best in Europe by ARWU) and has hosted 9 Nobel prize laureates.

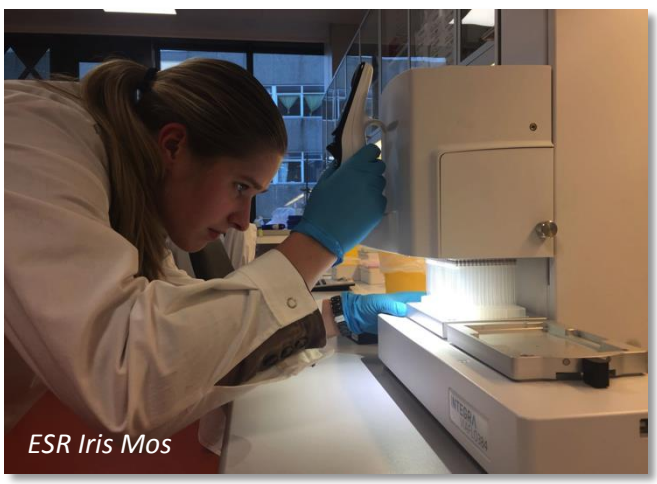

The Pharma Science Building


Atrium

Hans Bräuner-Osborne has studied molecular pharmacology of G protein-coupled receptors since 1992 and the CaSR since 1999.
On CaSR his group has been a key player in delineating Ca^{2+} binding sites, biased agonism in recombinant and native cell lines, and delineating molecular mechanisms of allosteric modulation within the receptor dimer.
His group currently consist of 5 postdocs, 6 PhD students and 1 master thesis student.

CONTACT DETAILS:
Prof Hans Bräuner-Osborne
Faculty of Health and Medical Sciences
University of Copenhagen
hbo@sund.ku.dk


Dr Hans Bräuner-Osborne (PI), Iros Mos (ESR), Dr. Petrine Wellendorph and Simon Foster (Co-PIs)


ESR Iris Mos

Iris Mos

"I am very excited to be involved in a project where I get the opportunity to investigate CaSR signalling from different research perspectives."

ETN research project: Delineation of CaSR signalling in primary cells and cell lines with native receptor expression
Iris Mos (ESR)

The overall aims of this PhD project are to:
1) Gain understanding in CaSR biased signalling on a molecular level.
2) Study biased signalling in cell lines with native CaSR expression.
3) Delineate the internalisation properties of CaSR.

To date, cell lines stably overexpressing CaSR have been successfully generated and validated. Furthermore, a TR-FRET based real-time internalization protocol has been developed to study CaSR internalization.

Jacobsen, S. E., Gether, U., and Brauner-Osborne, H. (2017) Investigating the molecular mechanism of positive and negative allosteric modulators in the calcium-sensing receptor dimer. *Sci. Rep.* 7, 46355
Thomsen, A. R. B., Worm, J., Jacobsen, S. E., Stahlhut, M., Latta, M., and Bräuner-Osborne, H. (2012) Strontium is a biased agonist of the calcium-sensing receptor in rat medullary thyroid carcinoma 6-23 cells. *J. Pharmacol. Exp. Ther.*343,638-649

Profiles of academic beneficiaries in workpackage 1

Medical University of Vienna; PIs: Prof Enikö Kallay & Prof Christian Nanoff

The Medical University of Vienna (MUW) is one of the world's leading medical universities, and hosts Europe's largest hospital. For the MUW, research, education, and patient care represent the three cornerstones of the university's system, which enables medical science to respond flexibly to the continually changing demands of the state and society. The MUW is one of the most important European centres for postgraduate training and promotion of young researchers.

Enikö Kallay (PI)
Taha Elajnaf (ESR)

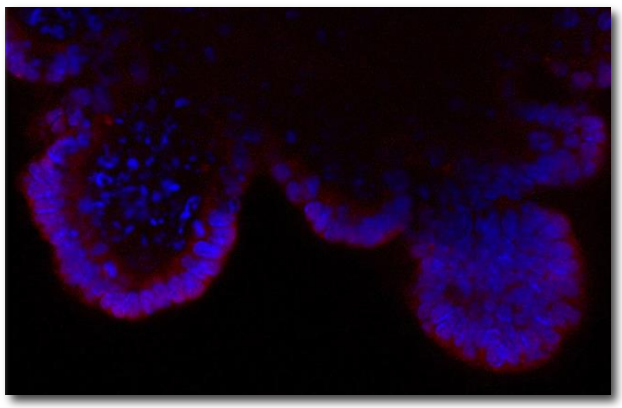
E. Kallay's research is focused on understanding the molecular mechanisms behind the tumour-preventing effects of calcium and vitamin D. She studies the molecular and functional aspects of the CaSR in human colon cancer cells and its role in colorectal neoplastic transformation. C. Nanoff focuses on G protein-coupled Receptors (GPCRs) and interacting Proteins.

ETN research project: *Intestine-specific CaSR signalling*

The objective of this project is to study intestine-specific CaSR signalling in a more physiologically relevant model, such as small intestinal organoids or human intestinal cell lines. We will investigate the potential benefits of CaSR positive allosteric modulators in intestinal inflammation and examine how "intestine-specific" ligands (L-Phenyalanine, poly-L-Arginine, or spermine) affect Ca2+- driven CaSR signalling pathways.

CONTACT DETAILS:
Prof Enikö Kállay
Center of Pathophysiology, Infectiology & Immunology
Medical University of Vienna
enikoe.kallay@meduniwien.ac.at
Taha Elajnaf: taha.elajnaf@meduniwien.ac.at

Taha:
*It has been an enriching learning **experience so far, filled** with many challenges. I am excited about adding new knowledge to the field of intestine-specific CaSR signalling.*



Cross Talk between the Calcium-Sensing Receptor and the Vitamin D System in Prevention of Cancer. Aggarwal A, **Kállay E**. Front Physiol. 2016 Oct 18;7:451.
Expression profiling of colorectal cancer cells reveals inhibition of DNA replication licensing by extracellular calcium. Aggarwal A, Schulz H, Manhardt T, Bilban M, Thakker RV, **Kallay E**. Biochim Biophys Acta. 2017 Jun; 1864(6):987-996. doi: 10.1016/j.bbamcr.2017.01.017.

Events

Midterm meeting of the CaSR Biomedicine Consortium, Manchester, UK, 14-15th September 2017







Hosted by Donald Ward, from the Division of Diabetes, Endocrinology and Gastroenterology at the University of Manchester, EU officer Audrey Arfi and the external expert Roberto Antolovic as well as all PIs and the advisors Ed Nemeth and Wenhan Chang witnessed the excellent scientific presentations of all 14 ESRs at the midterm meeting in Manchester. The stimmulating atmosphere peaked out at the Gala dinner at Christie´s Bistro, when charming host Donald Ward, project coordinator Enikö Kallay and advisor Wenhan Chang addressed the audience enjoyably.

Upcoming Events

4th ETN School: "Self-presentation & Communication", Gödölö, Hungary, 23-25th May 2018

Congratulations

Publications

Congratulations to Maria Lo Giudice and Mie Kronborg Olesen for their recent peer-reviewed publications:

• Ochalek A. Mihalik B. Avci HX, Chandrasekaran A, Téglási A, Bock I, **Giudice ML**, Táncos Z, Molnár K, László L, Nielsen JE, Holst B, Freude K, Hyttel P, Kobolák J, Dinnyes A. (2017)
Neurons derived from sporadic Alzheimer's disease iPSCs reveal elevated TAU hyperphosphorylation, increased amyloid levels and GSK3B activation.
Alzheimer's Research & Therapy; 2017 Dec 1;9(1):90. doi: 10.1186/s13195-017-0317-z.

• Hannan FM, **Olesen MK**, Thakker RV. (2017)
Calcimimetic and calcilytic therapies for inherited disorders of the calcium-sensing receptor signalling pathway.
British Journal of Pharmacology. 2017 Nov 11. doi: 10.1111/bph.14086. [Epub ahead of print]

Awards

• Well done to Anna Glück, Mie Kronborg Olesen and Preeti Sharma, who were the recipients of ASBMR Young Investigator Top Scoring Abstract Prizes at the 3rd International CaSR Symposium, Florence, 2017. Mie and Iris were awarded Poster Prizes at this meeting

• Congratulations to Luca Iamartino, who has been awarded a Travel Grant from the European Association for Cancer Research.

• Congratulations to Patricia Centeno, who has been awarded a Schachter Travel Award from the British Pharmacological Society.

Patricia Pacios Centeno

Luca Iamartino

Iris Mos, Mie Kronborg Olesen, Preeti Sharma and Anna Glück