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This issue focuses on the role of the CaSR in novel therapeutical applications in diseases of ageing

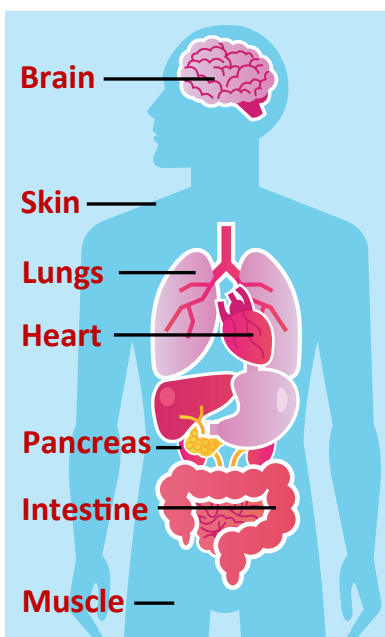
Introduction to the newsletter

Welcome to the 3rd 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 novel therapeutical applications in diseases of ageing.



Non-calcitropic roles of the CaSR

- The CaSR is a G-protein coupled receptor (GPCR) highly expressed in the parathyroid glands, where it plays a pivotal role in Ca²⁺ homeostasis.
- The CaSR is also widely expressed in non-calcitropic tissues such as the brain, skin, lungs, heart, skeletal muscle, pancreas and intestine.
- In non-calcitropic tissues, the CaSR has been shown to regulate key physiological processes such as: digestion; entero-endocrine hormone secretion; vascular tone; and the development of the lungs and central nervous system (CNS)¹.
- Abnormal function or expression of the CaSR in non-calcitropic organs has been associated with diseases leading to global health burdens such as Alzheimer's disease; chronic airways disease; diabetes mellitus; and cardiovascular disease¹.



Examples of non-calcitropic organs expressing the CaSR

¹Ref: Hannan FM, Kallay E, Chang W, Brandi ML, Thakker RV. Nat Rev Endocrinol 2018

Aims of the *therapeutics for ageing* workpackage

- To understand the role of the CaSR in the pathophysiology of Alzheimer's disease, diabetes mellitus, sarcopaenia, and chronic airways disease.
- Evaluate CaSR-targeted drugs as innovative therapeutic approaches for these major age-related diseases.



The University of Manchester



TISSUEGNOSTICS
IMAGING SOLUTIONS



Profiles of academic beneficiaries in work package 2

University of Liverpool; PI: Dr Fadil Hannan

Liverpool University

The University of Liverpool is a preeminent research-based institution. The Institute of Ageing and Chronic Disease (IACD) at Liverpool conducts research into musculoskeletal diseases, obesity and diabetes, and also eye diseases.

CONTACT DETAILS:

Dr Fadil Hannan; Senior Clinical Lecturer
Dept of Musculoskeletal Biology
Institute of Ageing and Chronic Disease
Email: fhannan@liverpool.ac.uk



Fadil Hannan (PI)

Research at the Hannan Lab:

Our work is focused on characterizing structure-function relationships of the CaSR, as well as evaluating CaSR-targeted drugs for calcitropic disorders such as hypoparathyroidism and non-calcitropic disorders such as diabetes mellitus. Dr Hannan is also involved in multi-centre clinical trials for rare bone disorders such as osteogenesis imperfecta.



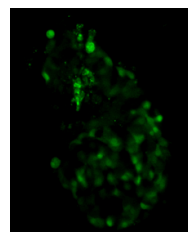
Institute of Ageing and Chronic Disease, Liverpool

ETN research project: Role of the CaSR in glucose homeostasis. Mie Kronborg Olesen (ESR)

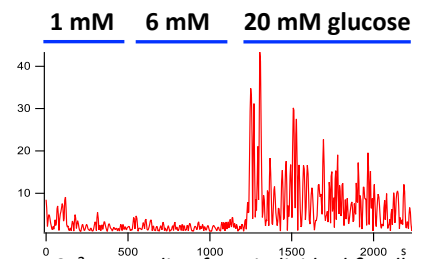
The goal of this project is to investigate the role of the CaSR in glucose homeostasis by using the *Nuf* mouse model with an activating CaSR mutation. Mie has successfully isolated pancreatic islets and measured intracellular Ca^{2+} responses in alpha- and beta-cells *ex-vivo*. She is also characterising the location of disease-causing CaSR mutations using the crystal structure of the human CaSR extracellular domain. Mie has also established a collaboration with Prof Ellinger's group and TissueGnostics GmbH in Vienna to evaluate parathyroid gland size in *Nuf* mice. She is the recipient of the 2018 Young Investigator PhD Training Award from the *American Society of Bone and Mineral Research (ASBMR)*.



Mie Kronborg Olesen (ESR)



Green fluorescence from an individual mouse islet loaded with Ca^{2+} -binding Fluo-4 dye



Ca^{2+}_i recording from individual β -cells of *Nuf* mice following glucose stimulation

Selected publications:

Gorvin CM et al. A calcium-sensing receptor mutation causing hypocalcemia disrupts a transmembrane salt bridge to activate β -arrestin biased signaling. *Sci Signal* 2018
Hannan FM, Olesen MK, Thakker RV. Calcimimetic and calcilytic therapies for inherited disorders of the calcium-sensing receptor signalling pathway. *Br J Pharmacol.* 2017

Profiles of academic beneficiaries in work package 2

Cardiff University; PI: Profs Daniela Riccardi and Paul Kemp

Cardiff University

Cardiff University is a research-led institution with 7,500 international students from more than 100 countries. Research within the School of Biosciences spans the full range of the biomedical and life sciences, from cancer and neuroscience to ecosystems and molecular biology.

CONTACT DETAILS:

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Daniela Riccardi (PI)

Research at the Riccardi Lab:

In my laboratory we have made the discovery that polycations activate the CaSR in the airways and drive hyper-responsiveness, bronchoconstriction and inflammation in allergic asthma models. Our goal is to develop calcilytics (both repurposing and new drug development) as a novel therapeutic for asthma and other lung disease such as COPD and pulmonary fibrosis.



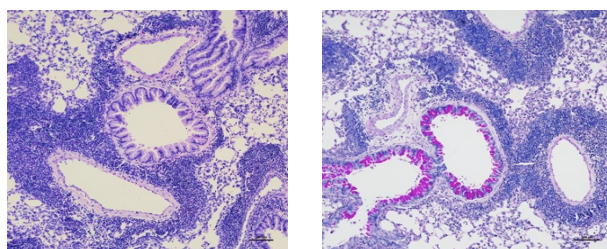
Sir Martin Evans Building

ETN research project: Developing calcilytics for inflammatory lung disease. Ping Huang (ESR)

The goal of this project is to investigate the role of the CaSR in pulmonary inflammatory disease and to develop inhaled calcilytics as a novel therapeutic for severe asthma. Ping has established several pre-clinical *in vivo* models of asthma. She has also undertaken a secondment to Prof Sun Ying's lab (Capital Medical University, China). Her main findings are: 1) inhaled calcilytics reduce lung inflammation as well the current standard of care in asthma treatment, inhaled corticosteroids; 2) inhaled calcilytics show therapeutic effects in *in vivo* models of both allergic and non-allergic asthma. Ping has also contributed to studies aimed at testing newly developed calcilytics. Ping's work has been presented at the last International Meeting of the European Respiratory Society (ERS) in Paris 2018 (poster discussion) and she is currently writing up a manuscript for publication.



Ping Huang (ESR)



Representative haematoxylin & eosin (L) and glycoprotein (R) staining images of lungs from a murine model of allergic asthma.

Selected publications:

Huang P, Yarova PL, Schepelmann MW, Kidd EJ, Ford WR, Broadley KJ, Corrigan CJ, Ward JPT, Kemp PJ and Riccardi D (2018). Comparable efficacy of calcilytic and corticosteroid in short-term and long-term allergic asthma models in vivo. ERS meeting abstract.
Yarova PL, Schepelmann MW, Ferla S, Huang P, Telezhkin V, Kidd EJ, Broadley KJ, Ford WR, Ward JPT, Corrigan CJ, Kemp PJ, Riccardi D (2018). Development of a new calcilytic for the treatment of inflammatory lung disease. ERS meeting abstract.

Profiles of academic beneficiaries in work package 2

University of Oxford; PI: Prof Rajesh Thakker FRS

Oxford University

The Oxford Centre for Diabetes, Endocrinology and Metabolism (OCDEM) is a pioneering centre that combines clinical care, research and education in diabetes, endocrine and metabolic diseases.

CONTACT DETAILS:

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Research at the Thakker Lab:

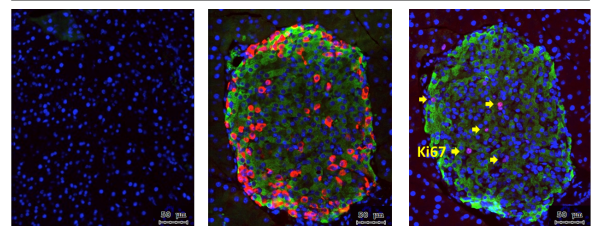
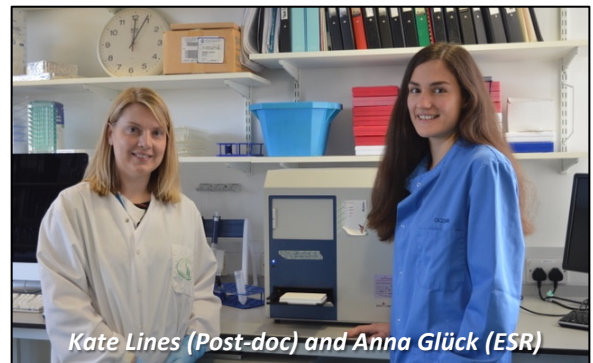
We investigate the genetic, molecular and physiological basis of endocrine disorders that affect calcium homeostasis, and endocrine tumour development. By identifying and understanding the underlying mechanisms, we aim to establish better diagnostic methods and develop novel targeted therapies for these disorders to improve patient care.



ETN research project: Role of $G\alpha_{11}$ in calcium and glucose homeostasis. Anna Glück (ESR)

This project investigates the roles of the two main G-proteins that interact with the calcium-sensing receptor: $G\alpha_{11}$ and $G\alpha_q$. Loss-of-function and gain-of-function mutations in GNA11, encoding $G\alpha_{11}$, cause FHH type-2 (FHH2) and ADH type-2 (ADH2), respectively. Mouse models for FHH and ADH recapitulate the calcitropic phenotypes of the human disorders. However, ADH1 mice also have glucose intolerance, and alterations of glucose homeostasis (if any) in the ADH2 mouse, known as Dsk7, remain to be determined.

The main aims are to: identify and characterise rare GNA11 variants within human populations; establish cell-lines to study the importance of $G\alpha_{11}$ and $G\alpha_q$ in CaSR signalling; and investigate the glucose metabolism of the Dsk7 mice.



Negative control (DAPI + secondary antibodies) Glucagon (alpha) Insulin (beta)
Insulin (beta) DAPI (nuclei) DAPI (nuclei)
DAPI (nuclei) Ki67 (proliferating cells)

Immunofluorescence staining of Dsk7 islets (20x magnification). In collaboration with R. Ecker (Tissuegnostics GmbH) and I. Ellinger (MedUni Vienna).

Selected publications:

Nesbit et al., Mutations affecting G-protein subunit α_{11} in hypercalcemia and hypocalcemia, *N Engl J Med*, 2013
Babinsky et al., Mutant Mice With Calcium-Sensing Receptor Activation Have Hyperglycemia That Is Rectified by Calcilytic Therapy, *Endocrinology*, 2017

Profiles of academic beneficiaries in work package 2

University of Florence; PI: Prof Maria Luisa Brandi

University of Florence:

The origins of the University date back to the Studium Generale set up by the Florentine Republic in 1321 and it boasts among its professors Giovanni Boccaccio and Galileo Galilei. Nowadays, the University of Florence is an important and influential center for research and higher training in Italy, with 1,800 lecturers and research staff, 1,600 technical and administrative staff, and over 1,600 research assistants and doctoral students.

CONTACT DETAILS:

Prof. Maria Luisa Brandi
Full Professor in Endocrinology and Metabolic Diseases; Dept. of Experimental and Clinical Biomedical Sciences; Chief of the Division of Bone & Mineral Diseases, AOU Careggi, Firenze.
Email: marialuisa.brandi@unifi.it



Research at the Brandi Lab:

Prof. Brandi graduated in medicine, with a specialization in endocrinology and a PhD in cell biology. She has a long expertise in clinical, genetic and basic research on disorders of the skeleton and mineral metabolism.

Her group has extensive experience in isolating and characterizing mesenchymal stem cells from different human tissues as well as investigating their differentiation. Their new established cellular models are used in the study of bone and mineral metabolism diseases, osteogenic differentiation, musculoskeletal regeneration, inherited endocrine syndromes and parathyroid diseases.



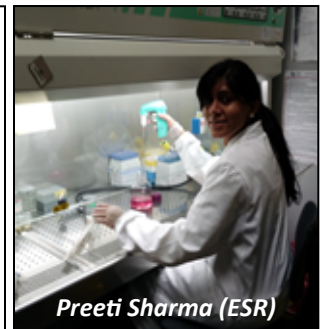
The Brandi Lab

ETN research project: Targeting the CaSR in human skeletal muscle cells to delay sarcopenia development. Preeti Sharma (ESR)

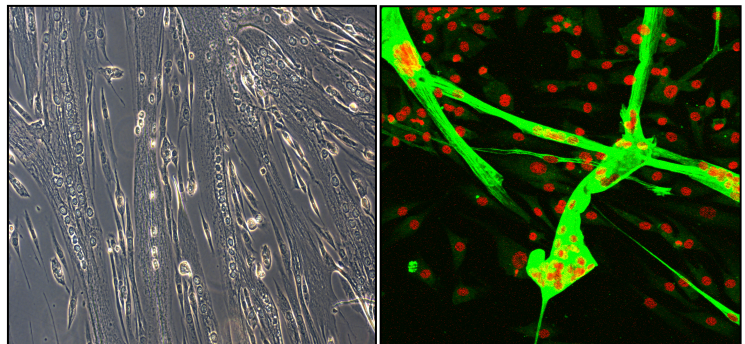
Sarcopenia, or the decline of skeletal muscle tissue with age, is one of the most important causes of functional decline and loss of independence in older adults. Satellite cells (SCs) are stem cells of skeletal muscle, which undergo myogenesis, and in turn are responsible for skeletal muscle regeneration. Failure of SCs to undergo myogenic differentiation has been observed in sarcopenia.

The aim of this project is to analyze the *in-vitro* expression of CaSR in human skeletal muscle tissues and isolated satellite cells, and characterise its potential role during myogenesis, in order to propose a new biological target and to contribute to the future therapies for sarcopenia.

Preeti: "It is a very fulfilling and enriching experience for me to work on this project. Although the project is very challenging, I can learn multiple novel things, which will enhance my research skills. I am very much hopeful and looking forward to contributing further in this project."



Preeti Sharma (ESR)



Multinucleated cells observed in phase contrast microscopy, objective 10x (Left), and Myosin Heavy Chain protein (green), nuclei (red/orange) observed in Laser Scanning Confocal Microscopy, objective 20x (Right) after 7 days of myogenic induction in satellite cells.

Selected publications:

Hannan FM, Kallay E, Chang W, Brandi ML, Thakker RV. The calcium-sensing receptor in physiology and in calcitropic and noncalcitropic diseases.. Nat Rev Endocrinol. 2018 Nov 15. doi: 10.1038/s41574-018-0115-0.

Awards

Congratulations to the ESRs who were the recipients of the following awards in 2018:

Patricia Pacios Centeno (University of Manchester, UK)

- Best Poster Presentation from the British Pharmacological Society
- Travel Grant from Böhringer Ingelheim

Souvik Das (Université de Picardie Jules Verne, France)

- Grant from the French Society for Mineralized Tissue Biology (SFBTM)
- Poster Award from the French Society for Mineralized Tissue Biology (SFBTM)

Maria Lo Giudice (BioTalentum, Hungary)

- Travel Grant from FENS and IBRO/PERC organizations

Luca Iarmartino (Medical University of Vienna, Austria)

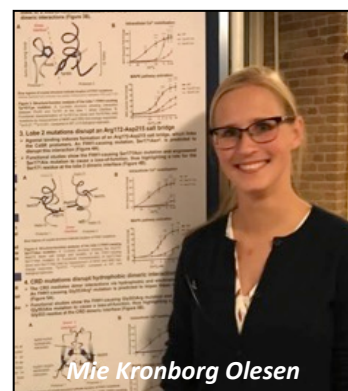
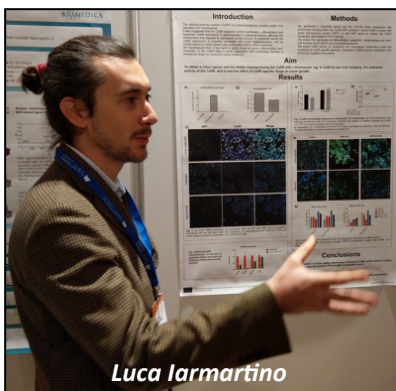
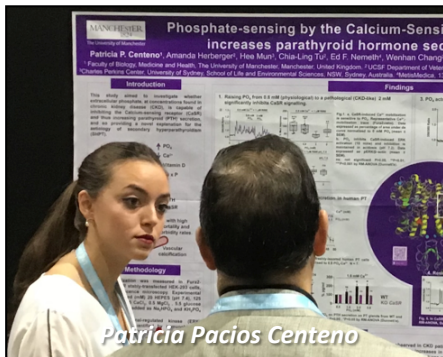
- Junior Travel Fellowship from the European Calcium Society
- Travel Grant from the Comprehensive Cancer Center, Vienna
- Trainee Travel Award from the 21st Vit-D Workshop

Amirreza Mahbod (TissueGnostics GmbH, Austria)

- Congress Scholarship from ÖH Med Vienna

Mie Kronborg Olesen (University of Liverpool, UK)

- ASBMR Young Investigator Award for the ECTS PhD Training



Outreach activities

European Researchers' Night 2018 in Hungary and Austria

28th of September 2018: ESRs Taha Elajnaf (MedUni Vienna), Wolfgang Schlattl (Safan), Amirreza Mahbod (Tissuegnostics GmbH), and Maria Lo Giudice (Biotalentum) presented the CaSR Biomedicine Project at the European Researchers' Night.

Long Night of Research 2018 in Vienna, Austria

13th of April 2018: the booth "Calcium is cool!" was presented by a team consisting of 18 peoples including ESRs Taha Elajnaf and Luca Iarmartino (MedUni Vienna) and Amirreza Mahbod (Tissuegnostics).

Guests of all ages had the opportunity to discover the importance of Calcium for our body by playing games and taking part in a quiz, using a microscope, discover 3D animations of the CaSR etc.



Amirreza, Eniko, Taha and Wolfgang presenting "Calcium is cool!" at the European Researcher's Night 2018 in Vienna



Taha, Isabella, Martin, Maria Elena and Luca presenting "Calcium is cool!" at the Long Night of Research 2018 in Vienna

Publications

Mahbod A, Schaefer G, Ellinger I, Ecker R, Pitiot A, Wang C. **Fusing fine-tuned deep features for skin lesion classification.** *Comput Med Imaging Graph.* 2019 Jan;71:19-29. doi: 10.1016/j.compmedimag.2018.10.007. Epub 2018 Nov 3. PubMed PMID: 30458354.

Hannan FM, Kallay E, Chang W, Brandi ML, Thakker RV. **The calcium-sensing receptor in physiology and in calcitropic and noncalcitropic diseases.** *Nat Rev Endocrinol.* 2018 Dec;15(1):33-51. doi: 10.1038/s41574-018-0115-0. Review. PubMed PMID: 30443043.

Iarmartino L, Elajnaf T, Kallay E, Schepelmann M. **Calcium-sensing receptor in colorectal inflammation and cancer: Current insights and future perspectives.** *World J Gastroenterol.* 2018 Sep 28;24(36):4119-4131. doi: 10.3748/wjg.v24.i36.4119. Review. PubMed PMID: 30271078; PubMed Central PMCID: PMC6158479.

Events

Hans Bräuner-Osborne from the Faculty of Health and Medical Sciences (University of Copenhagen) was the main organizer of the conference **"GPCR Pharmacology 2018 – The Next Generation"** which took place at The Royal Danish Academy of Sciences and Letters in Copenhagen from October 31st to November 2nd, 2018. Several of the ESRs from CaSR Biomedicine – Iris Mos, Wolfgang Schlattl, Anna Glück and Mie K. Olesen – participated with posters.



In Memoriam: Dr Carmen de Torres Gomez-Pallete

It is with great sadness that we announce the passing of Dr Carmen de Torres Gomez-Pallete. Carmen was a CaSR Biomedicine consortium PI and also a clinician and researcher at the Fundació Sant Joan de Déu, a private non-profit hospital associated with the University of Barcelona. Her work focused on characterising the role of the CaSR in the pathogenesis of neuroblastoma, which is a malignancy of childhood. She made seminal contributions to understanding how this GPCR mediates the normal and tumoral development of the nervous system. Carmen was also dedicated to developing CaSR-based therapies for children suffering from neuroblastoma. She mentored numerous technicians, PhD students and post-doctoral scientists, and also trained researchers in standardising molecular biology techniques for the diagnosis of paediatric solid tumours. We will miss the kind and thoughtful contributions that she made to our consortium.

