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

Introduction to the newsletter

Welcome to the 4th 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 cancer

CaSR and cancer

- The CaSR is a G-protein coupled receptor (GPCR), which contributes to the pathogenesis of tumours affecting the breast, colon and nervous system¹
- The CaSR has contrasting roles in different malignancies, and has been shown to have tumour-suppressing effects in colorectal cancer and neuroblastoma, whilst acting as an oncoprotein in metastatic breast cancer¹.
- Drugs modulating the expression and function of the CaSR have the potential to influence the development and progression of these malignancies.



Schematic representation of colorectal cancer (Adobe stock image: Peterschreiber.media). These tumours are characterized by a reduction in CaSR function and expression

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

Aims of the therapeutics for cancer workpackage

- Elucidate the contribution of changes in CaSR expression or function for the pathophysiology of neuroblastoma, breast and colon cancer
- Test CaSR modulators as innovative approaches for delaying the onset of tumourigenesis, or preventing metastases from these malignancies



The University of Manchester



TISSUEGNOSTICS
PRECISION THAT INSPIRES



Profiles of academic beneficiaries in work package 3

Medical University of Vienna; PI: Prof Enikő Kallay & Prof Sabina Baumgartner-Parzer

The Medical University of Vienna is one of the most renowned medical universities. It is the largest medical training facility in the German-speaking area and one of the best cutting-edge research institutions in the field of biomedicine. Its three cornerstones: research, education and the treatment of patients, contribute equally to the medical and scientific quality of the university.



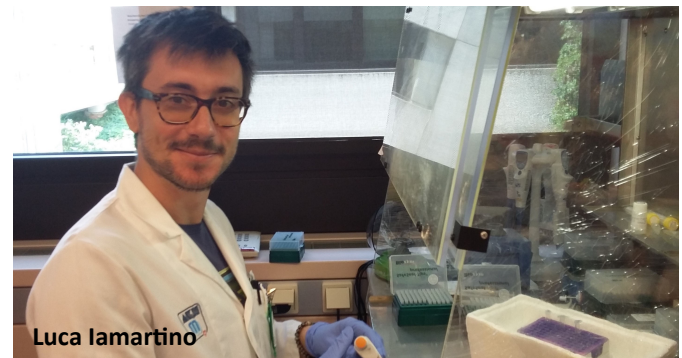
E. Kallay studies the molecular mechanisms behind the tumour-preventing effects of calcium and vitamin D. Her group also studies the molecular and functional aspects of the CaSR in colorectal inflammation and neoplastic transformation. S. Baumgartner-Parzer's expertise is endocrine diseases, molecular genetics and tumor biology.

ETN research project: **Evaluation of CaSR-based therapeutics for preventing colorectal tumourigenesis and metastatic potential**

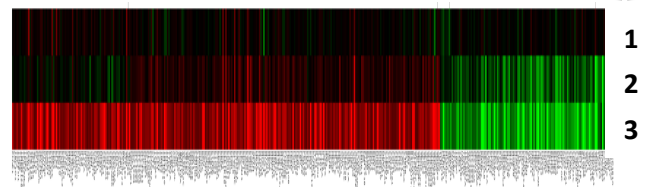
Luca Iamartino (ESR)

This project investigates whether the CaSR is a tumor suppressor and whether it constitutes a target for colorectal cancer therapy. Luca has generated a model to study the role of the CaSR in colorectal cancer cells by inducing the expression of the CaSR via a lentiviral system. These cells will be used in a mouse model to test the role of the CaSR in tumourigenesis.

Luca: Being part of this ETN gave me the possibility to travel, attend numerous conferences and also to establish collaborative networks with other ESRs and also with the PIs and the members of the advisory board.



Effect of R-568 treatment on mRNA levels in cells expressing (HT29^{CaSR-GFP}) or lacking (HT29^{GFP}) the CaSR



- 1: HT29^{GFP} cells treated with 1 μ M R-568;
 - 2: HT29^{CaSR-GFP} cells treated with DMSO;
 - 3: HT29^{CaSR-GFP} cells treated with 1 μ M R-568;
- Relative to HT-29^{GFP} cells treated with DMSO.

CONTACT DETAILS:

Prof E. Kállay: enikoe.kallay@meduniwien.ac.at

Prof. S. Baumgartner-Parzer:

sabina.baumgartner-parzer@meduniwien.ac.at

Luca Iamartino: luca.iamartino@meduniwien.ac.at

Calcium-sensing receptor in colorectal inflammation and cancer: Current insights and future perspectives. Iamartino L, Elajnaf T, Kallay E, Schepelmann M. World J Gastroenterol. 2018 Sep 28;24(36):4119-4131. doi: 10.3748/wjg.v24.i36.4119. The calcium-sensing receptor in physiology and in calcitropic and noncalcitropic diseases. Hannan FM, Kallay E, Chang W, Brandi ML, Thakker RV. Nat Rev Endocrinol. 2018 Dec;15(1):33-51. doi: 10.1038/s41574-018-0115-0.

Profiles of academic beneficiaries in work package 3

University of Picardie Jules Verne; PI: Prof Romuald Mentaverri

University of Picardie Jules Verne

UPJV welcomes more than 30,000 students each year and has 35 research units. The MP3CV laboratory which is located within the University Center for Health Research, is dedicated to medical research. Its proximity to the University Hospital Centre facilitates interactions between scientists, medical teams and patients, which is to everyone's benefit.

CONTACT DETAILS:

Prof. Romuald Mentaverri

- University of Picardie Jules Verne, Amiens, EA 7517 MP3CV, CURS, Amiens, 80054 France
- Department of biochemistry, Amiens University Hospital, 80054 France



Romuald Mentaverri

Research at the Mentaverri Lab:

We are mainly involved in the study of physiopathological mechanisms and consequences of valvular and vascular calcifications, our team is also studying the role played by CaSR in pathologies where phosphocalcic disorders are associated with the pathological development such as in breast cancer bone metastases.



University Centre for Health Research (CURS), Amiens

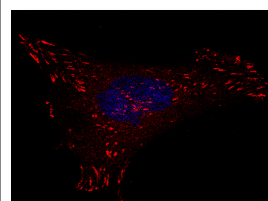
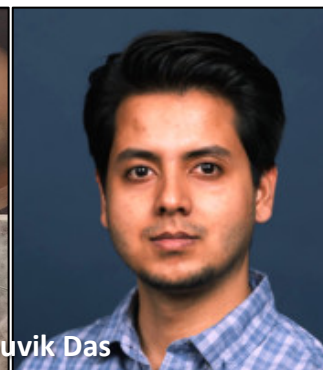
ETN research project: Role of the CaSR in early bone metastasis of breast cancer cells and evaluation of CaSR - based therapeutics in prevention or delay of metastasis

Souvik Das (ESR)

The aim of this project is to investigate the role of CaSR in breast cancer and to follow the bone marrow invasion of triple-negative breast cancer cells in mice treated with calcilytics (pharmacological antagonists of the CaSR). Souvik has been able to study the effect of calcilytics on metastasis using an *in vitro* model involving bone fragments from humans. He was awarded with a "Inter-laboratory exchange grant" from SFBTM (France) which helped him collaborate with Prof. Clezardin's eminent unit in Lyon (France) to test calcilytics *in vivo* for bone metastases from breast cancer and also to train in related techniques. This is an ongoing and extremely beneficial collaboration. Souvik also recently won a "Young Researcher award" at the 21st SFBTM, which he plans to use for attending future conferences in his field.



Souvik Das



A triple negative breast cancer cell, stained for vinculin- the focal adhesion points where the cells stick to surfaces (red specks)



Metastatic bone lesions formed in the hind limbs of mice who were injected with breast cancer cells

Selected publication:

C. Boudot et al., "Overexpression of a functional calcium-sensing receptor dramatically increases osteolytic potential of MDA-MB-231 cells in a mouse model of bone metastasis through epiregulin-mediated osteoprotegerin downregulation," *Oncotarget*, Aug. 2017

Profiles of academic beneficiaries in work package 3

Fundació Sant Joan de Déu; PI: Dr Silvia Mateo-Lozano

Fundació Sant Joan de Déu

The Fundació Sant Joan de Déu addresses research activity towards biological and psychological problems related to pediatric diseases and adult health problems which can originate and develop in childhood. This scientific and technological knowledge is the ideal platform to offer innovative clinical, diagnostic, therapeutic and preventive solutions to patients in their project of personal and social life.

CONTACT DETAILS:

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Dr. Silvia Mateo



Dr. Cinzia Lavarino

Research at the Neuroblastoma Lab:

Our research group studies and identifies new therapeutic targets in neuroblastoma and provides personalized treatment to pediatric patients based on knowledge of their genetic alterations. Our work is focused on the evaluation of the calcium-sensing receptor and parathyroid hormone-related protein as new therapeutic targets in neuroblastoma.



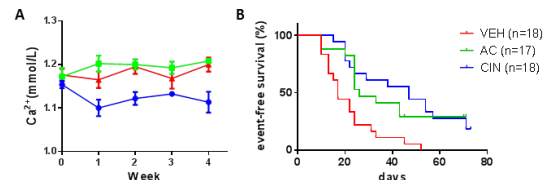
ETN research project: Combined therapies for neuroblastoma based on the activation of the calcium-sensing receptor.

Eliana Gonçalves-Alves (ESR)

Our group identified two genes involved in the differentiation and growth of neuroblastoma (NB), the calcium-sensing receptor (CaSR) and parathyroid hormone-like hormone (PTHrP). After showing that cinacalcet, an allosteric activator of the CaSR, induces apoptosis and/or differentiation in NB models, Eliana is testing potentially synergistic combination therapies with cinacalcet that might promote CaSR upregulation, apoptosis and/or differentiation. Moreover, based on biased signaling of CaSR allosteric modulators, Eliana is also identifying and characterizing calcimimetics that exhibit NB-specific activity without disturbing normal CaSR-expressing tissues.



Eliana Gonçalves-Alves (center)



In vivo effects of AC-265347 (AC) and Cinacalcet (CIN). (A) Hypocalcemia induced by AC in healthy mice was milder than the one induced by CIN. (B) CIN and AC inhibited neuroblastoma tumor growth similarly in a mouse xenograft model.

Selected publications:

Rodríguez-Hernández CJ et al. Cinacalcet inhibits neuroblastoma tumor growth and upregulates cancer-testis antigens. *Oncotarget*. 2016 Mar 29;7(13):16112-29. doi: 10.18632/oncotarget.7448.

Mateo-Lozano S et al. Regulation of Differentiation by Calcium-Sensing Receptor in Normal and Tumoral Developing Nervous System. *Front Physiol*. 2016 May 10;7:169. doi: 10.3389/fphys.2016.00169. eCollection 2016. Review.

Personal highlights of the ESRs



"My colleagues and I had the privilege to attend the exclusive 'GPCR pharmacology conference 2018' in Copenhagen. The latest breakthroughs presented there help me to think outside the box and to pursue new strategies for my own project"

Wolfgang Schlattl,
ESR at S.A.F.AN.
BIOINFORMATICS



"My personal highlight was the first few months in Oxford. Everything was new and exciting; new country, new University, new lab, new friends and new hobbies."

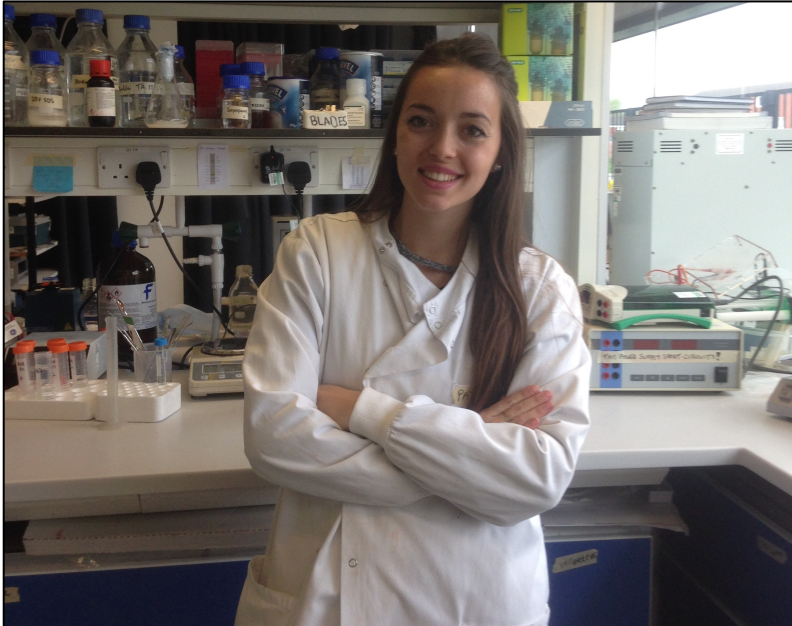
Anna Glück, ESR at University of Oxford



"My secondment at the LYOS lab in Lyon was an unforgettable experience. The lab focuses on breast cancer and bone metastasis, which was an ideal setting for me as it opened my mind to a myriad of relevant research, helped me connect with eminent researchers in the field, carry out my in vivo studies, and update my skill set."

Souvik Das, ESR at Universite de Picardie Jules Verne

Personal highlights of the ESRs



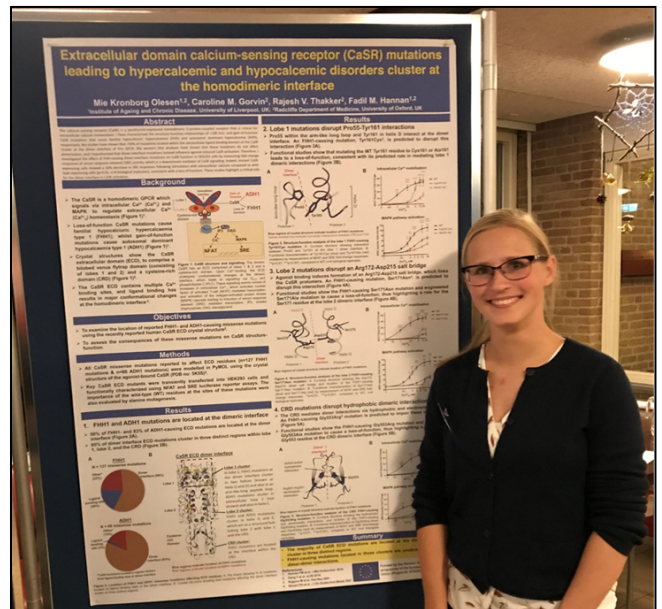
“My project focused on the new role of the CaSR as a phosphate sensor. During my 2nd year, after carefully studying the crystal structure during weeks, I identified three residues potentially involved in phosphate sensitivity. So, I did mutagenesis and expressed the mutant receptors in cells. Weeks later, in the darkroom measuring intracellular Ca²⁺ mobilisation with the fluorescent microscope I found that one of the mutants was insensitive to phosphate. Eureka! I had found the residue explaining phosphate sensitivity of the CaSR.”

Patricia Pacios Centeno; ESR at the University of Manchester



“During my PhD I learned a lot, traveled a lot, attended various national and international conferences, met a lot of new people, extended my scientific network, published in journals, gained valuable experiences in time management, working in a team, collaborating with others, leadership, grant writing, etc but most importantly I worked on amazing scientific projects which hopefully will enhance the healthcare in the near future.”

Amirreza Mahbod; ESR at TissueGnostics GmbH



“During my PhD studies a memorable moment was when I was awarded the ASBMR PhD in training award to go to an introductory bone biology course, where I met a lot of great people and got to present a poster.”

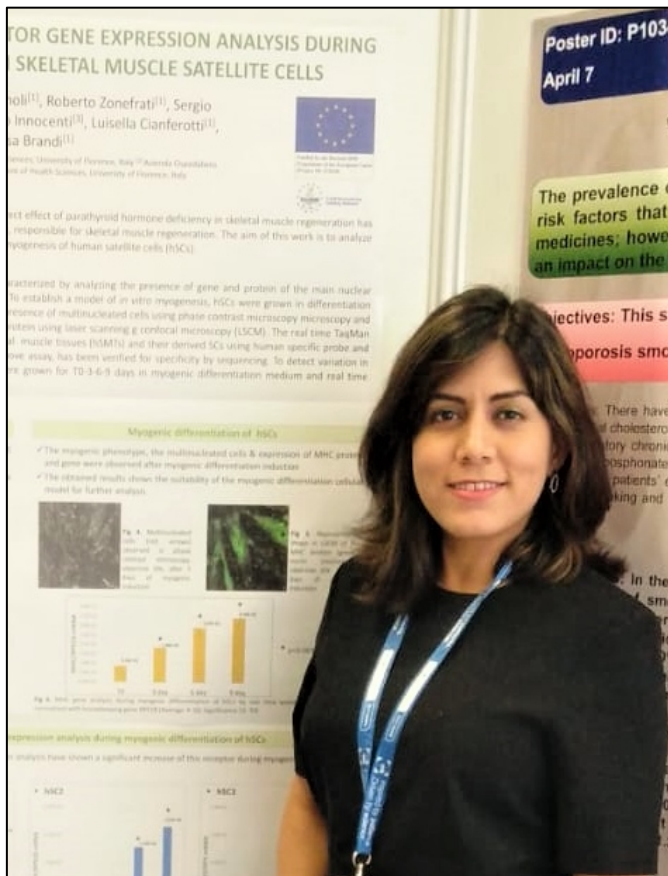
Mie Kronborg Olesen; ESR at the University of Liverpool

Personal highlights of the ESRs



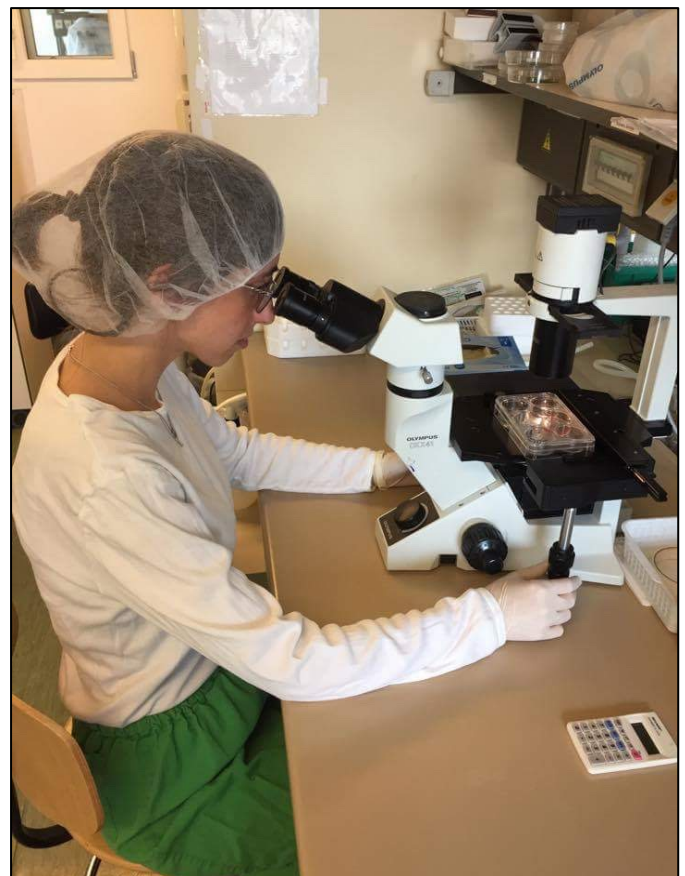
“My most memorable moment was in the 2nd ETN School in Copenhagen. It was an inspiring lecture by Edward Nemeth on studying the CaSR where he shared his personal success story..”

Taha Elajnaf; ESR at the Medical University of Vienna



“My eureka moment involved detecting parathyroid hormone receptor mRNA during myogenesis. I presented my results at an international conference and received scholarship awards for my work..”

Preeti Sharma; ESR at the University of Florence



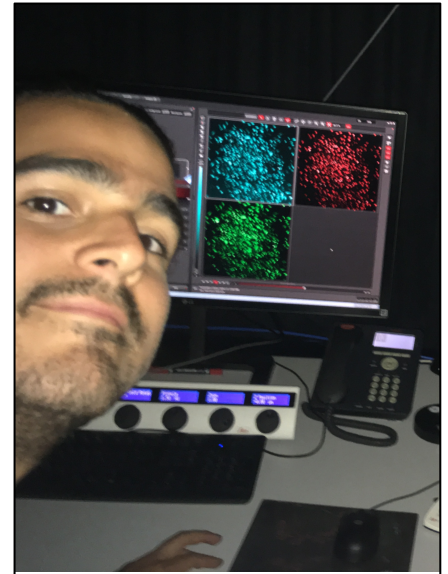
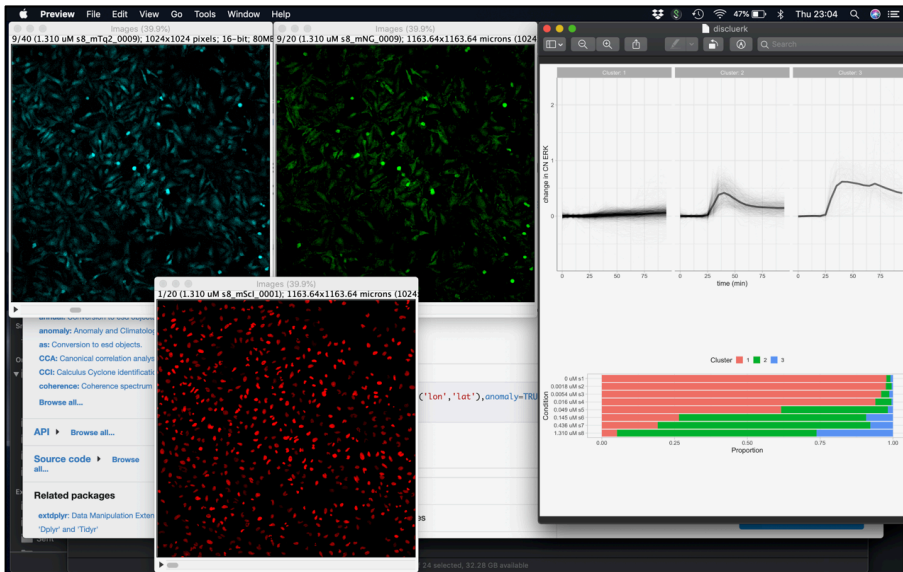
“My eureka moment was in the cell culture room, when I saw the human iPSC-derived neurons for the very first time! I remember that I thought: these are human neurons generated from blood cells!!!...WOW!!! How cool is my job!!!! :)”

Maria Lo Guidice; ESR at BioTalentum

Personal highlights of the ESRs

"This screenshot represents well most of my work from the past year, from the "raw" data to fragments of the analysis. It has taken way too long to reach this point, but it was well worth it!"

Sergei Chavez Abiega; ESR at Vrije Universiteit Amsterdam



Awards

Congratulations to the ESRs who were the recipients of the following awards or grants in 2019:

Ping Huang (Cardiff University, UK)

- Sponsorship for European Respiratory Society Meeting in Madrid 28 .09. - 02 10.2019

Preeti Sharma (University of Florence, Italy)

- ESCEO Eli Lilly Scholarship to attend the World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (WCO-IOF-ESCEO) held in Paris, 4-7 April 2019.

Amirreza Mahbod (TissueGnostics GmbH, Austria)

- NVIDIA GPU (TITIAN V Volta video card) by the NVIDIA Developer programme, 2019
- Postgrad Congress Scholarship from ÖH Med Vienna, 2019
- PostDoc position in a Bridge Young Scientists project from FFG / Austria (2020-2021)

Souvik Das (University of Picardie Jules Verne, France)

- Young researcher award; oral presentation at the 21st French Society for Mineralized Tissue Biology conference, 2019

Luca Iamartino (Medical University of Vienna, Austria)

- Travel grant from the Österreichische Forschungsgemeinschaft to attend the conference "Advances in Biomedical Research III" Split, Croatia, 17 – 21 June, 2019.

Sergei Chavez Abiega (Vrije Universiteit Amsterdam, Netherlands)

- Grant from the "Prins Bernard Cultuurfonds", 2019

Publications

The following articles were published by the CaSR Biomedicine Training Network in 2019:

Mos I, Jacobsen SE, Foster S, Brauner-Osborne H.

Calcium-sensing receptor internalization is β -arrestin-dependent and modulated by allosteric ligands. *Mol Pharmacol.* 2019 Aug 9. doi: 10.1124/mol.119.116772. [Epub ahead of print]

García M*, Rodríguez-Hernández CJ*, Mateo-Lozano S*, Pérez-Jaume S, Gonçalves-Alves E, Lavarino C, Mora J, de Torres C.

Parathyroid hormone-like hormone plays a dual role in neuroblastoma depending on PTH1R expression. *Mol Oncol.* 2019 Jul 10. doi: 10.1002/1878-0261.12542. [Epub ahead of print]. *These authors have contributed equally to this work

Giudice ML, Mihalik B, Dinnyés A, Kobolák J.

The Nervous System Relevance of the Calcium Sensing Receptor in Health and Disease. *Molecules.* 2019 Jul 12;24(14). pii: E2546. doi: 10.3390/molecules24142546. Review.

Binmahfouz LS, Centeno PP, Conigrave AD, Ward DT.

Identification of Serine-875 as an Inhibitory Phosphorylation Site in the Calcium-Sensing Receptor. *Mol Pharmacol.* 2019 Jun 12. pii: mol.119.116178. doi: 10.1124/mol.119.116178. [Epub ahead of print]

Roberts MS, Gafni RI, Brillante B, Guthrie LC, Streit J, Gash D, Gelb J, Krusinska E, Brennan SC, Schepelmann M, Riccardi D, Bin Khayat ME, Ward DT, Nemeth EF, Roskamp R, Collins MT.

Treatment of Autosomal Dominant Hypocalcemia Type 1 With the Calcilytic NPSP795 (SHP635). *J Bone Miner Res.* 2019 May 7. doi: 10.1002/jbmr.3747. [Epub ahead of print]

Mahbod A, Schaefer G, Wang C, Ecker E, and Ellinger I.

Skin Lesion Classification Using Hybrid Deep Neural Networks, ICASSP 2019 - 2019 IEEE International Conference on Acoustics, Speech and Signal Processing (ICASSP), Brighton, United Kingdom, 2019, pp. 1229-1233. doi:10.1109/ICASSP.2019.8683352

Anna Glück.

The challenges of researching rare genetic diseases THE ENDOCRINOLOGIST. ISSUE 132 SUMMER 2019.

Mahbod A, Schaefer G, Ellinger I, Ecker R, Smedby Ö, Wang C.

A Two-Stage U-Net Algorithm for Segmentation of Nuclei in H&E-Stained Tissues, 15th European Congress, ECDP 2019, Warwick, UK, April 10–13, 2019, Proceedings, Series: Lecture Notes in Computer Science, Vol. 11435.

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.* 2019 **15**, 33-51. doi: 10.1038/s41574-018-0115-0.

Iamartino 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.

