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This issue presents key facts and project highlights of the CaSR Biomedicine training network.

**Introduction to the newsletter**

Welcome to the 5<sup>th</sup> issue of the calcium-sensing receptor (CaSR) Biomedicine newsletter. We report on the results of the last project year and summarize major achievements made in the project course. We happily announce that all ESRs finalized their PhD studies and take a glimpse at their future career steps.

**CaSR Biomedicine key facts**

**If you want to go fast, go alone. If you want to go far, go together!** (African proverb)



**People**

- 14 ESRs, 8 young women and 6 young men, from 8 countries
- 10 academic beneficiaries, 3 non-academic beneficiaries and 13 international partner organisations
- 5 advisory board members
- 24 awards

**Training**

- 19 Secondments
- 5 ETN schools

**Dissemination**

- 32 peer-reviewed publications
- 72 posters and 18 oral presentations at conferences
- 24 outreach activities + 5 newsletters + 1 round table discussion
- 1 Patent



The University of Manchester



**TISSUEGNOSTICS**  
PRECISION THAT INSPIRES



## Highlights from the 4<sup>th</sup> annual meeting: Patient round table discussion



A round table discussion was held at the final annual meeting at TissueGnostics GmbH, Vienna, on 13<sup>th</sup> September 2019. The purpose of this **public engagement** session was: 1) to allow **ESRs to discuss their research with patients, patient representatives, and members of the public**; and 2) to provide patients and members of the public with the opportunity to learn more about the work undertaken by CaSR Biomedicine.

The meeting began with Prof Kallay (ETN Coordinator) outlining the scope and aims of CaSR Biomedicine.

All **ESRs gave short presentations of their work**, which was judged by patients and patient representatives.

This was followed by a **round table discussion** chaired by Dr Hannan (PI). The audience had the opportunity to enquire about the scientific and clinical goals of the CaSR Biomedicine consortium. Key topics discussed included: the importance of the CaSR for controlling calcium and phosphate levels in the body; how abnormalities of the CaSR may contribute to common diseases such as asthma; and also how CaSR Biomedicine is researching the potential application of CaSR-targeted drugs for major non-communicable diseases.





Highlights from the 4<sup>th</sup> Annual Meeting in Vienna: the *Carmen de Torres* award



At the last annual meeting, all ESRs gave oral and poster presentations about their research to patients and members of the public. The top scoring presentation was delivered by *Patricia Pacios Centeno*, who thus received the Carmen de Torres Award. Patricia is the first recipient of this award, which commemorates the life and work of Dr. Carmen de Torres Gomez-Pallete, who was a consortium PI and pioneering clinical researcher in the field of paediatric oncology. The second and third place presentations were delivered by *Amirreza Mahbod* (TissueGnostics GmbH) and *Taha Eljanef* (MedUni Vienna).



Project highlight from the academic beneficiaries

MANCHESTER  
1824

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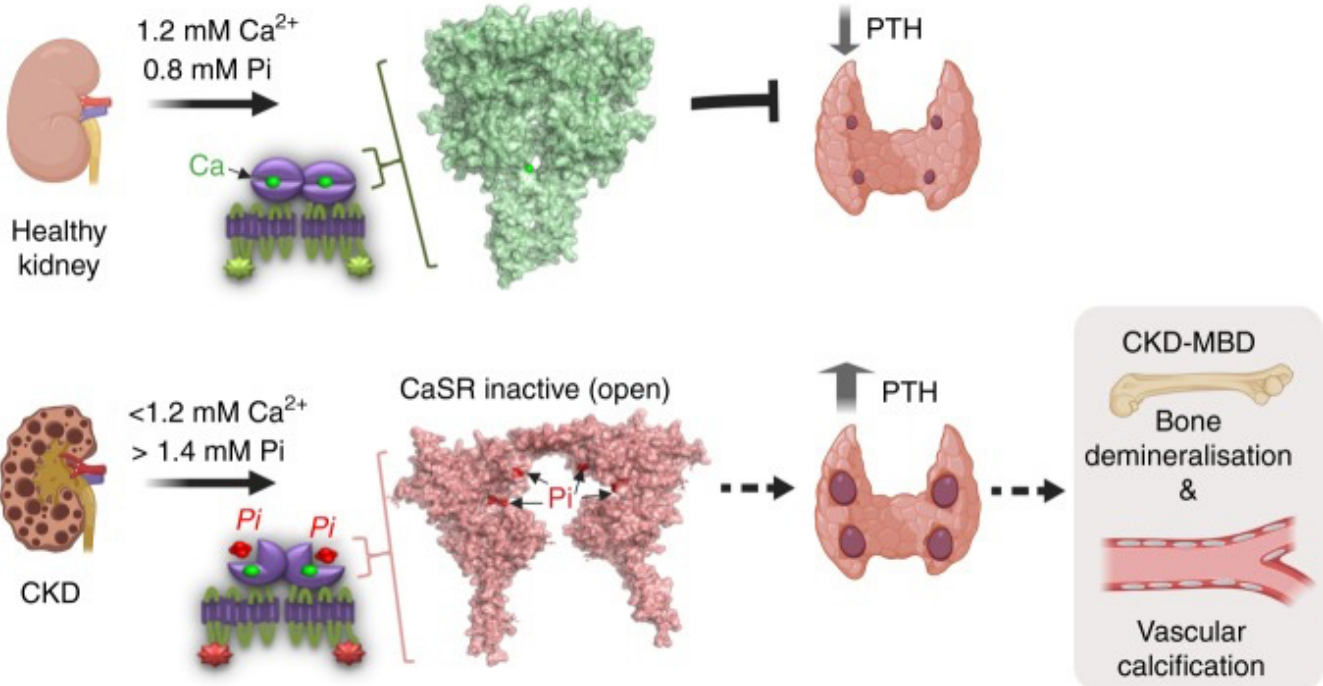
Centeno PP, Herberger A, Mun HC, Tu C, Nemeth EF, Chang W, Conigrave AD, Ward DT

**Phosphate acts directly on the calcium-sensing receptor to stimulate parathyroid hormone secretion.**

Nat Commun. 2019 Oct 16;10(1):4693. doi:10.1038/s41467-019-12399-9.

In health, the calcium-sensing receptor (CaSR) lowers parathyroid hormone (PTH) secretion to prevent blood calcium ( $\text{Ca}^{2+}$ ) levels from rising too high. Our newly-published paper suggests that a rise in blood phosphate levels will inhibit the CaSR and thus permit higher PTH secretion which we already know will, in turn, direct the kidney to clear out this excess phosphate. However, in chronic kidney disease (CKD), phosphate is no longer cleared by the kidneys and thus the constantly raised blood phosphate levels will contribute to the continuously increased PTH secretion. This excess PTH secretion will cause bone loss, parathyroid gland enlargement and life-threatening blood vessel calcification. Thus, by better understanding the process by which this occurs we hope with further research to improve the treatment of high PTH secretion in CKD.

CaSR active (closed)



Taken from Centeno *et al.*, (2019)

Project highlight from the academic beneficiaries

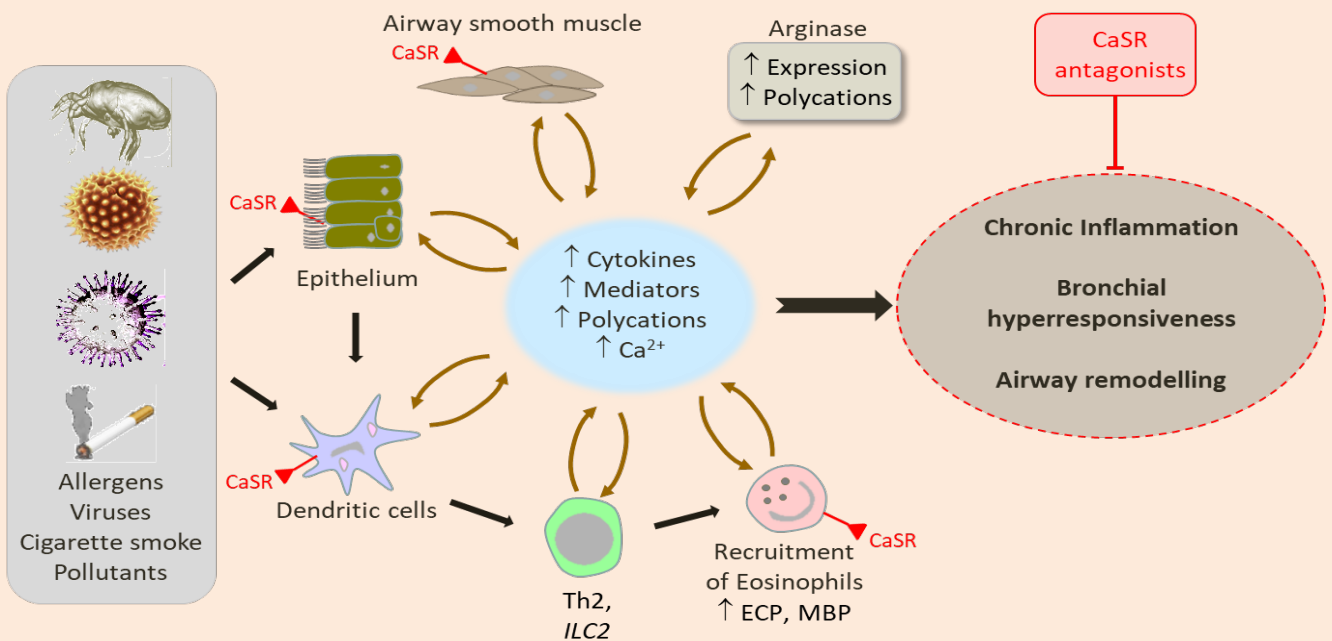


Ping Huang, Bethan Mansfield, Tse-Ren Ho, Catherine Hawrylowicz, Sun Ying, Christopher J Corrigan, Jeremy Ward, Paul J Kemp, Daniela Riccardi

**Inhaled calcilytics: a treatment that has the potential to address the root cause of asthma**

Asthma affects 340 million people worldwide, causing a high burden of death and disability. Treatment is focussed on bronchodilators ( $\beta_2$  agonists), and anti-inflammatory drugs (corticosteroids). Although most people with asthma can be well controlled by such therapy, about 10% have severe, steroid-resistant asthma, which does not respond adequately to any existing drug.

Activation of airway epithelial and dendritic cells by stimuli such as allergens or pollutants is the key initiator of asthma, leading to recruitment and activation of other inflammatory cells (e.g. Th2 lymphocytes, ILC2, eosinophils) and development of the pro-inflammatory milieu that drives the pathology. We now have compelling evidence that: i) the Calcium Sensing Receptor (CaSR) is present on most (if not all) of these cells and airway smooth muscle, and its expression is increased in asthma; ii) activation of CaSR drives the disease process, and; iii) all pathological effects can be prevented by CaSR antagonists (calcilytics). By targeting the CaSR with inhaled calcilytics, we suppress the common, upstream origins of non-specific bronchial hyperresponsiveness (BHR; a hallmark symptom of asthma), inflammation and remodelling.



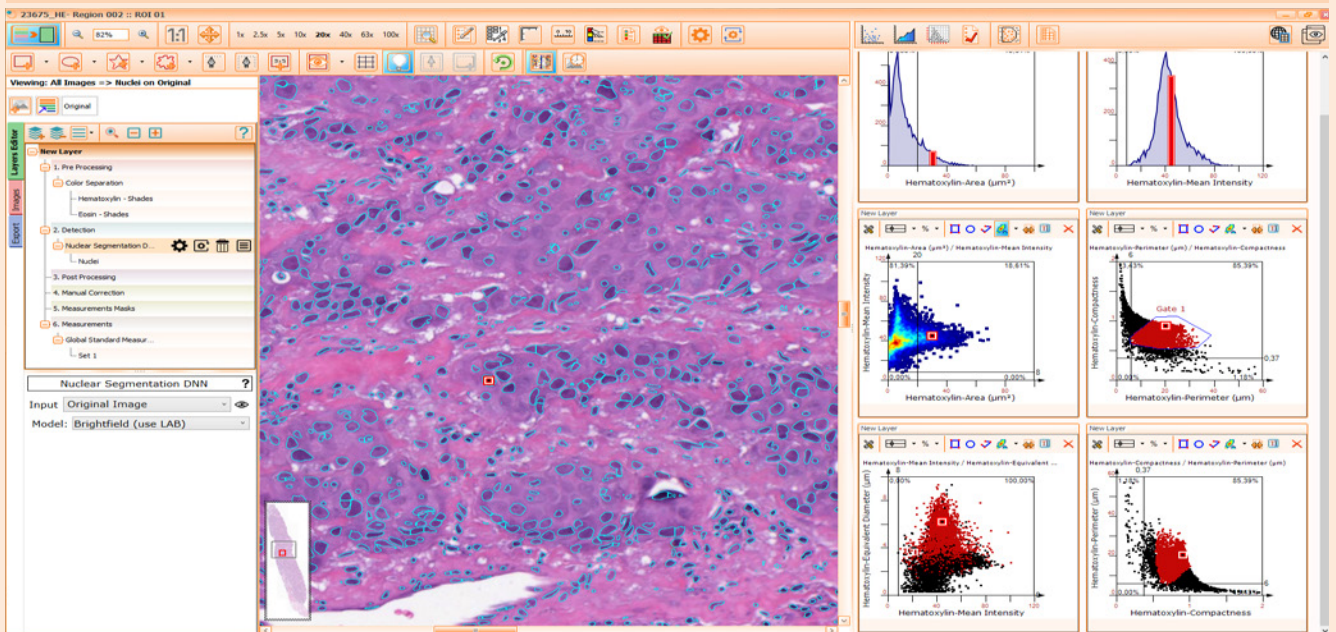


Project highlights from the non-academic beneficiaries



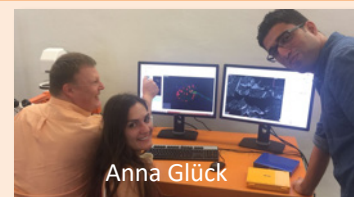
In the course of the CaSR project the team of TissueGnostics gained significant experience in the growing field of Deep Learning. TissueGnostics has provided state-of-the-art instruments for tissue-based research since 2003. The result of this EU-funded project is an advanced algorithm for nuclear segmentation using deep learning technology, which is applicable to various tissue types and staining methods. It works well even under conditions of densely packed cells and contributes to consolidate TG's position in the biomedical market.

This new solution will even help researchers in fighting the current COVID-19 pandemic crisis!

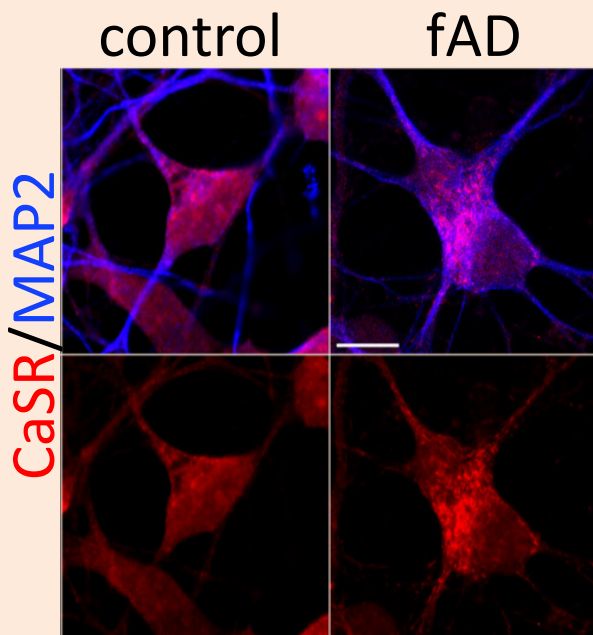


The new Deep Learning-based Nuclear Segmentation algorithm has been launched with TG's new version StrataQuest 7. This innovative Deep Learning algorithm does not even require a single parameter to be adjusted by the user (left part) but shows highly accurate segmentation results (middle part of the screenshot) in multiple tissue types and staining protocols. Interactive scattergrams allow the user to explore the tissue sample for cellular subpopulations by using gates (right part).

9 ESRs visited TG to learn quantitative tissue analysis during their secondment.



Project highlights from the non-academic beneficiaries



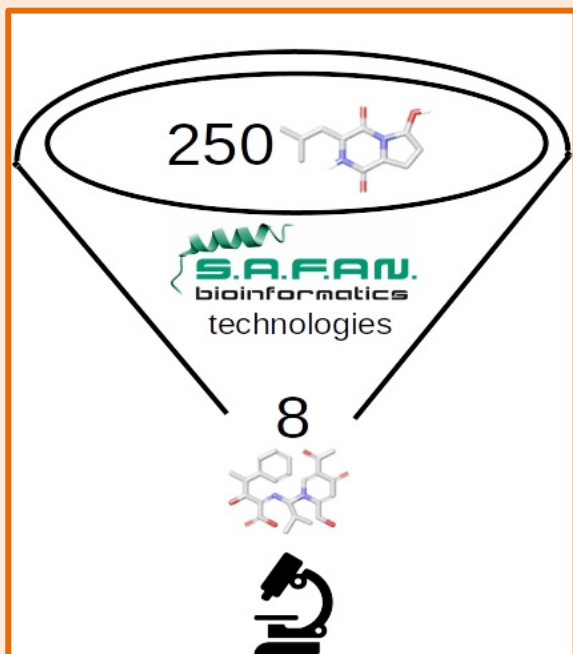
CaSR expression in human iPSC derived neurons. Immunocytochemical analysis showing the CaSR expression (in red) co-stained with Microtubule-associated protein 2 (MAP2; in blue) in neurons differentiated from control and familial AD (fAD) patients (with presenilin-1 mutation) derived hiPSCs.



BioTalentum

In the frame of the CaSR-Biomedicine project, we assessed the potential of our human induced pluripotent stem cell (iPSC)-based Alzheimer disease (AD) cellular model as a platform for drug testing.

- We showed that the iPSC-derived neurons were able to respond to treatment with a  $\gamma$ -secretase inhibitor, modifying physiological amyloid- $\beta$  protein precursor processing and amyloid- $\beta$  ( $A\beta$ ) secretion.
- We demonstrated CaSR protein expression in human neurons derived from healthy and AD subjects (see image) and showed that the calcilytic NPS 2143 modulated  $A\beta$  processing, CaSR and Presenilin-1 expression at the plasma membrane of AD neurons.
- Overall, our findings suggest that NPS 2143 affects important AD processes in a relevant *in vitro* system of familial AD which should be investigated in sporadic cases in the future.



The experimental validation revealed **1** new potent positive allosteric modulator for the **Calcium Sensing Receptor**

S.A.F.A.N. BIOINFORMATICS s.a.s

During the CaSR project S.A.F.A.N. BIOINFORMATICS validated its proprietary technology SAFAN-ISPSM on CaSR allosteric modulators identifying a potent new positive allosteric modulator.

The experience gained during the project now aids the S.A.F.A.N. BIOINFORMATICS team in the search of new potential inhibitors of SARS-CoV2-mediated infections.

The project allowed S.A.F.A.N. BIOINFORMATICS to expand its international network

## Recent publications (i)

Mahbod A, Schaefer G, Wang Ch, Dorffner G, Ecker R, Ellinger I.

**Transfer Learning Using a Multi-Scale and Multi-Network Ensemble for Skin Lesion Classification.**

Computer Methods and Programs in Biomedicine, Volume 193, 2020, 105475, ISSN 0169-2607, doi.org/10.1016/j.cmpb.2020.105475

Boisen IM, Mos I, Lerche-Black EM, Juul A, Bräuner-Osborne H, Jensen MB.

**Heterozygous mutation (Q459R) in the calcium-sensing receptor gene causes familial hypocalciuric hypercalcemia 1 (FHH1).**

J. Clin. Endocrinol. Metab. 2020 Apr 1;105(4):dgz205. doi: 10.1210/clinem/dgz205.

Gorvin CM, Stokes VJ, Boon H, Cranston T, Glück AK, Bahl S, Homfray T, Aung T, Shine B, Lines KE, Hannan FM, Thakker RV.

**Activating Mutations of the G-protein Subunit  $\alpha 11$  Interdomain Interface Cause Autosomal Dominant Hypocalcemia Type 2.**

J Clin Endocrinol Metab. 2020;105(3):952–963. doi:10.1210/clinem/dgz251

Romagnoli C, Zonefrati R, Sharma P, Innocenti M, Cianferotti L, Brandi ML.

**Characterization of Skeletal Muscle Endocrine Control in an In Vitro Model of Myogenesis.**

Calcif Tissue Int. 2020, 7. doi: 10.1007/s00223-020-00678-3.

Chavez-Abiega S, Mos I, Centeno PP, Elajnaf T, Schlattl W, Ward DT, Goedhart J, Kallay E.

**Sensing Extracellular Calcium - An Insight into the Structure and Function of the Calcium-Sensing Receptor (CaSR).**

Adv Exp Med Biol. 2020;1131:1031-1063. doi: 10.1007/978-3-030-12457-1\_41. Review.

Das S, Clézardin P, Kamel S, Brazier M, Mentaverri R.

**The CaSR in Pathogenesis of Breast Cancer: A New Target for Early Stage Bone Metastases.**

Front Oncol. 2020 Feb 5;10:69. doi: 10.3389/fonc.2020.00069. eCollection 2020. Review. .

Elajnaf T, Iamartino L, Mesteri I, Müller Ch, Bassetto M, Manhardt T, Baumgartner-Parzer S, Kallay E, Schepelmann M. **Nutritional and Pharmacological Targeting of the Calcium-Sensing Receptor Influences Chemically Induced Colitis in Mice.** Nutrients, 2019, 11 (12). DOI: 10.3390/nu11123072

Centeno PP, Herberger A, Mun HC, Tu C, Nemeth EF, Chang W, Conigrave AD, Ward DT.

**Phosphate acts directly on the calcium-sensing receptor to stimulate parathyroid hormone secretion.**

Nat Commun. 2019 Oct 16;10(1):4693. doi: 10.1038/s41467-019-12399-9.

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 Sep;34(9):1609-1618. doi: 10.1002/jbmr.3747.



### Recent publications (ii)

Kobolák J, Molnár K, Varga E, Bock I, Jezsó B, Téglási A, Zhou S, Lo Giudice M, Hoogeveen-Westerveld M, Pijnappel WP, Phanthong P, Varga N, Kitiyanant N, Freude K, Nakanishi H, László L, Hyttel P, Dinnyés A. **Modelling the neuropathology of lysosomal storage disorders through disease-specific human induced pluripotent stem cells.**

Exp Cell Res. 2019 Jul 15;380(2):216-233. doi: 10.1016/j.yexcr.2019.04.021.

Lo Giudice M, Mihalik B, Turi Z, Dinnyés A, Kobolák J.

**Calcilytic NPS 2143 Reduces Amyloid Secretion and Increases sA $\beta$ PP $\alpha$  Release from PSEN1 Mutant iPSC-Derived Neurons.**

J Alzheimers Dis. 2019;72(3):885-899. doi: 10.3233/JAD-190602.

### News from our ESRs



What made the CaSR Biomedicine Training network a unique experience for me?

The Early Stage Researcher of the CaSR Biomedicine Training Network share their thoughts...with you.

[Please, follow this link to their video.](#)



#### Anna Glück – ESR University of Oxford

Anna recently returned to the Thakker group, after a Boehringer Ingelheim Fonds funded research visit in the lab of Prof. Bouvier (Montreal) where she learnt new methods to investigate GPCR signalling. While she is writing up her thesis, she is volunteering in a local pharmacy to help them deal with the overwhelming demand during the Covid-19 pandemic.

Photo: Anna working in the Flora Fountain Pharmacy in Uxbridge, London.





News from our ESRs

**Amirreza Mahbod – ESR TissueGnostics GmbH**

On 21<sup>st</sup> of January 2020, Amirreza defended his PhD thesis. His supervisors, Rupert Ecker and Isabella Ellinger shared his happiness. Amirreza will continue his career as a post-doctoral research fellow at the MedUni Vienna. His next research project will last till 2022 and the topic is: “Deep learning for improved nuclei segmentation and knowledge transfer methods in microscopic images” (funded by the Austrian FFG).

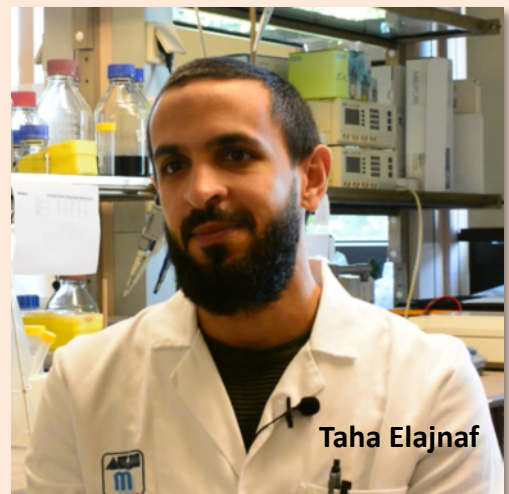


**Preeti Sharma – ESR Universita' degli Studi di Firenze**

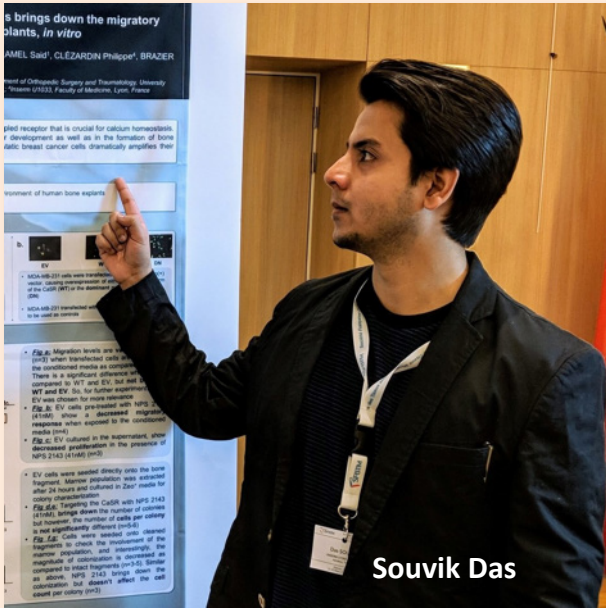
Preeti has defended her PhD thesis on 27<sup>th</sup> of March 2020. Currently, she is looking for a postdoctoral research fellowship in the field of biomedicine at the best institutions around the globe. In the long run, she is interested in pursuing her career as a research scientist either in industry or academia, where she could contribute to the new drug therapies for human diseases.

**Taha Elajnaf – ESR Medical University of Vienna**

Taha is due to have his viva as soon as COVID-19 measures end. For the next 3 years, Taha will be doing postdoctoral research on the endocrinology of lactation at the Nuffield Department of Women's and Reproductive Health, University of Oxford.



News from our ESRs



Souvik Das – ESR Université de Picardie Jules Verne

Souvik will be defending his thesis as soon as the global situation improves. The consortium has really broadened his horizon, especially the industrial partnerships, which he hopes to leverage in the near future. For the present, he wants to establish himself as a cancer researcher and primarily wants to grow his acumen in a biotech / industry environment, depending on the opportunities that present themselves.



Wolfgang Schlattl - ESR S.A.F.AN.-BIOINFORMATICS

Wolfgang will defend his Ph.D. thesis in autumn 2020. He finished his project successfully with the support of his supervisor Luisa Pugliese and discovered a novel active compound. He currently works in a pharmacy in Austria to support the local community in this difficult time of the Covid-19 pandemic. In his future career, he will work on the next scientific challenges either in industry or academia.



Iris Mos – ESR University of Copenhagen

Iris Mos successfully defended her PhD thesis on the 27<sup>th</sup> of November 2019. She will pursue her career as an industrial postdoctoral scientist at the Janssen Pharmaceutical Companies of Johnson and Johnson, from June 15, 2020. Her postdoc project is part of the European consortium EIT health (<https://eithealth.eu>). In the upcoming 3 years, Iris will focus on the development of translational *in vitro* assays which can predict drug-induced cardiac and neuronal toxicities in humans in a robust manner.



**Congratulations to the ESRs who received the following awards or grants**

**Souvik Das (Université de Picardie Jules Verne, France)**

- Grant from the French Society for Mineralized Tissue Biology (SFBTM)
- Young researcher award from the French Society for Mineralized Tissue Biology (SFBTM)

**Luca Iarmartino (Medical University of Vienna, Austria)**

- Junior Travel Fellowship from the European Calcium Society
- Travel grant from the Österreichische Forschungsgemeinschaft to attend the Conference "Advances in Biomedical research III", Split.

**Amirreza Mahbod (TissueGnostics GmbH, Austria)**

- Kaggle Open Data Research Grant (2000 USD)

**Anna Glück (University of Oxford, UK)**

- Boehringer Ingelheim Fonds grant for a three-month research project in the laboratory of Professor Michel Bouvier, University of Montreal, CA (€ 2910)

**Ping Huang (University of Cardiff, UK)**

- European Respiratory Society "Young Scientist" Award 2019

**At the end....**



...this project would not have been possible without our **coordinator, Assoc. Prof. Dr. Enikö Kállay**, and our **project manager, Dott.ssa Maria Elena Manfredini**.

Enikö brought this team together and both of them took care of the project from the beginning to the very end.

Thank you so much for your dedication!



...we are extremely thankful and grateful to the members of the Advisory Board **Edward F. Nemeth, PhD**, **Arthur Conigrave BSc (Med), MBBS, MSc, PhD, MD, FRACP**, **Gerda E. Breitwieser, PhD**, **Wenhan Chang, PhD** and **Edward M. Brown MD, PhD** for their valuable and friendly feedback to our young researchers. All our ESRs benefited significantly from their knowledge and experience. They are real role models for the young scientists.