3RD INTERNATIONAL SYMPOSIUM ON: THE CALCIUM SENSING RECEPTOR (CASR)

Florence (Italy), May 11-13, 2017

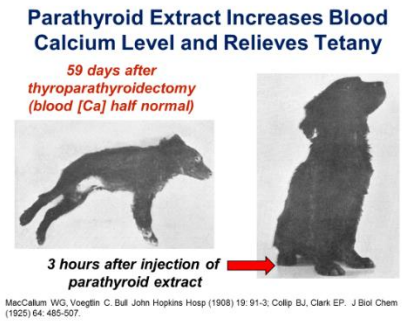
Highlights

Introduction

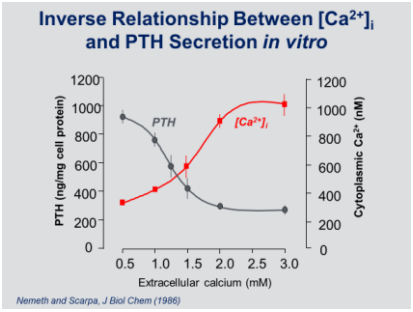
Prof. Brandi, Prof. Kállay, Prof. Thakker and Prof. Changi, co-chairmen of the symposium, opened the congress, by highlighting the high scientific level of this meeting and the history of the Calcium Sensing Receptors congresses already organized in other countries like USA and Austria. This congress was a very unique occasion for a very full update in CaSRs, attended by the top researchers coming from all the world

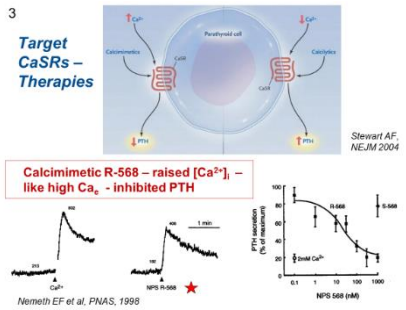
To follow the presentations of this congress, click on the link below: http://www.fondazione-menarini.it/Home/Eventi/The-3rd-International-Symposium-onThe-Calcium-sensing-Receptor-CaSR/VIDEO-SLIDE … and, after having logged in, enter in the multimedia area.

The CaSR discovery opens way to the future



The CaSR discovery opens way to the future, was the topic discussed by Prof. Shoback in her lecture. The speaker, coming from San Francisco (USA), went deeper in her talk and presented very interesting data on the history of this discovery started in 1850 till now. Going deeper in her lecture the speaker presented very interesting data given by the literature on CaSR animal and human studies. More in particular Prof. Shoback talked about the main steps of this history like the first production of the parathyroid extracts, the determination of the amino acid PTH sequence, the relationship between calcium blood levels and PTH, the first radioimmunoassay for the PTH detection. The speaker presented also other data on the so called "paradoxes" of the parathyroid, characterized by studies performed in the 80th years, by highlighting that these studies on the intracellular parathyroid calcium were the first steps toward the later discovery of the calcium sensing receptors. Finally, Prof. Shoback talked about the main signalling studies performed on the parathyroid cells and more in particular on the identification of the Ca receptor cDNA trough the expression cloning in oocytes, on the role of the CaSR in the human disorders of the Ca^{2+} sensing, on the structure-function studies and finally on the therapeutic success of the calcimimetics.





- What's about the paradoxes of the parathyroid in 1980, based on the data presented by the speaker?
- What's about the Calcimimetics as therapeutic success from the speaker point of view?
- What are the mouse models of Targeted CaSR deletion, presented by the speaker?
- When was discovered the first radioimmune essay for the PTH detection?
- What's about the study performed by Brown in 1976 on the development of in vitro system of viable, purified dispersed parathyroid cells?

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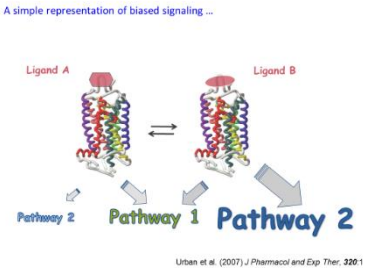
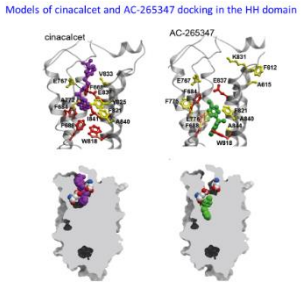
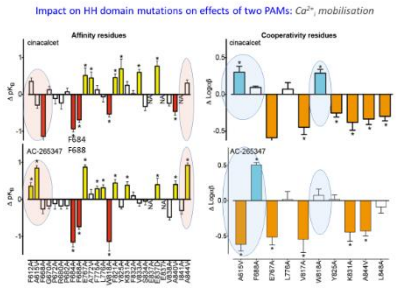
Biased signalling from CaSR



Prof. Conigrave from Sydney (AUS), spoke about the biased signalling coming from CaSR. The speaker went deeper in his talk and presented very interesting data on the CaSR and its signalling capabilities. Going deeper in his lecture, Prof. Conigrave talked about the differences in signalling due and not due to biases. More in particular the speaker presented experimental data on the CaSR biased agonism and modulation and other non-biased signals like off-target effects, differences in receptor chaperoning or in kinetics of responses. In the main part of his presentation, Prof. Conigrave talked about the positive modulators that exhibit biases, like amino acids and mutants and presented many data on the effects of these mutants on CaSR and Ca^{2+}. Finally, the speaker talked about models built for the identification of the residues that present biased properties like the ones of cinacalcet and AC-265347. In conclusion, Prof. Conigrave pointed out that CaSR presents biased signalling properties, but their significance is still not clear.





- What's about the simple representation of the biased signalling, presented by the speaker?
- Why do biased signalling arise?
- What are the main allosteric modulators presented by the speaker?
- What are the main CaSR signalling capabilities?
- When there are differences in signalling not due to bias?
- What are the main positive modulators that exhibit bias, presented by the speaker?
- What are the main models able to identify residues that support biased properties, presented by the speaker?

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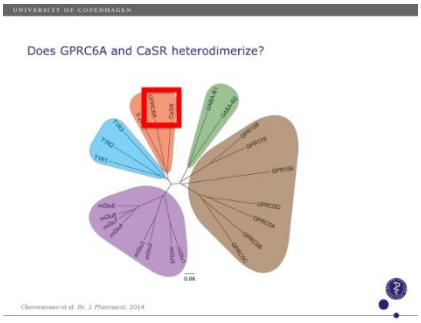
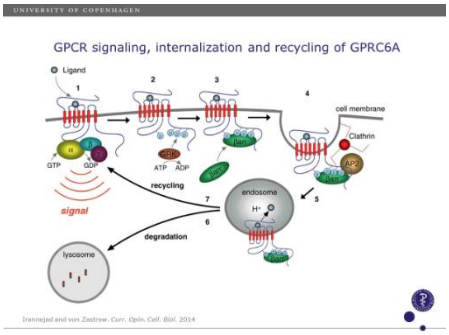
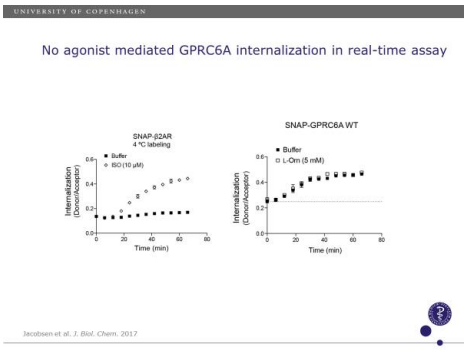
Trans-activation and allosteric modulation of the calcium-sensing receptor



The trans-activation and allosteric modulation of the calcium-sensing receptor, was the topic Prof. Bräuner-Osborne spoke about in his lecture. The speaker coming from Copenhagen (DK), started his talk, by presenting the main G protein-coupled receptor families composing the human genome. Going deeper in his lecture, Prof. Bräuner-Osborne talked about the ligand binding sites in class C GPCRs, its activation mechanism and about the dimerization and hetero-dimerization of the class C GPCRs and presented very interesting experimental data on the GPRC6A and CaSR formation of homodimers. In the main part of his talk, Prof. Bräuner-Osborne spoke about the activation mechanism of class C receptors and presented very interesting data on the CaSR dimer activation, on the GPCR signalling leading to the internalization and the recycling of GPRC6A. Finally, the speaker talked about the models developed for testing the functional allosteric binding sites and presented very interesting data on the localization of active PAM and NAM sites, on the internalization and recycling of GPRC6A, GLP-1 receptor and CaSR.





- Does GPRC6A and CaSR heterodimerize?
- What's about the mechanism of allosteric modulation making a PAM/NAM inactive mutant, based on the data presented by the speaker?
- Do CaSR display constitutive internalization and recycling?
- What are the main activation mechanisms of class C receptors, presented by the speaker?
- What are the main class C GPCR activation mechanisms presented by the speaker
- What's about the internalization and recycling of the GPRC6A receptors, based on the data presented by the speaker?

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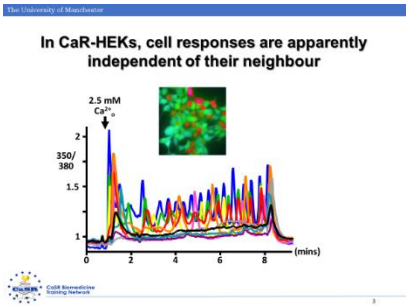
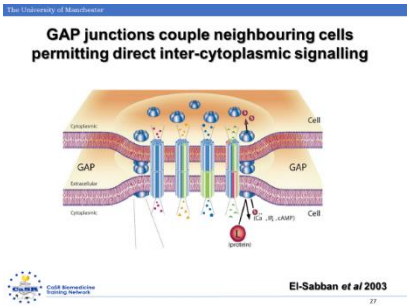
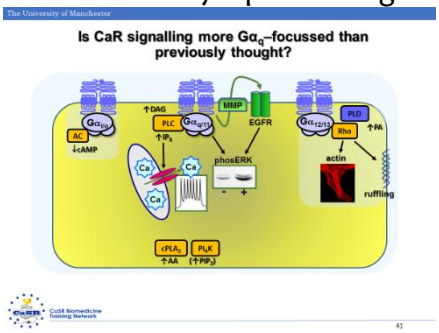
Cell-specific CaSR signalling: effector feedback modulation of receptor responsiveness



The cell-specific CaSR signalling: effector feedback modulation of receptor responsiveness, was the topic at the core of the lecture discussed by Prof. Ward. At the beginning of his talk the speaker, coming from Manchester (UK), presented very interesting data on the Ca2+ mobilization CaSR induced in HEK-293 cells, by highlighting that in CaR-HEKs, the cells responses are apparently independent of their neighbours. Going deeper in the lecture, Prof. Ward talked about the CaSR signal transduction through a bovine cell cluster, showing that these cells are closely linked one each-other and this phenomenon is due to the presence of GAP junctions that couple neighbouring cells and permit direct inter-cytoplasmic signalling. In the main part of his talk Prof. Ward, presented very interesting data on the relationship between the Gap junctions and the CaSR signalling at different cells type levels. In the second part of his lecture, the speaker talked about the CaSR signalling and its relationship with the Gaq inhibitor. Finally, Prof. Ward, presented a lot of experimental data on the relationship beteween Ca^{2+}_i, CaSR and cAMP, by highlighting that the CaSR signalling can vary quite considerably between cells based on many factors like the cross-talk with other signals.





- What are the main characteristics of the Car signalling in rat MTC cells, presented by the speaker?
- Is CaR signalling more Gaq-focused than previously thought?
- Is there crosstalk between Ca^{2+}_i and cAMP signalling downstream of CaR activation?
- What's about the effects of Forskolin on CaR in different cell models?
- What's about the effects of calyculin on CaR based on the data presented by the speaker?

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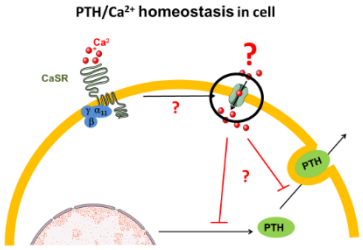
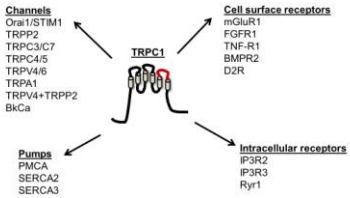
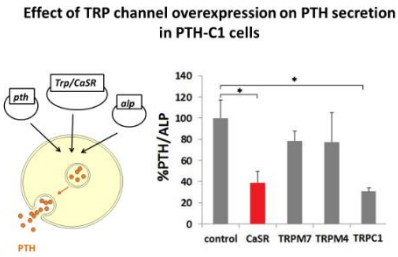
Regulation of CaSR by TRPC1 channels



The regulation of CaSR by TRPC1 channels was the topic at the core of the lecture discussed by Prof. Tsiokas. The speaker, coming from Edmond (USA), introduced his talk by presenting data on the PTH/Ca^{2+} homeostasis model in the cells. Going deeper in his lecture, Prof. Tsiokas talked about the channels that mediated the Ca balance into cells and presented very interesting data on the main Ca channel mutations effects detected in patients affected by the Stormorken syndrome, characterized by muscle disorders, also called tubular aggressive tubulopathy, secondary to profound alterations of the Ca channels interactions. In the main part of his lecture, the speaker talked about the main TRPC-1 gene mutations and their effects on channels, pumps, cells surface and intracellular receptors leading to primary hyperparathyroidism and hypocalciuria, by highlighting that at the cellular level, TRCP1 is the channel or the channel subunit that mediates the Ca $^{2+}$ entry into the cells. In conclusion, Prof. Tsiokas pointed out that his data support that deletion of TRCP1 in mice produces hyperparathyroidism and increases the bone volume, mimicking the familial hypocalciuric hypercalcemia in humans.





- What is the channel that mediates the Ca balance into the cells?
- What are the main effects of the TRP channel overexpression on PTH secretion in PTH-C1 cells, based on the data presented by the speaker?
- What are the major roles played by the TRCP1 channel from the speaker point of view?
- What's about the familial hypocalciuric hypercalcemia, based on the data presented by the speaker?

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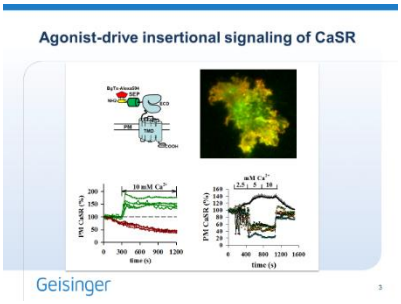
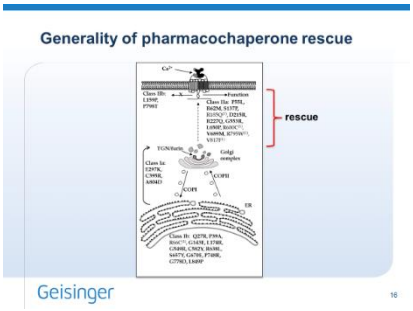
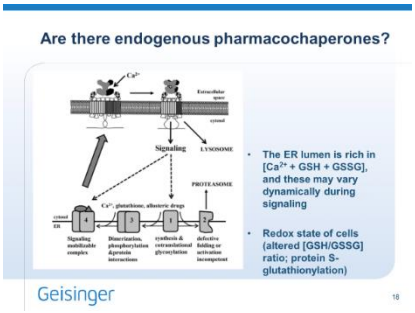
Pharmacochaperones: can they be harnessed to regulate CaSR signalling



Pharmacochaperones was the topic of Prof. Breitwieser presentation. The speaker, coming from Danville (USA), talked about CaSR and its agonist-drive insertional signalling, by highlighting that the ADIS mechanism presents several intracellular sites for the modulation of the CaSR signalling. Going deeper in her lecture, Prof. Breitwieser presented many experimental data on the detection of these sites and their effects on CaSR activity. In the main part of her lecture, the speaker talked about the so called "CaSR pharmacochaperones", by highlighting that these elements can bias conformations in order to modulate the stability and/or the maturation at the plasma membrane level. Finally, Prof. Breitwieser spoke about the possible interactions of some CaSR pharmacochaperones with drugs like polycationic antibiotics or dihydropyridines that can increase the CaSR expression leading to the onset or the progression of the pulmonary hypertension. In conclusion, the speaker, pointed out that Pharmacochaperones may be particularly effective for the rescue of missense variants which compromise the ER release to the plasma membrane.





- What are the essential features of ADIS based on the data presented by the speaker?
- What are the sites of allosteric modulation, based on the data presented by the speaker?
- What's about the generality of the pharmacochaperone rescue presented by the speaker?
- Do unintended CaSR pharmacochaperones contribute to drug side effects?

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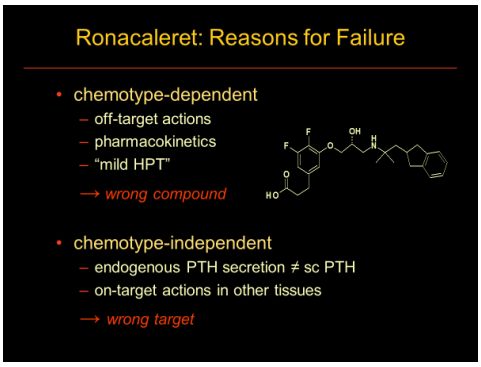
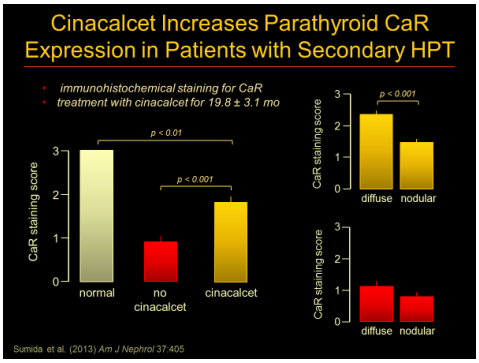
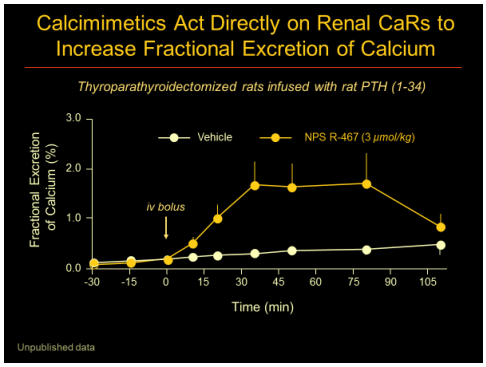
Calcimimetic and Calcilytic Drugs



Calcimimetic and Calcilytic Drugs was the topic of Prof. Nemeth presentation. The speaker, coming from Toronto (CND), talked about calcylitics, their lack of effect in osteoporosis and their repurposing for new indications and about cinacalcet, its clinical experience, its effects and its pharmacodynamics. Going deeper in his lecture, Prof. Nemeth presented very interesting data on Ronacaleret the reasons for its failure and the possible new indications in ADH, inflammatory lung disorders and pulmonary arterial hypertension. In the main part of his lecture, the speaker talked about calcimimetics and their recent development, by highlighting their role as CaR-active therapeutics thanks to their nature as allosteric agonists. More in particular Prof. Nemeth presented very interesting data on Cinacalcet and its three compounds, all of them taking part of the calcimimetic family. The speaker talked about the non-clinical pharmacodynamics of cinacalcet and its effects on the parathyroid CaR and on the synthesis of PTH. Finally, Prof. Nemeth spoke about the pharmacodynamic properties of a third generation calcimimetics for the treatment of the secondary of HPT, by highlighting the importance of the receptors in the secondary HPT.





- What are the main reasons of Ronacaleret failure from the speaker point of view?
- What's about the new indications of the Calcilytics?
- What are the recent developments about Calcimimetics?
- What's about the non-clinical pharmacodynamics of Cinacalcet, based on the data presented by the speaker?
- What are the main pharmacodynamic properties of the third generation calcimimetics for secondary HPT?

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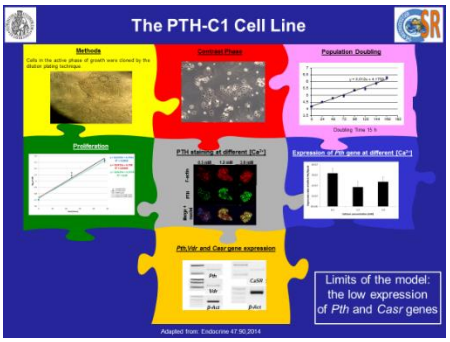
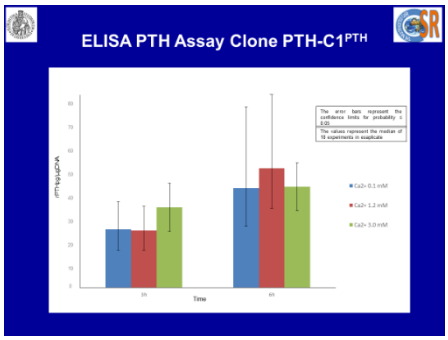
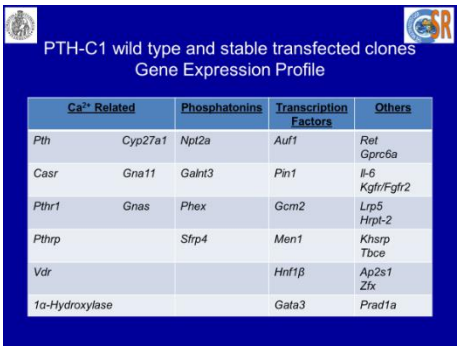
Parathyroid cell lines: a model for in vitro drug testing



Dr. Vannucci coming from Florence (IT) spoke about the parathyroid cell lines as a model for in vitro drug testing and presented very interesting data on parathyroids, their cell types and the in vitro cells models. Going deeper in her lecture, Dr. Vannucci talked about the history of the parathyroid cell cultures from the first production of the parathyroid hormone, the PTH synthesis from adenoma, till the human "encapsulated" models and the PT-r, a cell line derived from rat cells, used for cloning the rat CaSR gene. In the main part of her lecture, the speaker presented very interesting data on the PTH-C1 cell line model and its application in vitro studies. In conclusion, Dr. Vannucci pointed out that thanks to these cells, the research could be very useful for understanding their secretory machinery and these models could also be used for the evaluation of the mechanism of action of new compounds.





Ca2+ Related		Phosphatonins	Transcription Factors	Others
Pth	Cyp27a1	Npt2a	Auf1	Ret
				Gprc6a
Casr	Gna11	Galnt3	Pin1	Il-6
				Kgfr/Fgfr2
Pthr1	Gnas	Phex	Gcm2	Lrp5
				Hrpt-2
Pthrp		Sfrp4	Men1	Khsrp
				Tbce
Vdr			Hnf1β	Ap2s1
				Zfx
1α-Hydroxylase			Gata3	Prad1a

- What are the main uses of the PTH-C1 model, from the speaker point of view?
- What is the gene expression profile of the PTH-C1 cell line?
- What's about the human "encapsulated" models, based on the data presented by the speaker?
- What's about the parathyroid pseudoglands presented by the speaker?

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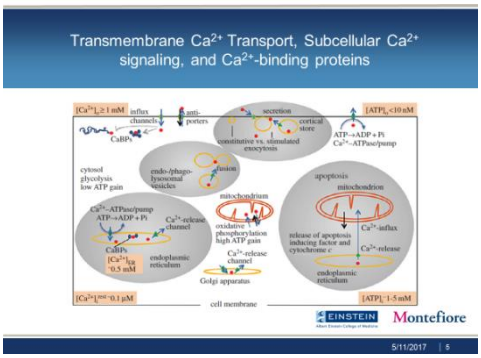
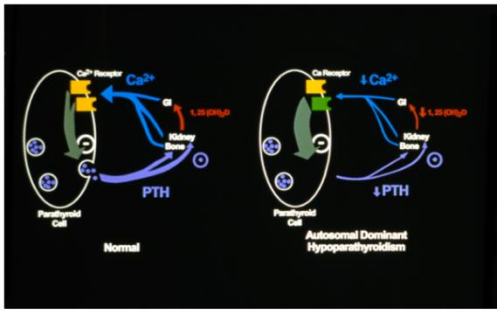
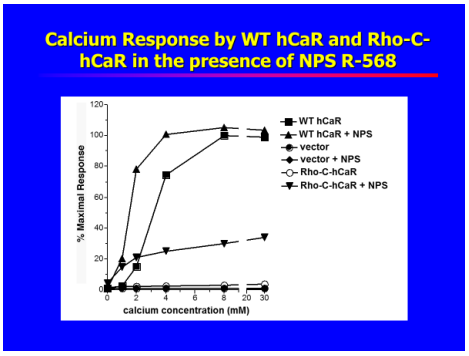
Calcium actions and its regulators: from basic research to clinical applications



Calcium actions and its regulators: from basic research to clinical applications was the topic at the core of Prof. Spiegel presentation. The speaker, coming from New York (USA), presented very interesting data on the evolutional biology of the intracellular Ca^{2+}, the comparative biology of the parathyroid glands, the emergence of the extracellular Calcium-Sensing Receptor, the inborn errors of signal transduction caused by mutations in G proteins and GPCRs and finally on the clinical implications for the disorders of the calcium metabolism. Going deeper in his lecture, Prof. Spiegel talked about the CaSR structure and more in particular on the human extracellular Ca^{2+} receptor and the role played by cysteines. In the main part of his talk, the speaker presented very interesting data on the mutations in G proteins and G protein-coupled receptors present in many endocrine diseases and leading to enzyme deficiency, loss of function and also in some cases gain of function. More in particular Prof. Spiegel talked about the main CaSR and G mutations characterizing the Familial Hypocalciuric Hyerpcalcemia (FHH), the Neonatal Severe Hyperparathyroidism (NSH) and the Autosomal Dominant Hpocalcemia (ADH) and presented a lot of data given by studies performed by his team of researches. Finally, the speaker talked about therapy and presented very interesting data on the effects of the calcimimetics on the cardiovascular diseases in patients undergoing dialysis and on the serum PTH levels in secondary hyperparathyroidism patients receiving hemodialysis.





- What are the main mutations in G protein and GPCR in human diseases of the extracellular Ca^{2+} metabolism, based on the data presented by the speaker?
- What are the main errors leading to the mutation in G proteins and GPCR in endocrine disease?
- What's about the model of the human extracellular Ca^{2+} receptor, presented by the speaker?
- What's about the CaSR structure from the speaker point of view?
- What's about the CaSR and Glutamate Receptor-like GPCR phylogeny presented by the speaker?

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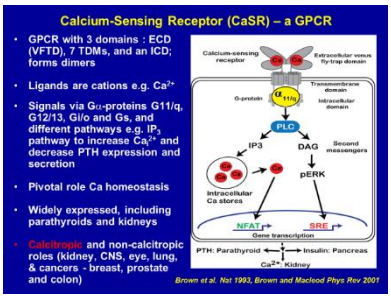
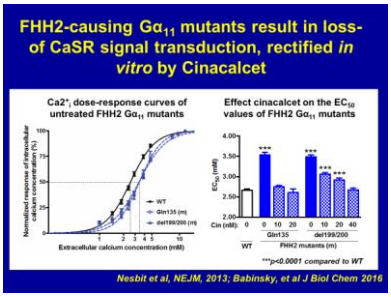
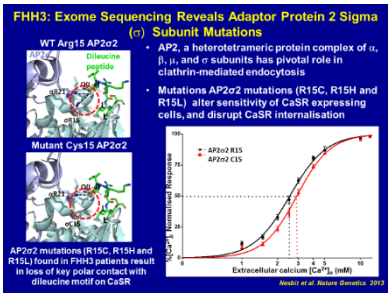
CaSR signalling pathways and hypercalcemia in humans



CaSR signalling pathways and hypercalcemia in humans, was the topic discussed by Prof. Thakker. The speaker, coming from Oxford (UK), presented very interesting data on CaSR and its calcitropic and non-calcitropic role. Going deeper in his lecture, Prof. Thakker spoke about the seven calcitropic disorders linked to CaSR and more in particular presented very interesting experimental data on one syndrome, the familial hypocalciuric hypercalcemia divided into three forms the FHH1, 2 and 3. The speaker spent the main part of his presentation in describing the main genetic defects leading to these three disorders, thanks to very interesting experimental data given by animal and in vitro studies. Finally, Prof. Thakker presented very impressive data on the effect of Cinacalcet on the CaSR signal transduction and on the serum calcium levels in FHH3 patients. In conclusion, the speaker pointed out that Cinacalcet has the potential to rectify the signalling defects due to FHH2 and FHH3 associate mutations.





- What are the seven calcitropic disorders due to CaSR mutations, based on the data presented by the speaker?
- What are the calcaemic disorders due to loss of function CaSR mutations?
- What is the calcaemic disorder due to the gain of function CaSR mutations?
- What is the mutation responsible for the onset of the FHH2, based on the data presented by the speaker?
- What is the mutation responsible for the onset of the FHH3, based on the data presented by the speaker?
- What are the GNA11 mutations identified in FHH2 patients presented by the speaker?
- What is the effect of Cinacalcet on calcaemia in FHH2 proband with Phe220Ser $G\alpha_{11}$?
- How many FHH patients have CaSR mutations, based on the data presented by the speaker?

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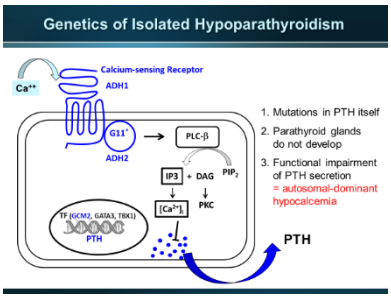
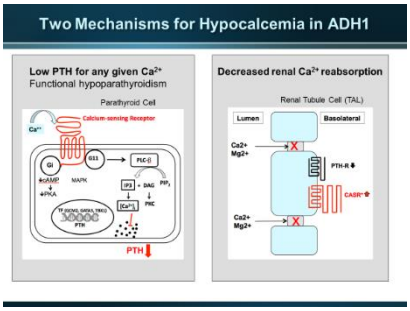
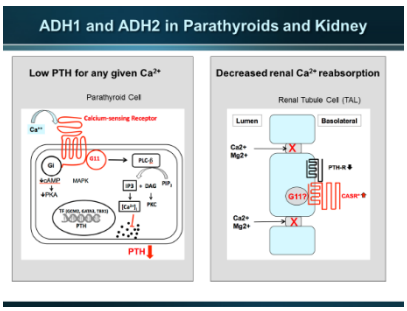
CaSR and Gα11 in hypoparathyroidism in humans



Prof. Mannstadt from Boston (USA), spoke about CaSR and Gα11 in hypoparathyroidism in humans, by presenting very interesting data on PTH as the principal regulator of serum calcium through the intervention of bone and kidney. Going deeper in his lecture, Prof. Mannstadt spoke about the genetics of isolated hypoparathyroidism and more in particular on ADH1 that is the autosomal-dominant hypocalcaemia 1 due to CaSR mutations. The first part of his lecture was spent in presenting very interesting experimental data on this familial disease, its causal mutations and the pathophysiologic mechanisms responsible for the hypocalcaemia and finally on its management. In the second part of his lecture, Prof. Mannstadt talked about ADH2 the autosomal-dominant hypocalcaemia and presented very interesting experimental data on the main mutations responsible for the onset of this disease, like the Gα11 or the S211W. Finally, the speaker presented other data on three main unanswered questions on the role of G11 in the renal tubular function of the CaSR, on the biochemical mechanisms leading to gain of function of the mutated Gα11 and on the reason for the involvement of the parathyroids only, despite the ubiquitary of Gα11.





- What are the main diseases associated with the Gα protein, based on the data presented by the speaker?
- What are the effects of ADH1 and ADH2 in the parathyroids and the kidney?
- What are the main oncogenic mutations secondary to ADH mutations presented by the speaker?
- What's about PTH for the treatment of ADH1 patients, based on the data presented by the speaker?
- What are the two main mechanisms leading to hypercalcaemia in ADH1 patients?

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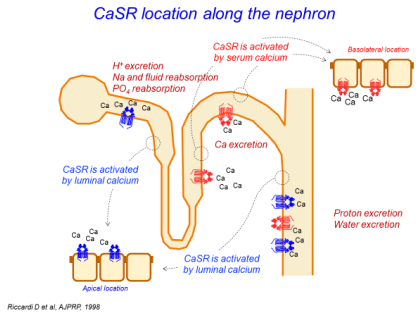
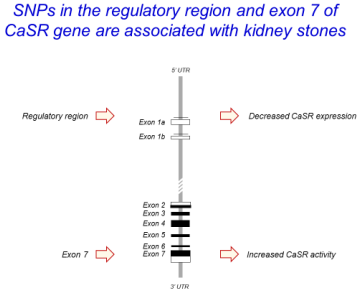
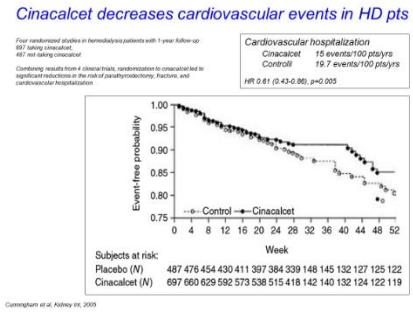
Kidney disorders



The Kidney disorders, was the topic discussed by Dr. Vezzoli from Milan (IT), more in particular the speaker presented very interesting data on the CaSR expression in the human kidney. Going deeper in his lecture, Prof. Vezzoli talked about CaSR and its effects on glomerular cells and nephrons and presented very interesting experimental data given by animal studies aiming to identify the CaSR location along the nephron and its effects. In the main part of his lecture, the speaker talked about the role played by CaSR in the kidney regulation of calcium at the tubular and glomerular level. Prof. Vezzoli presented also data on CaSR mutations in patients affected by calcium nephrolithiasis, by highlighting that many of these mutations are associated with the kidney stone formation. In the second part of his presentation, the speaker talked about the renal mechanisms leading to stones formation and the role played by CaSR, by highlighting that the risk of calcinosis at the interstitial level raises in case of its decreased expression and on the contrary, in case of increased CaSR activity is the risk of stone formation to be increased. Finally, Prof. Vezzoli talked about the relationship between CaSR activity at the vascular level and the risk of CVD and presented very impressive data on the inhibitory effect of cinacalcet against the calcification progression in hemodialysis patients. In conclusion, the speaker pointed out that CaSR plays a key role for the kidney contribution in the calcium homeostasis.





- What's about the effects of calcimimetics on the tissue calcification, based on the data presented by the speaker?
- What are the main mechanisms linking CaSR and the calcium stone production?
- What's about CaSR SNPs in patients affected by nephrolithiasis, based on the data presented by the speaker?
- What are the main mechanisms linking CaSR activity and the kidney calcium regulation?
- What are the main CaSR locations along the nephron?

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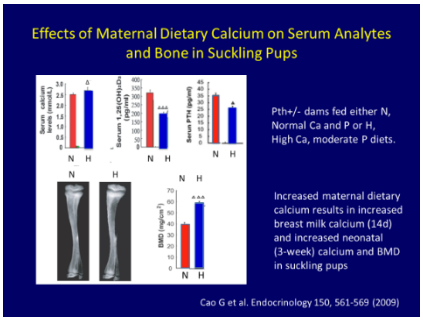
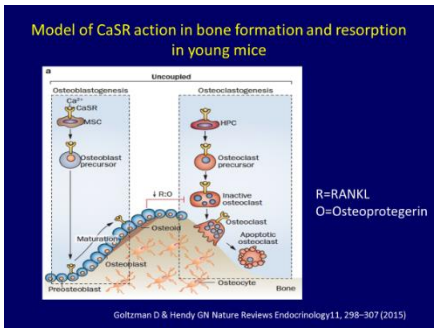
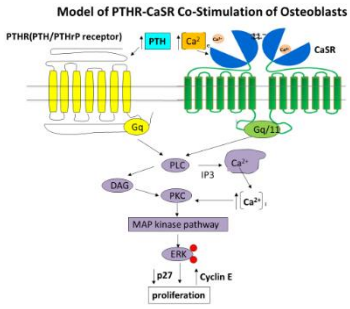
Bone diseases



Prof. Goltzman from Montrial (CND), spoke about bone diseases. At the beginning of his lecture, the speaker talked about the relationship between CaSR single nucleotide polymorphisms (SNPs) and the bone mineral density (BMD) suggesting that CaSR plays an important role not only in the human mineral homeostasis, but also in the skeletal homeostasis. Going deeper in his lecture, Prof. Goltzman presented very interesting experimental data given by animal studies on the CaSR effects on BMD in neonates and more in particular on the mediatory CaSR effect on the bone turnover induced by the dietary calcium in mice. In the main part of his lecture, the speaker presented very interesting and unpublished experimental data given by animal studies in adult mice aiming to investigate the interactions between CaSR and PTH on BMD through the osteoblast/osteoclast regulation. In conclusion, Prof. Goltzman pointed out that in young animals the CaSR activation enhances the osteoblast activity leading to the bone formation and inhibits osteoclasts and the bone reabsorption, but on the contrary in older animals, the osteoblast CaSR activation may increase the bone loss.





- What's about the main bone alterations in response to calcium acting via the CaSR, based on the data presented by the speaker?
- What are the CaSR effects in young and older mice, based on the data presented by the speaker?
- What's about the interaction between CaSR and the anabolic effects of intermittent PTH?
- What are the key points of the model explaining the CaSR activation in bone formation and resorption in adult mice, based on the data presented by the speaker?

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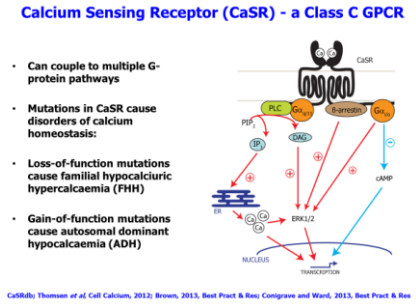
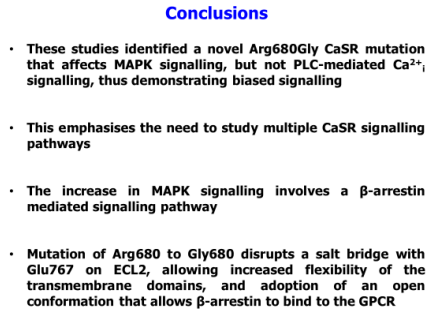
Studies of an autosomal dominant hypocalcemia Type-1 (Adh1) associated Calcium-sensing Receptor (CaSR) mutation, ARG680GLY, provides insights into biased signalling



Studies of an autosomal dominant hypocalcemia Type-1 (Adh1) associated Calcium-sensing Receptor (CaSR) mutation, ARG680GLY, provides insights into biased signalling, was the topic discussed by Dr. Gorvin in his talk. The speaker coming from Oxford (UK), presented very interesting data on the identification in two patients, father and son, affected by ADH of a novel CaSR mutation, identified as Arg680Gly and located within the transmembrane domain 3. Going deeper in her presentation, the speaker presented all the experimental data of these studies. More in particular Dr. Gorvin demonstrated that Arg680 Gly mutant has no effect on Ca^{2+} signalling, that CaSR Gly680 mutant activates MAPK signalling by a non-Gaq/11 pathway but not through a Gai/o pathway and finally, that Gly680 activates MAPK by a G-protein independent β-arrestin pathway. In conclusion Dr. Gorvin pointed out that these studies emphasise the need to study the multiple CaSR signalling pathways.



- What's about the methods of the functional analysis of Arg680Gly CaSR mutation presented by the speaker?
- What are the mechanisms by which Gly680 activates the β-arrestin-mediated MAPK pathway?
- What are the key points of the functional analysis of the MAPK pathway presented by the speaker?

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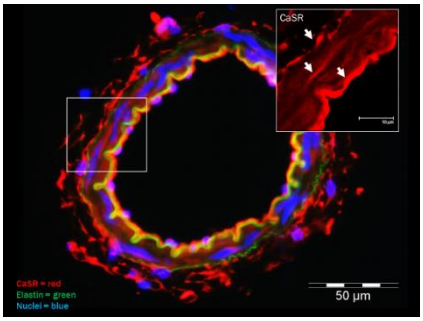
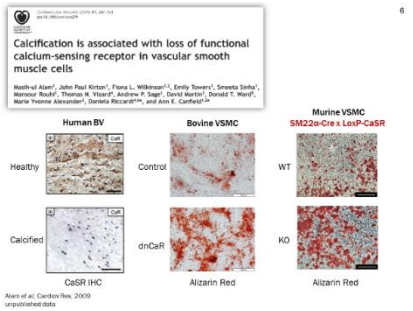
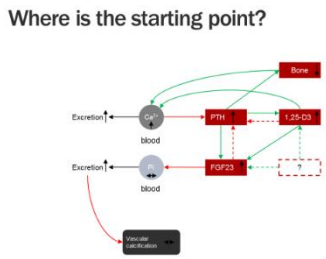
Altered mineral ion metabolism in a mouse model of targeted CaSR deletion from vascular smooth muscle cells



Dr. Schepelmann from Cardiff (UK), presented very interesting and impressive data on the altered mineral ion metabolism in a mouse model of targeted CaSR deletion from vascular smooth muscle cells. More in particular the speaker talked about the characterisation of his CaSR mouse model, through experiments on the smooth muscle tone, the vascular smooth muscle calcification and finally on the mineral ion dyshomeostasis. Going deeper in his lecture, Dr. Schepelmann presented very interesting data on CaSR at the vascular smooth muscle cells level in this specific mouse model. In the main part of his presentation, the speaker talked about the CaSR modulation of the smooth muscle tone, the ex vivo and in vivo calcification processes, the Ca^{2+} /Pi metabolism at the blood, urine and bone levels. In the second part of his talk, Dr. Schepelmann presented very interesting data on the CaSR effect in the kidney and in the parathyroid glands. In conclusion, the speaker pointed out that these data for the first time connect the body Ca^{2+} homeostasis to the vascular smooth muscle function via a yet unknown mechanism.





- What is the mouse model developed by the speaker?
- What are the relationships between calcification and the loss of functional CaSR in the vascular smooth muscle cells?
- What's about the Ca^{2+}/Pi metabolism, based on the data presented by the speaker?
- What is the starting point between bone, kidney and smooth muscle cells on the Ca^{2+}/Pi metabolism from the speaker pint of view?

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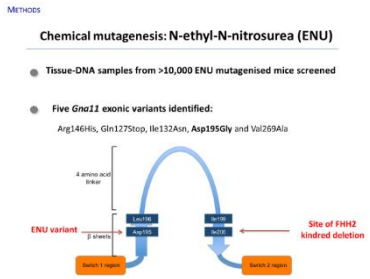
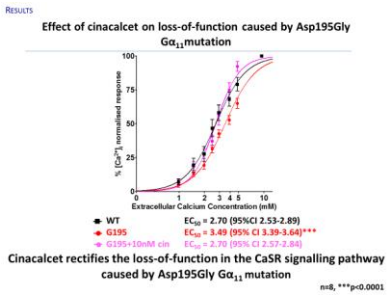
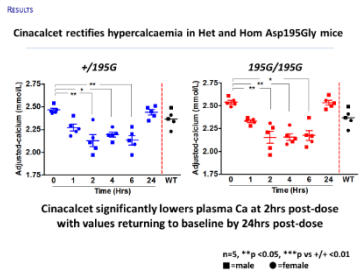
Mice with an inactivating ASP195GLY mutation in G-protein Subunit Alpha-11 (Gα11) are a model for familial hypocalciuric hypercalcaemia type 2 (FHH2)



The main topic at the core of Dr. Howles presentation, was "Mice with an inactivating ASP195GLY mutation in G-protein Subunit Alpha-11 (Gα11) are a model for familial hypocalciuric hypercalcaemia type 2 (FHH2)". The speaker, coming from Oxford (UK), presented very interesting data on FHH and its relationship with CaSR, by highlighting that till now no mouse model has been developed for studying FHH2. Going deeper in her lecture, Dr. Howles presented very interesting data on a new innovative mouse model of FHH2 and on the assessment of the in vivo efficacy of cinacalcet in the FHH2 syndrome. In the main part of her lecture, the speaker talked about the methods used for the generation of this new mouse model and presented her experimental data on the chemical mutagenesis. Dr. Howles spoke also about the in vitro studies designed for assessing the efficacy of cinacalcet in rectifying well identified signalling defects and about the in vivo studies and the effects of cinacalcet on the calcium and PTH plasma levels, on the urinary calcium excretion and finally on the DEXA bone studies. In conclusion, Dr. Howles pointed out that cinacalcet in her FHH2 new mouse model demonstrated to rectify the hypercalcaemia in Asp195Gly mutant mice.





- What's about the Chemical mutagenesis for the generation of the new mouse model of FHH2, based on the data presented by the speaker?
- What's about the effect of cinacalcet on the loss of function caused by the Asp195Gly mutation on the CaSR signalling presented by the speaker?
- What's about the in vivo effect of cinacalcet in rectifying hypercalcaemia in Asp195Gly mutant mice, based on the data presented by the speaker?

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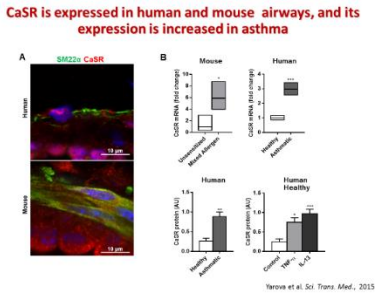
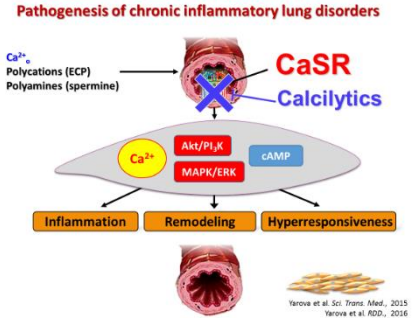
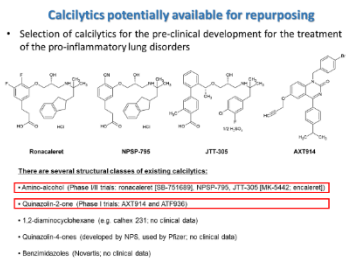
Towards the repurposing existing clinical-grade calcilytics for allergic asthma



The main topic at the core of Dr. Yarova presentation, was "Towards the repurposing existing clinical-grade calcilytics for allergic asthma". The speaker, coming from Cardiff (UK), presented very interesting data, starting from the burden of the chronic pro-inflammatory airway diseases and the unmet clinical need for novel therapeutics for the treatment of these disorders.



Going deeper in her presentation, Dr. Yarova talked about CaSR and its increased expression in asthmatic patients, by highlighting its role in the pathogenesis of the chronic inflammatory lung disorders. In the main part of her talk the speaker presented very interesting data given by animal studies on the repurpose of the inhaled calcilytics for the treatment of asthma and COPD. More in particular the speaker talked about the efficacy and the potency of the calcilytics at the CaSR level, about their bronchodilatory effects in the animal trachea, about the formulation and the pharmacokinetics of inhaled calcilytics in mice and finally about the calcilytics effects on the airway hyper responsiveness and inflammation in a mouse model of asthma. In conclusion, Dr. Yarova pointed out that all the compounds tested in vivo models display a similar potency in preventing AHR and inflammation.



- What are the calcilytics compounds tested by the speaker?
- What are the main structural classes of existing calcilytics presented by the speaker?
- What's about the bronchodilatory effects of calcilytics in a mouse trachea presented by the speaker?
- What are the main characteristics of the pharmacokinetic of the inhaled calcilytics presented by the speaker?

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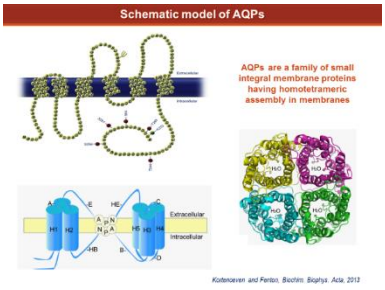
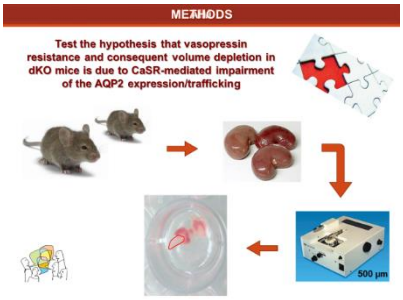
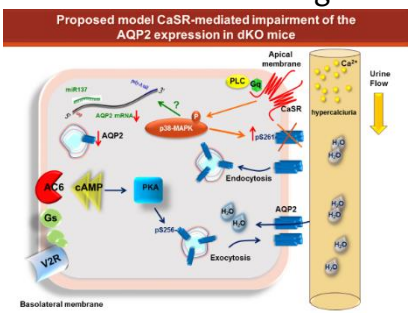
Novel CaSR- dependent microRNA pathway is involved in the downregulation of AQP2 expression contributing to volume depletion in Pendrin/Na-Cl cotransporter dKO mice



Dr. Ranieri from Bari (IT) spoke about "Novel CaSR-dependent microRNA pathway is involved in the downregulation of AQP2 expression contributing to volume depletion in Pendrin/Na-Cl cotransporter dKO mice". In her lecture, the speaker talked about the extracellular CaSR in the kidney and more in particular about the schematic model of AQPs. Dr. Ranieri presented very interesting data given by an experimental study running on dKO mice, with the intention to demonstrate a tight relationship between the CaSR impairment and the AQP2 expression/trafficking leading to the vasopressin resistance and volume depletion. In conclusion, the speaker pointed out that, based on her data, CaSR signaling in dKO mice reduces the AQP2 expression through the increase of its degradation via the increased pAQP2-ser2621 and through the activation of the miRNA.137 synthesis. The reduced expression of AQP2, leads to the volume depletion in dKO mice.





- What is the proposed model of the CaSR-mediated impairment of the AQP2 expression in dKO mice presented by the speaker?
- What's about the AQP2 expression in dKO mice presented by the speaker?
- What's about the CaSR and AQP2 interplay in the renal collecting duct, based on the data presented by the speaker?

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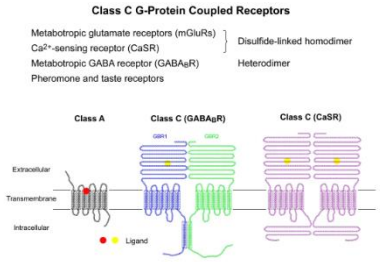
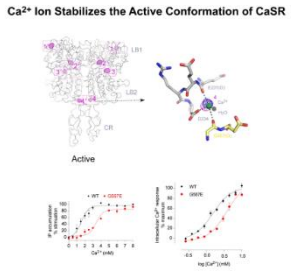
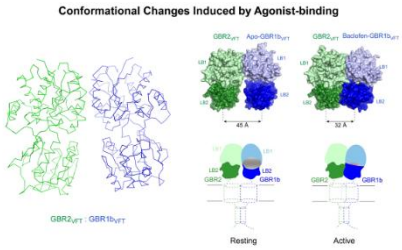
Crystal structure of CaSR



Crystal structure of CaSR was the topic at the core of Prof. Fan presentation. The speaker coming from New York (USA), at the beginning of her presentation talked about the extracellular CaSR function, its mechanism of action and the related diseases and drugs. Going deeper in her lecture, Prof. Fan raised three questions about the way of interaction of the receptor subunits in the formation of a dimer, the methods of recognition of the extracellular stimuli and finally about the pathways through which the receptors become activated upon agonist binding. All the lecture was spent by the speaker for presenting a huge amount of experimental data in order to answer to these three questions in a very comprehensive way. More in particular Prof. FAN spoke about the homodimer interface, the L-amino acid recognition, the Ca^{2+} binding sites, the anion binding sites, the agonist-induced conformational changes and finally about the activation mechanism of class C GPCRs.





- How do the receptor subunits interact to form a dimer?
- How does the receptor recognize the extracellular stimuli?
- How does the receptor become activated upon agonist binding?
- What's about the active structure of human CaSR extracellular domain, based on the data presented but the speaker?
- What are the main functions of CaSR?
- What are the main CaSR orthosteric agonists, based on the data presented by the speaker?

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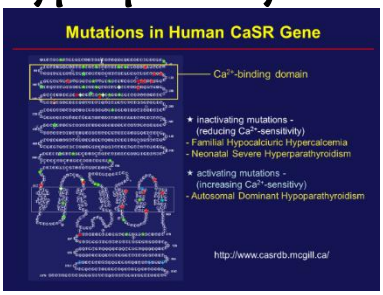
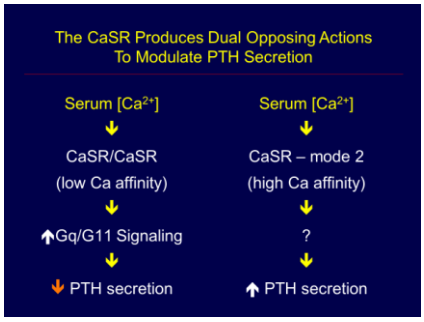
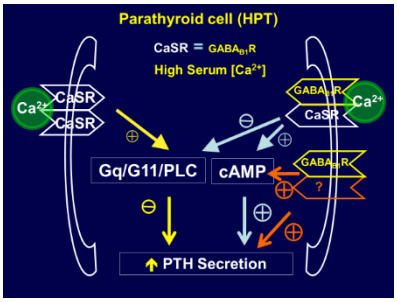
CaSR/GABAbR1 heteromers mediate PTH hypersecretion in hyperparathyroidism



CaSR/GABAbR1 heteromers mediating PTH hypersecretion in hyperparathyroidism was the topic at the core of Prof. Chang presentation. The speaker coming from San Francisco (USA), at the beginning of his presentation talked about the regulation of Ca^{2+} homeostasis in land vertebrates, by highlighting the inverse tight correlation between PTH secretion and Serum Ca^{2+} levels. Going deeper in his lecture, Prof. Chang talked about the main mutations in human CaSR gene leading to the familial diseases like the familial hypocalciuric hypercalcaemia, the neonatal severe hyperparathyroidism and the autosomal hypoparathyroidism. The speaker presented also data on the non-familial HPT like the parathyroid adenoma in primary HPT and the CKD-induced secondary and tertiary HPT. In the main part of his lecture, Prof. Chang, presented very interesting experimental data given by animal studies on an HTP mouse model, starting from biochemistries till the presentation of a parathyroid cell model explaining the complex mechanisms of the correlation between CaSR, Ca^{2+} GABA $_{B1}$R on the PTH secretion. In conclusion, the speaker pointed out that should be necessary to develop specific pharmaceutics targeting CaSR/$GABA_{B1}$R for the treatment of the parathyroid diseases characterized by PTH hypersecretion.





- How reduced CaSR expression does promote PTH secretion in the non-hereditary HPT, based on the data presented by the speaker?
- What is the HTP mouse model presented by the speaker?
- What are the actions of $GABA_{B1}$R in vivo, based on the data presented by the speaker?
- How does $GABA_{B1}$R impact on the CaSR signalling, based on the data presented by the speaker?
- Could PTCs expressing GABAB1R alter the CaSR signalling responses and the PTH secretion?

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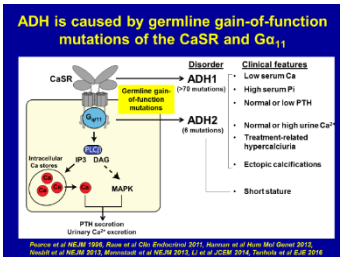
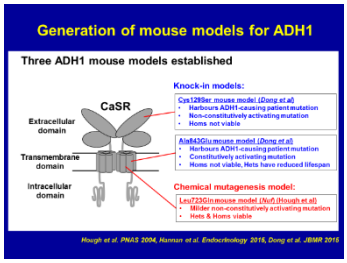
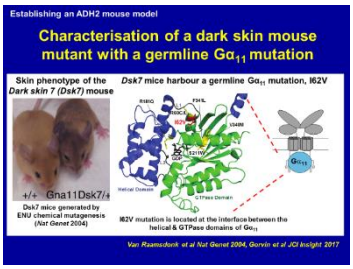
Mouse models for ADH1 and ADH2



Mouse models for ADH1 and ADH2 was the topic at the core of Prof. Hannan presentation. The speaker coming from Liverpool (UK), talked about the main autosomal dominant hypocalcaemia (ADH) mouse models, the calcitropic and non-calcitropic phenotypes and finally, about an evaluation of the therapies for ADH. Going deeper in his lecture, Prof. Hannan presented many experimental data on ADH, its two forms and its mouse models for ADH1 and ADH2. In the main part of his lecture, Prof. Hannan talked also about therapy, by presenting very interesting data on the calcilytic drugs that have the potential to correct the molecular defects causing ADH1 and ADH2, like NPS-214. In conclusion, the speaker pointed out that these mouse models have also shown the potential of calcilytic therapies for patients affected by ADH1 and ADH2.





- Why is it necessary to study mouse models for ADH?
- What is the effect of NPS-2143 in the mouse model for ADH1, based on the data presented by the speaker?
- What are the main calcitropic phenotype of ADH2 mouse models presented by the speaker?
- What are the established ADH1 mouse models presented by the speaker?

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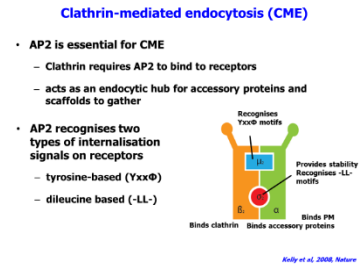
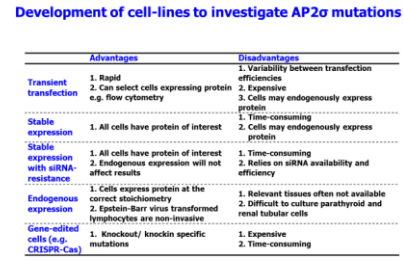
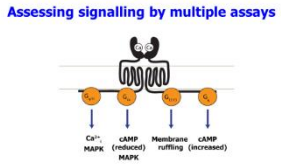
Stable cell lines expressing adaptor protein 2 mutations to investigate signalling pathways



The Stable cell lines expressing adaptor protein 2 mutations to investigate signalling pathways was the topic Dr. Gorvin talked about. The speaker coming from Oxford (UK), talked about the CaSR signalling pathways and the role played by AP2 in endocytosis and FHH3, about the approaches to assess signalling and trafficking using cell-lines and finally about the effects of AP2 mutations on signalling and trafficking. Going deeper in her talk, Dr. Gorvin presented very interesting experimental data on CaSR signalling through multiple pathways, the role played by AP2 in the clathrin-mediated endocytosis and the effects of FHH3 mutations on the AP2 Arg 15 residue. In the main part of his presentation, the speaker talked about the development of cell-lines for the investigation of the AP2 mutations thanks to many experimental data given by her animal studies. Finally, Dr. Gorvin presented very interesting data on the effects of the AP2 mutations on signalling and trafficking, by highlighting that AP2 mutants impair CaSR mediated signalling.





- What are the multiple pathways of CaSR signals, based on the data presented by the speaker?
- What are the cell-lines development methods presented by the speaker?
- What are the key topics presented by the speaker in the summary of the signalling and trafficking studies?

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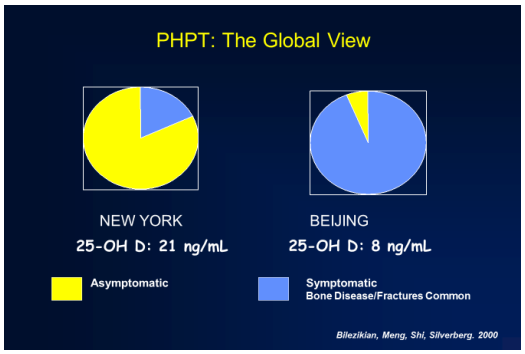
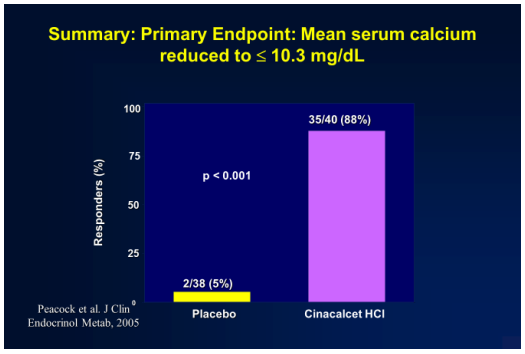
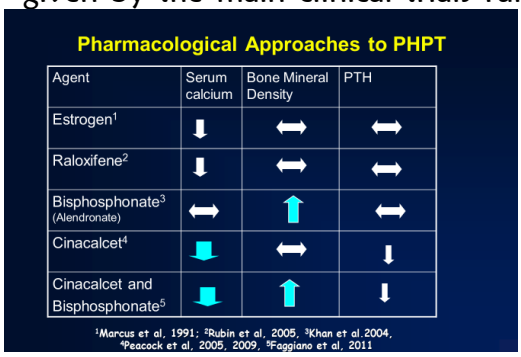
Primary hyperparathyroidism



Primary hyperparathyroidism was the topic Prof. Bilezikian talked about. The speaker coming from New York (USA), at the beginning of his lecture, highlighted that the primary hyperparathyroidism before 1970 was considered a disease of bone, stones and groans, but after 1970 a disease with primarily biochemical and densitometric signatures. Going deeper in his talk, Prof. Bilezikian presented very interesting data on the emergence of the asymptomatic primary HPT, by highlighting the role played by simple biochemical screening tests and spoke about the so called "subsequent dilemma" basically characterized by the need to understand which patients need and do not need surgery. In the main part of his lecture, the speaker presented the 2014 guidelines for surgery in asymptomatic HPT patients and the non-surgical options, by highlighting the central role played by Vit D deficiencies leading to the switch from asymptomatic to symptomatic disease. In the second part of his lecture, Prof. Bilezikian talked about the pharmacological options to be applied in patients with low bone density and high serum calcium levels. More in particular the speaker presented very interesting data given by the main clinical trials running in PHTP and parathyroid cancer patients, on the principal drugs approved for the treatment of PHPT like estrogen, raloxifene, bisphosphonates, denosumab, cinacalcet and the combination therapy. In conclusion, Prof. Bilezikian pointed out that the pharmacological approaches to the management of the hypercalcaemia and the reduced BMD in PHTP patients are available and effective in those patients which do not have the indication for parathyroid surgery.





- What are the key points of the pharmacological approaches to PHPT?
- What's about the cinacalcet experience in PHTP patients, based on the data presented by the speaker?
- What is the effect of cinacalcet in parathyroid cancer patients?
- What's about the effects of denosumab in PHTP patients, based on the data presented by the speaker?
- What's about bisphosphonates in PHPT patients
- What are the ideal characteristics of the best drug to be used in PHTP patients, based on the data presented by the speaker?

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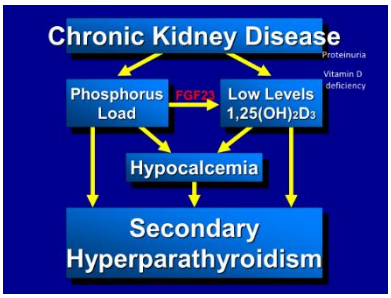
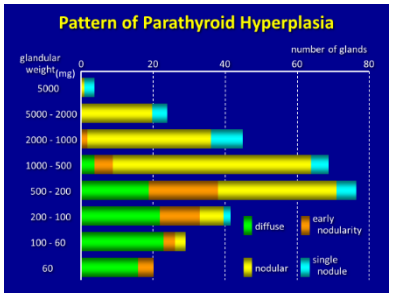
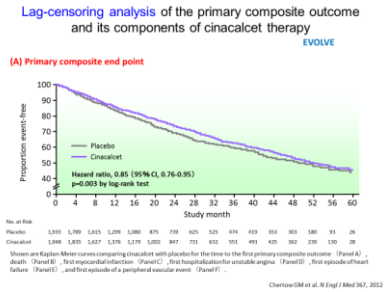
Secondary hyperparathyroidism



Prof. Fukagawa talked about Secondary hyperparathyroidism. The speaker coming from Isehara (J), introduced his talk, by highlighting the deep relationship between CKD, mineral and bone disorders leading to CVD, fractures and mortality through the onset of vascular calcifications, bone and laboratories abnormalities. Prof. Fukagawa talked about the control of the PTH levels in CKD patients and about the pathogenesis and the treatment of secondary HPT patients also affected by CKD. The speaker presented also very interesting data on bone turnover, the control of Pi and Ca^{2+}, the progression of the parathyroid hyperplasia and finally on survival. In the main part of his presentation, the speaker talked about a model leading to the onset of the secondary HPT in CKD patients and about the strategies for controlling the high PTH levels. Finally, Prof. Fukagawa presented very interesting experimental data on the intravenous vit. D receptors activators and on calcimimetics.





- How to control high PTH levels, from the speaker point of view?
- What's about the efficacy of the intravenous vit. D receptor activators, based on the data presented by the speaker?
- What's about the unmet needs for new calcimimetics from the speaker point of view?
- What's about the control of PTH by calcimimetics from the speaker point of view?
- How to prevent high PTH level, from the speaker point of view?
- What are the PTH targets recommended by the professional organizations guidelines?

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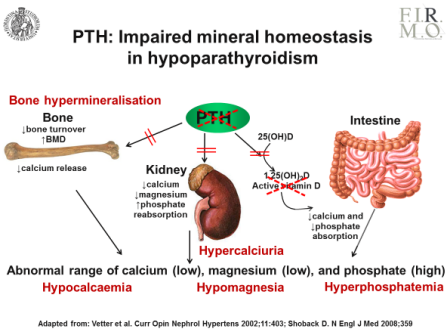
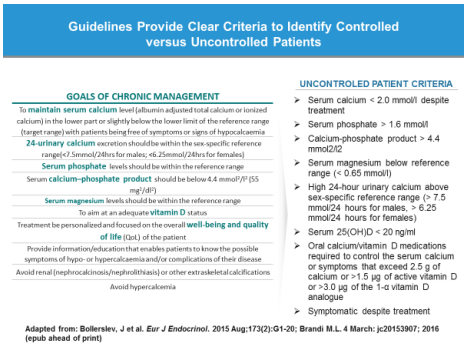
Hypoparathyroidism

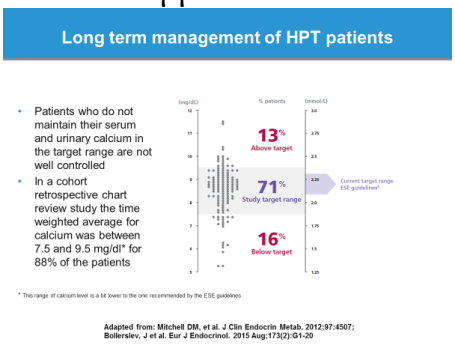


Adapted from: Vetter et al. Curr Opin Nephrol Hypertens 2002;11:403; Shoback D. N Engl J Med 2008;359

Hypoparathyroidism was the topic at the core of Prof. Brandi presentation. The speaker coming from Florence (IT), spoke about the acquired and the idiopathic hypoparathyroidism. Going deeper in her lecture, Prof. Brandi presented very interesting data on the pathophysiology of hypoparathyroidism, by highlighting the effects on bone, kidney and GUT metabolism due to the PTH deficiency. More in particular prof. Brandi pointed out that these patients are treated only with calcium and vit.D supplementations and in many cases it is a very therapeutic challenge to maintain normal serum calcium levels with these tools. In the main part of her talk, the speaker presented very interesting data on the acute symptoms and long-term complications affecting hypoparathyroidism patients and on the 2015 guidelines for the management of chronic hypoparathyroidism, by highlighting that these guidelines provide clear criteria for identifying controlled versus uncontrolled patients. Finally, Prof. Brandi talked about the new full-recombinant replica of the endogenous parathyroid hormone approved for the treatment of hypoparathyroidism patients not well-controlled with calcium and vit. D supplementation and presented very interesting data given by the clinical trials running in patients treated with these new compounds. Finally, the speaker talked about the treatment for patients affected by the autosomal dominant hypocalcaemia and presented preliminary data on PC0371 that is an orally active small molecule PTHR1 agonist identified as a potential new treatment option for the PTH related disorders.



Adapted from: Bollerslev, J et al. *Eur J Endocrinol.* 2015 Aug;173(2):G1-20; Brandi M.L. 4 March: jc20153907; 2016 (epub ahead of print)



Adapted from: Mitchell DM, et al. J Clin Endocrin Metab. 2012;97:4507; Bollerslev, J et al. Eur J Endocrinol. 2015 Aug;173(2):G1-20

- What are the structures of the main calcilytic compounds and their potential use in the autosomal dominant hypocalcaemia?
- What are the main key points of the 2015 guidelines for the management of chronic hypoparathyroidism?
- What are the therapeutic considerations on the hypoparathyroidism treatment from the speaker point of view?
- What's about the impaired mineral homeostasis in hypoparathyroidism presented by the speaker?
- What are the main acute symptoms and the long-term complications affecting the hypoparathyroidism patients, based on the data presented by the speaker?

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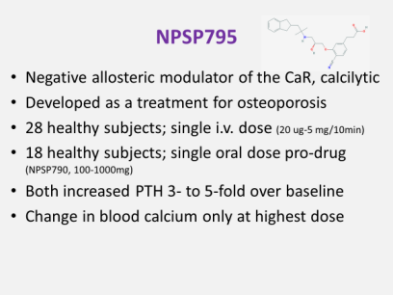
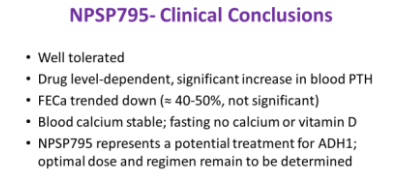
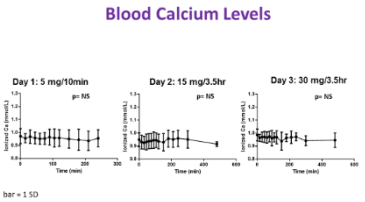
Treatment for ADH1 in humans





Prof. Collins talked about the treatment for ADH1 in humans. The speaker coming from Bethesda (USA), presented very interesting data on NPSP795 that is a calcilytic compound developed for the treatment of ADH1 and actually under study. More in particular Prof. Collins spoke about this compound and its first data produced in a pharmacokinetic study aiming to its repurpose for the treatment of ADH1 patients. Prof. Collins highlighted that NPSP795 was well tolerated, with a significant increase in blood PTH, drug-level dependent and a stable blood calcium level. In conclusion, the speaker pointed out that NPSP795 represents a potential treatment for ADH1 patients, but further tests are needed for assessing the doses and the variability of the effects.



- What are the key points of the calcilytic drug development presented by the speaker?
- What's about the study overview?
- What are the main inclusion and exclusion study criteria?
- What's about the clinical and in vitro study design presented by the speaker?
- What are the main characteristics of the enrolled patients?
- What are the main NPSP795 clinical conclusions presented by the speaker?

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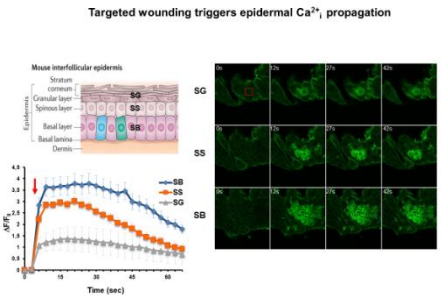
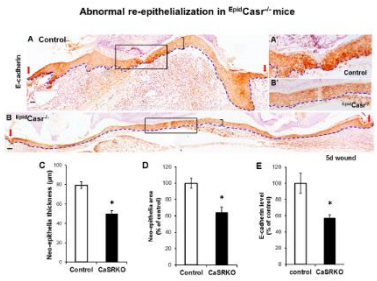
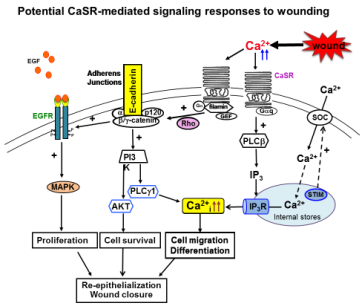
Role of CaSR in skin wound healing



The role of CaSR in skin wound healing was the topic Prof. Ling Tu talked about. The speaker coming from San Francisco (USA), introduced her talk by presenting the epidermal functions regulated by the calcium signals and the calcium-dependent signaling in epidermal keratinocytes CaSR controlled. Going deeper in her lecture Prof. Ling Tu presented many experimental data demonstrating the deep correlation between CaSR and E-cadherin in the nascent epithelium. In the main part of her lecture, the speaker proposed a very innovative model explaining the potential CaSR-mediated signalling responses to wounding, by highlighting the key role played by CaSR in the re-epithelialization processes. Prof. Ling Tu presented also other data demonstrating that the inhibition of CaSR expression blocks the formation of the adherence junctions and the actin-cytoskeletal reorganization and supresses the $Ca^{2+}i$ propagation after wounding. Finally, the speaker presented very interesting data on the treatment and more in particular on the effect of calcimimetic, that is a CaSR activator, on the $Ca^{2+}i$ propagation. In conclusion, Prof. Ling Tu pointed out that Calcimimetic enhances CaSR-mediated $Ca^{2+}I$ response and E-cadherin signaling and accelerates the wound closure.





- What's about the opposite effects of calcimimetics and calcilytics on the wound closure, based on the data presented by the speaker?
- What are the key points of the potential CaSR-mediated signalling responses to wounding, presented by the speaker?
- What are the main controls performed by CaSR on the calcium-dependent signalling in the epidermal keratinocytes?
- What are the main epidermal functions regulated by the Calcium signals?

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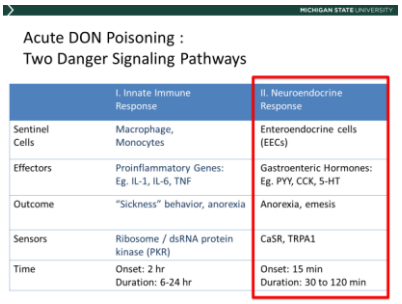
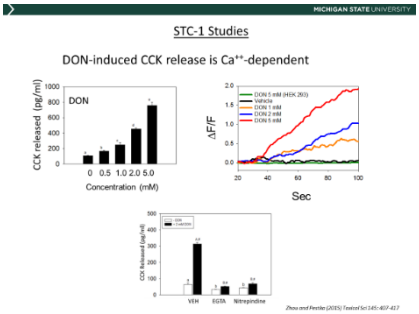
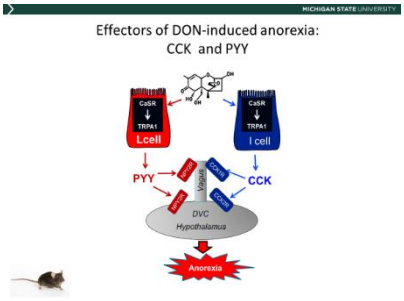
Control of gastroenteric hormones by CaSR



Control of gastroenteric hormones by CaSR was the topic presented by Prof. Pestka. The speaker coming from East Lansing (USA), talked about deoxynivalenol (DON) a fungal toxin contaminating wheat, barley and corn that causes anorexia and vomiting, regulated by FDA. Going deeper in his lecture, Prof Pestka, presented very interesting data on the DON mechanism of action leading to anorexia and emesis, by highlighting the role played by specific GUT hormones like PYY, CCK and 5-HT as effectors and the role played by CaSR and TRPA1 as sensors. In the main part of his lecture, the speaker talked about the enteroendocrine cells (EEC) as regulators of the post-meal homeostasis and their interactions with the effectors, CCK and PYY for anorexia and PYY and 5-HT for emesis. In the second part of his talk Prof. Pestka presented very interesting experimental data on the role of STC-1 cells-murine neuroendocrine tumor line and CaSR-transfected HEK 293 cells through which DON induces the hormones release from EECs. Based on these data the speaker was able to present a very interesting biological model. Finally, the speaker presented in vivo experimental data demonstrating the presence of the same mechanisms on CaSR and TRPA1 DON induction shown in the in vitro studies. In conclusion, Prof. Pestka pointed out that DON causes anorexia and vomiting by eliciting the GUT hormone secretion.





- What is the deoxynivalenol (DON), based on the data presented by the speaker?
- How does DON cause anorexia and emesis?
- How does DON induce hormone release from EECs?
- Can in vitro findings for CaSR and TRPA1 be verified in vivo?

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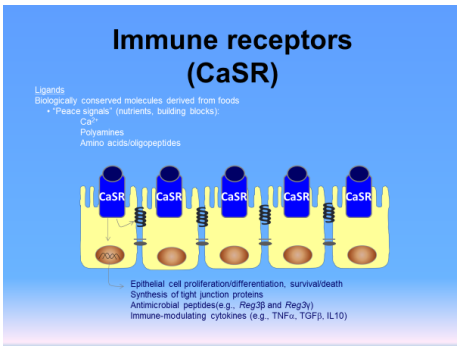
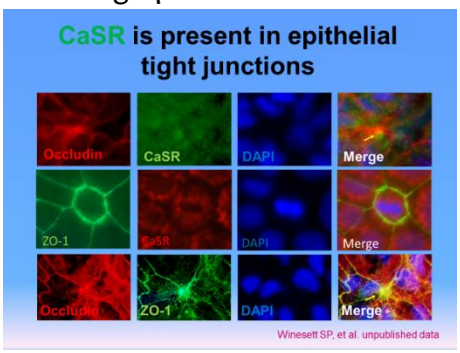
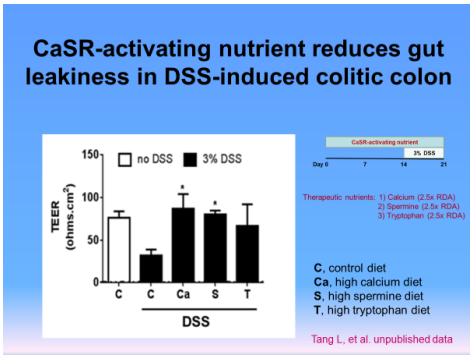
The role of the CaSR in gastrointestinal inflammation



Prof. Cheng talked about the role of the CaSR in the gastrointestinal inflammation. The speaker coming from Gainesville (USA), presented very interesting data on the intestinal CaSR function as an immune receptor and on the anti-inflammatory potential of CaSR agonists. Going deeper in his lecture, Prof. Cheng spoke about the role played by CaSR for the integrity of the intestinal barrier function, by highlighting that Ca^{2+} is required for the stabilization of the epithelial tight junctions. In the main part of his lecture, Prof. Cheng presented very interesting experimental data demonstrating that CaSR is present in the epithelial tight junctions and its relevant role in the TJ protein distribution to the plasma membrane. The speaker demonstrated also that CaSR deficiency alters the TJ mRNA expression leading to the GUT microbe imbalance. Finally, Prof. Cheng presented very interesting data on the therapeutic anti-inflammatory potentials of CaSR agonists. In conclusion, the speaker pointed out that his data suggest a new paradigm for the regulation of the intestinal immune homeostasis where CaSR modulates the intestinal permeability and the immune responses.





- What are the main characteristics of the CaSR agonists presented by the speaker?
- Does the defect in epithelial CaSR signalling lead to GUT microbe imbalance, based on the data presented by the speaker?
- How does intestinal CaSR contribute to the intestinal barrier function integrity?
- Does the intestinal CaSR function influence the GUT immune responses?

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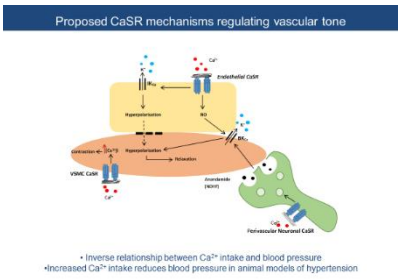
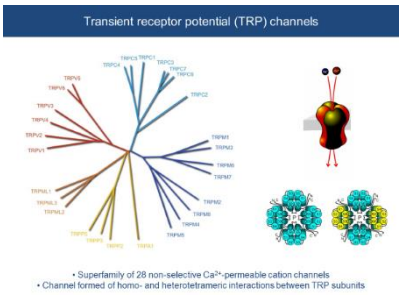
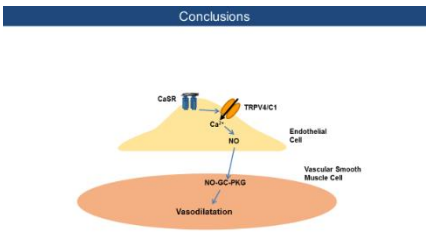
Nitric oxide signalling mediates CaSR-induced vasodilatations



Nitric oxide signalling mediates CaSR-induced vasodilatations was the topic Prof. Greenberg talked about. The speaker coming from London (UK), presented very interesting data on CaSR and its signalling in vascular smooth muscle cells, perivascular neurones and endothelial cells. Going deeper in his lecture, Prof. Greenberg talked about the CaSR mechanisms that regulate the vascular tone, by presenting very interesting experimental data on the underlying CaSR-induced mechanisms. In the main part of his lecture, the speaker talked about the way CaSR stimulation produce an endothelium dependent vasodilation and about the possible role of nitric oxide in this process and presented very interesting experimental data demonstrating that CaSR stimulation induces N0 synthesis in the endothelial cells through the activation of heteromeric TRPV4/C1 channels. Finally, Prof. Greenberg spoke about the possibility that these mechanisms are also functionally expressed in freshly isolated mouse arterial cells. In conclusion, the speaker pointed out that the vessel vasodilation is mediated through the stimulation starting from CaSR and involves NO.





- How does the CaSR stimulation produce an endothelium dependent vasodilations?
- How does CaSR stimulation produce NO?
- Are CaSR responses impaired in TRPC1-/- mice lacking heteromeric TRPV4/C1 channels?
- Are homomeric TRPV4 channels also functionally expressed in freshly isolated MAECs?

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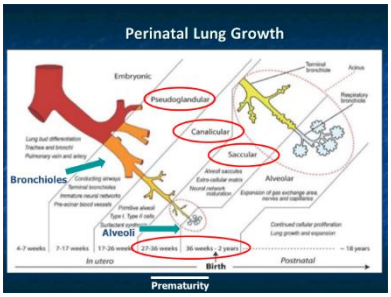
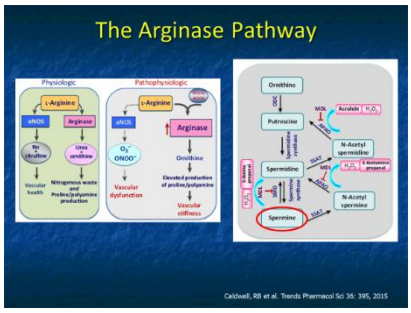
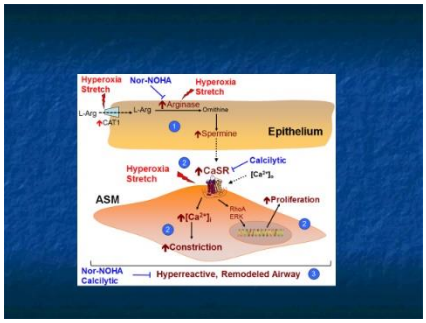
Calcium sensing receptor in perinatal airway disease



Calcium sensing receptor in perinatal airway disease was the topic Prof. Prakash talked about. The speaker coming from Rochester (USA), presented very interesting data on the main functions of CaSR. Going deeper in his presentation, Prof. Prakash talked about Prematurity, and the bronchopulmonary dysplasia, by highlighting that the major short-term and long-term problem for survivors of the prematurity period remains the chronic bronchial airway disease. In the main part of his lecture, the speaker presented very interesting data on the perinatal lung growth, on oxygenation and ventilation in premature babies, the use of CPAP with hyperoxia and on the way babies can develop asthma through CPAP use. Prof. Prakash presented very interesting data, demonstrating that polycations like Arginine, Spermine and Lysine, all of them truly CaSR agonists, are markers of the asthma severity. In the second part of his lecture, the speaker talked about human and animal models and presented very interesting experimental data demonstrating that hyperoxia and CPAP cause airways remodeling and that smooth muscle CaSR is involved in the hyperoxia and CPAP effects. In conclusion, Prof. Prakash pointed out that targeting CaSR in perinatal period may help in alleviating the unfortunately necessary insults of the ICU.





- What are the causes that determine the bronchial disease initiation and progression in case of prematurity?
- Can early interventions prevent or decrease disease, later in life?
- What are the models presented by the speaker for studying the fetal airway tissues?
- What's about CaSR in neonatal airways?
- What's about polycations and asthma from the speaker point of view?

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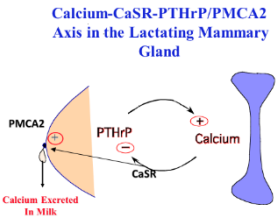
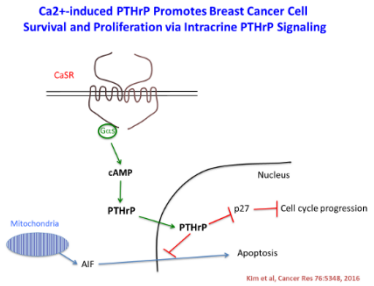
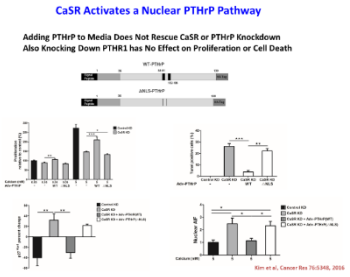
CaSR actions on PTHrP in breast cancer



CaSR actions on PTHrP in breast cancer, was the topic Prof. Wysolmerski talked about. The speaker coming from New Haven (USA), presented very interesting data on the calcium-CaSR-PTHrP/PMACA2 axis in the lactating mammary gland. Going deeper in his lecture, Prof. Wysolmerski spoke about the tight inverse correlation between CaSR and PTHrP production, by taking care of the central role played by PTHrP for lactating. In the main part of his lecture, Prof. Wysolmerski talked about the hypothesis that the dysregulation of CaSR-PTHrP axis contributes to the pathogenesis of breast cancer and especially bone metastases, by presenting very impressive experimental data on the relationship between CaSR, PTHrP and the cell in vitro and in vivo proliferation in breast cancer cells. In the second part of his lecture, the speaker presented new experimental data on the possibility that blocking CaSR- PTHrP axis, can prevent the in vivo development of bone metastases.





- Can the dysregulation of the CaSR-PTHrP Axis contribute to the pathogenesis of breast cancer especially of bone metastases?
- Does CaSR affect breast cancer proliferation in vivo?
- Will blocking CaSR-PTHrP axis impede the development of bone metastases in Vivo?
- Will blocking CaSR-PTHrP axis sensitize to DNA-damaging agents?
- How does nuclear PTHrP affect the nuclear accumulation of AIF?

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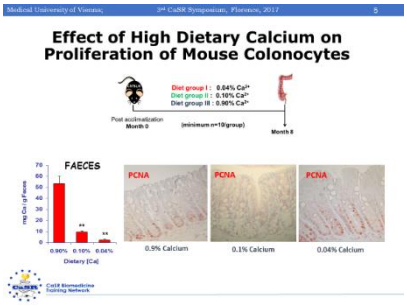
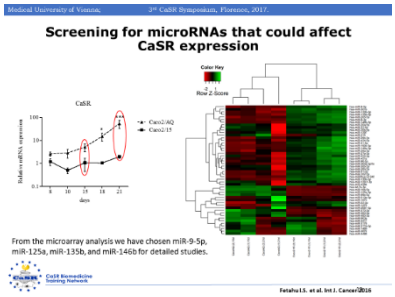
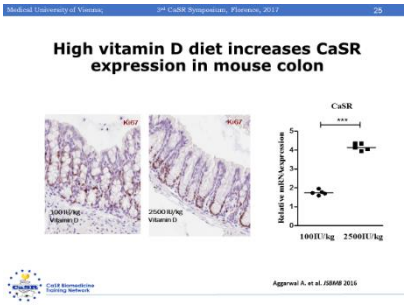
The role of CaSR in colon cancer



The role of CaSR in colon cancer was at the core of Prof. Kállay presentation. The speaker coming from Vienna (A), talked about the factors that cause loss of CaSR in the colorectal tumours, the role of CaSR in colon cancer cells, the means of restoring CaSR expression and finally about the cross-talk between CaSR and Vit. D in colon cancer cells. Going deeper in her lecture, Prof. Kállay presented very interesting data on the inverse correlation between the colon cells proliferation and the levels of the calcium intake. The speaker talked also about the inverse correlation between CaSR and colon cells proliferation, differentiation and apoptosis. In the main part of her lecture, Prof. Kállay presented very interesting experimental data on the inverse correlation between CaSR and the colon cancer cells, demonstrating that the CaSR over-expression inhibits the cancer stem cell-like phenotype in the colon cancer cells. In the last part of her presentation Prof. Kállay spoke about the ways to restore the expression of CaSR and presented very impressive data on the factors that affect the CaSR expression and more in particular on the Vit. D diet intake and its direct correlation with the CaSR expression. In conclusion, the speaker pointed out that vit. D and some cytokines are able to restore CaSR expression and that vit. D and calcium have the potential to reduce the risk of the colon rectal cancer.





- Why is CaSR lost in colon cancer cells?
- What is the role of t CaSR in colon cancer cells?
- What are the ways to restore the expression of CaSR?

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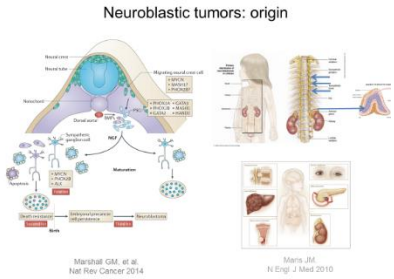
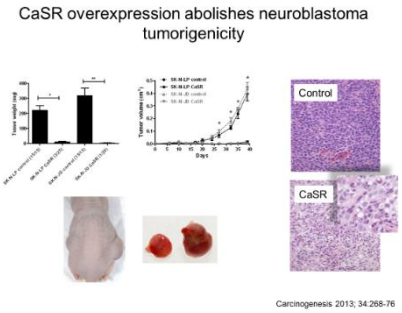
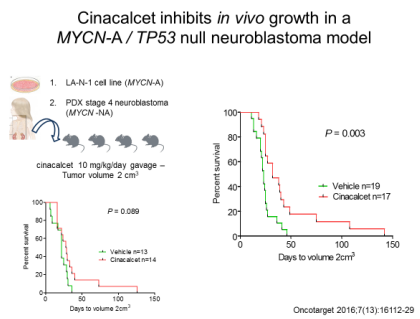
The role of the CaSR in neuroblastoma



Prof. de Torres, talked about the role of CaSR in neuroblastoma. The speaker coming from Barcelona (E), presented very interesting data on neuroblastic tumors origin, clinical findings, treatment and on CaSR in neuroblastic tumors. Going deeper in her lecture, Prof. de Torres presented very interesting data on the origin of the neuroblastic tumors, their clinical genetic and histological heterogeneity and finally on treatment, by highlighting that the key point seems to be histopathology, in order to try to transform an incurable disease in a chronic disease. In the main part of her lecture, the speaker talked about CaSR and its role in the neuroblastoma control and presented very impressive data on the epigenetic mechanisms leading to the neuroblastoma cells dynamic regulation through the CaSR overexpression.



More in particular the speaker presented very interesting experimental data demonstrating that the CaSR overexpression reduces the in vitro neuroblastoma growth and abolishes the neuroblastoma tumorigenicity. In the second part of her lecture, Prof. de Torres spoke about the role played by Cinacalcet in order to understand if the CaSR effect on neuroblastoma can be applied in therapy. The speaker, more presented a lot of experimental data derived from animal models on the effects of cinacalcet on the neuroblastoma cells, demonstrating that Cinacalcet inhibits the cell growth in an in vivo neuroblastoma model.



- What are the main epigenetic mechanisms of the neuroblastoma cells dynamic regulation based on the data presented by the speaker?
- What's about the effect of the CaSR overexpression on the neuroblastoma cells growth?
- What is the effect of the CaSR overexpression on the neuroblastoma tumorigenicity, based on the data presented by the speaker?
- What's about the effect of cinacalcet in the survival cells, based on the data presented by the speaker?
- What's about the effects of cinacalcet in neuroblastoma tumors from the speaker point of view?

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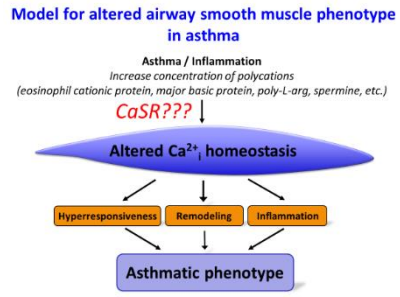
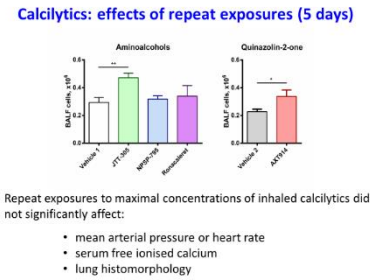
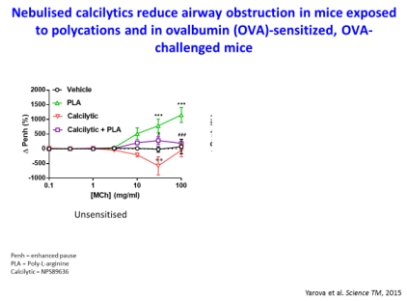
Asthma



Asthma was the topic of Prof. Riccardi presentation. The speaker coming from Cardiff (UK), presented very interesting data on the role played by CaSR in promoting and responding to inflammation. Going deeper in her presentation, Prof. Riccardi talked about the inflammatory lung disease and more in particular on asthma and COPD, by highlighting that they are predicted to be the world biggest killer by 2020 but the existing drugs treat only symptoms, because of the poor understanding of the underlying disease mechanisms. In the main part of her lecture, the speaker presented very interesting experimental data, starting from a model for altered airway smooth muscle phenotype in asthma where CaSR can play a central role in the activation of the altered $Ca^{2+}i$ homeostasis. Prof. Riccardi presented also other very interesting data on the effects of CaSR antagonists like calcilytics. In the second part of her lecture, the speaker, starting from very interesting data on the in vitro effects of nebulised calcilytics on the increased airway resistance in mice sensitized with mixed allergens, presented an innovative theory that explains why calcilytics are potentially better than any other existing treatment in the management of asthma and COPD.





- What are the key points of the model for altered airway smooth muscle phenotype in asthma presented by the speaker?
- What's about the effect of calcilytics on the airway smooth muscle cell hyperresponsiveness, based on the data presented by the speaker?
- What's about the effects of repeat exposures to maximal concentrations of inhaled calcilytics, based on the data presented by the speaker?
- Why calcilytics are potentially better than any other existing treatment in asthma and COPD management, from the speaker point of view?

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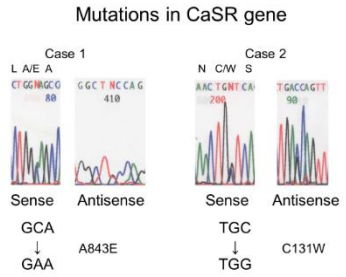
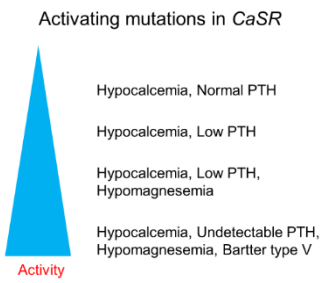
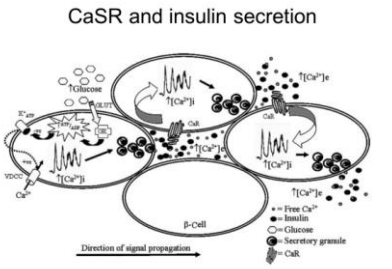
Glucose metabolism



Glucose metabolism was the topic Prof. Fukumoto talked about. The speaker coming from Tokushima (J), talked about the activating mutations in Bartter syndrome type V, the knock-out mice of activating mutations of CaSR and finally about CaSR and glucose metabolism. Going deeper in his lecture, Prof. Tokushima presented very interesting data on two different clinical syndromes like the PTH-deficient hypoparathyroidism with hypercalciuria and the Bartter-like nephropathy, with an underlying common cause, the presence of specific mutations in the CaSR gene. More in particular the speaker talked about the CaSR activity and the activating mutations in CaSR and their correlation with the development of specific diseases. In the second part of his lecture, Prof. Fukumoto presented very interesting experimental data on the effects of calcilytics in knock-in mice, on the relationship between CaSR and the glucose metabolism and the effect of JTT-305, a new calcilytic compound actually under investigation and on the glucose tolerance in these mutant mice. In conclusion, the speaker pointed out that calcilytics are able to improve the glucose tolerance in the knock-in mutant mice.





Hodgkin MN, et al. J Endocrinol 199:1,2008

- What's about the correlation between the clinical syndromes and the level of the activating mutations in CaSR, based on the data presented by the speaker?
- What are the effects of calcilytics in the mutant knock-in mice from the speaker point of view?
- What is the relationship between CaSR and the insulin secretion?
- What is the effect of JTT-305 on the glucose tolerance in knock-in mice, based on the data presented by the speaker?

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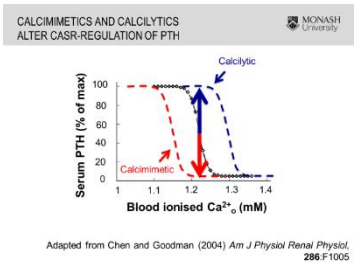
Rational design of CaSR therapeutics for diverse disorders



Adapted from Chen and Goodman (2004) *Am J Physiol Renal Physiol*, **286**:F1005

Prof. Leach, talked about the rational design of CaSR therapeutics for diverse disorders. The speaker coming from Melbourne (AUS) presented very interesting data on CaSR as a therapeutic target in osteoporosis, ADH and Bartter type V syndrome, FHH and NSHPT, HPT, Alzheimer disease, Cancer and in the airways hypersensitivity. Going deeper in her lecture, Prof. Leach spoke about the pharmacology of calcilytics and calcimimetics starting from the concept that despite their opposite effect, both pharmaceutical classes alter the CaSR regulation of PTH. In her lecture the speaker presented very interesting data on the main effects of these compounds in all these diseases, pointing to the indications and the more interesting promises and problems. In conclusion, Prof. Leach pointed out that combined SAR, analytical pharmacology, mutagenesis, and computational modelling is critical for understanding CaSR allostery as a fundamental step for the development of CaSR therapeutics for the treatment of many disorders.

DISEASE	DRUG TYPE
Osteoporosis	Calcilytic
ADH and Bartter syndrome type V	Calcilytic
FHH and NSHPT	Calcimimetic
HPT	Calcimimetic
Alzheimer's Disease	Calcilytic
Cancer	Calcimimetic / calcilytic
Airway hypersensitivity	Calcilytic

Drug	Indication	Promise	Problem
Cinacalcet	HPT, FHH, NSHPT	↓ PTH & Ca^{2+}	Hypocalcaemia, Adverse GI effects
Etelcalcitide	HPT secondary to CKD	↓ PTH	Hypocalcaemia
NPS2143	Osteoporosis	↑ rat bone turnover	No ↑ in rat bone density
Ronacaleret	Osteoporosis	↑ bone formation markers	Insufficient ↑ in human bone density
ATF936 & AXT914	Osteoporosis	↑ PTH (rapid,robust)	Insufficient ↑ in human bone formation markers, Hypercalcaemia

- What is the main problem of calcilytics from the speaker point of view?
- Why is analytical pharmacology important from the speaker point of view?
- What are the main applications of the computational modelling based on the data presented by the speaker?
- What's about Cinacalcet and its residues based on the data presented by the speaker?

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These are only some of the topics addressed in the congress's sections

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