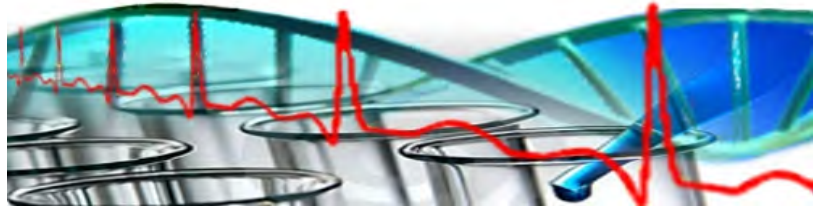


DISCAB Research News



Newsletter July 2015

Issue 2

page 1

Contents

- p.1: Editorial
- p.2: Research Breakthroughs
- p.4. Highlighting DISCAB Skeletal Disease Lab
- p.5. Recent DISCAB Publications
- p.6. Conferences; News & Views, Grants
- p.9. Job Opportunities
- p.10. Humour
- p.11 Cell-fie of the day

In this second issue of DISCAB Research News we continue where we left off in the inaugural issue. We highlight the DISCAB Skeletal Disease Research laboratory of Dr. Nadia Rucci, update recent DISCAB publications, bring you another selection of interesting research breakthroughs and publicize upcoming funding opportunities, meetings and events.

The next issue is programmed for mid-September and until then the DISCAB Research News team wishes you all a very pleasant and restful holiday.

*Novel DNA repair mechanism brings new horizons

Structure of transcribed chromatin is a sensor of DNA damage

Nikolay A. et al., *Science Advances* 03 Jul 2015: Vol. 1, no. 6, e1500021 DOI: 10.1126/sciadv.1500021

Early detection and repair of damaged DNA is essential for cell functioning and survival. Although multiple cellular systems are involved in the repair of single-strand DNA breaks (SSBs), it remains unknown how SSBs present in the non-template strand (NT-SSBs) of DNA organized in chromatin are detected. The effect of NT-SSBs on transcription through chromatin by RNA polymerase II was studied. NT-SSBs localized in the promoter-proximal region of nucleosomal DNA and hidden in the nucleosome structure can induce a nearly quantitative arrest of RNA polymerase downstream of the break, whereas more promoter-distal SSBs moderately facilitate transcription. The location of the arrest sites on nucleosomal DNA suggests that formation of small intra-nucleosomal DNA loops causes the arrest. This mechanism likely involves relief of unconstrained DNA supercoiling accumulated during transcription through chromatin by NT-SSBs. These data suggest the existence of a novel chromatin-specific mechanism that allows the detection of NT-SSBs by the transcribing enzyme.

* Scientists Freeze Atoms to Near Absolute Zero

Ground-State Cooling of a Trapped Ion Using Long-Wavelength Radiation

S. Weidt, et al., *Phys. Rev. Lett.* **115**, 013002

We demonstrate ground-state cooling of a trapped ion using radio-frequency (rf) radiation. This is a powerful tool for the implementation of quantum operations, where rf or microwave radiation instead of lasers is used for motional quantum state engineering. We measure a mean phonon number of $n=0.13(4)$ after sideband cooling, corresponding to a ground-state occupation probability of 88(7)%. After preparing in the vibrational ground state, we demonstrate motional state engineering by driving Rabi oscillations between the $|n=0\rangle$ and $|n=1\rangle$ Fock states. We also use the ability to ground-state cool to accurately measure the motional heating rate and report a reduction by almost 2 orders of magnitude compared with our previously measured result, which we attribute to carefully eliminating sources

of electrical noise in the system.

*Interesting Review on TP53

TP53: an oncogene in disguise

T Soussi and KG Wiman. *Cell Death and Differentiation* (2015) **22**, 239 –1249 doi:10.1038/cdd.2015.53

The standard classification used to define the various cancer genes confines tumor protein p53 (TP53) to the role of a tumor suppressor gene. However, it is now an indisputable fact that many p53 mutants act as oncogenic proteins. This statement is based on multiple arguments including the mutation signature of the TP53 gene in human cancer, the various gains-of-function (GOFs) of the different p53 mutants and the heterogeneous phenotypes developed by knock-in mouse strains modeling several human TP53 mutations. In this review, we will shatter the classical and traditional image of tumor protein p53 (TP53) as a tumor suppressor gene by emphasizing its multiple oncogenic properties that make it a potential therapeutic target that should not be underestimated. Analysis of the data generated by the various cancer genome projects highlights the high frequency of TP53 mutations and reveals that several p53 hotspot mutants are the most common oncoprotein variants expressed in several types of tumors. The use of Muller's classical definition of mutations based on quantitative and qualitative consequences on the protein product, such as 'amorph', 'hypomorph', 'hypermorph', 'neomorph' or 'antimorph', allows a more meaningful assessment of the consequences of cancer gene modifications, their potential clinical significance, and clearly demonstrates that the TP53 gene is an atypical cancer gene.

*Fully Implantable Artificial Pancreas Delivers Insulin as Needed

Design and Evaluation of a Robust PID Controller for a Fully Implantable Artificial Pancreas

Huyett L. et al., *Ind. Eng. Chem. Res.*, DOI: 10.1021/acs.iecr.5b01237

Treatment of type 1 diabetes mellitus could be greatly improved by applying a closed-loop control strategy to insulin delivery, also known as an artificial pancreas (AP). In this work, we outline the design of a fully implantable AP using intraperitoneal (IP) insulin delivery and glucose sensing. The design process utilizes the rapid glucose sensing and insulin action offered by the

IP space to tune a PID controller with insulin feedback to provide safe and effective insulin delivery. The controller was tuned to meet robust performance and stability specifications. An anti-reset windup strategy was introduced to prevent dangerous undershoot toward hypoglycemia after a large meal disturbance. The final controller design achieved 78% of time within the tight glycemic range of 80–140 mg/dL, with no time spent in hypoglycemia. The next step is to test this controller design in an animal model to evaluate the *in vivo* performance.

*cKit linked to obesity

Hematopoietic Kit Deficiency, rather than Lack of Mast Cells, Protects Mice from Obesity and Insulin Resistance

Dario A. Gutierrez, et al., *Cell Metabolism* 21, 678-691, 2015 DOI: <http://dx.doi.org/10.1016/j.cmet.2015.04.013>

Obesity, insulin resistance, and related pathologies are associated with immune-mediated chronic inflammation. *Kit* mutant mice are protected from diet-induced obesity and associated co-morbidities, and this phenotype has previously been attributed to their lack of mast cells. We performed a comprehensive metabolic analysis of *Kit*-dependent *Kit^{W/W^v}* and *Kit*-independent *Cpa3Cre/+* mast-cell-deficient mouse strains, employing diet-induced or genetic (*LepOb/Ob* background) models of obesity. Our results show that mast cell deficiency, in the absence of *Kit* mutations, plays no role in the regulation of weight gain or insulin resistance. Moreover, we provide evidence that the metabolic phenotype observed in *Kit* mutant mice, while independent of mast cells, is immune regulated. Our data underscore the value of definitive mast cell deficiency models to conclusively test the involvement of this enigmatic cell in immune-mediated pathologies and identify *Kit* as a key hematopoietic factor in the pathogenesis of metabolic syndrome.

*How round cells decide their backside during chemotaxis

Novel protein Callipygian defines the back of migrating cells

Kristen F, et al., <http://www.pnas.org/content/early/2015/06/29/1509098112.full.pdf>

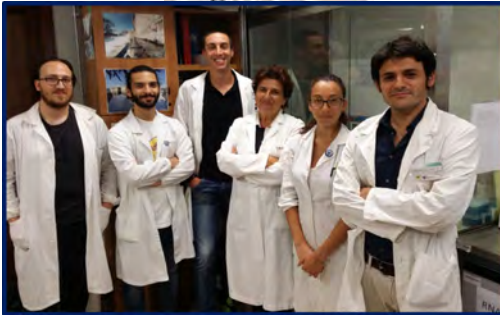
Significance

Though the asymmetric distribution of proteins is a crucial first step in establishing polarity and

guiding cell migration, the molecular mechanisms regulating many of these localizations are unknown. Our study reports on the novel protein Callipygian (CynA), which localizes to the rear of cells during symmetry breaking, thereby promoting polarity and increasing migration efficiency. Our data indicate that CynA localization is mediated by two distinct mechanisms, which may be important for segregating proteins in other polarized cell types including epithelial cells, neurons, and immune cells. Thus, our findings have implications for tissue formation during embryonic development, the migration of immune cells during wound healing and infection, and the aberrant migrations associated with arthritis, asthma, atherosclerosis, cancer metastasis, and other diseases.

Abstract

Asymmetric protein localization is essential for cell polarity and migration. We report a novel protein, Callipygian (CynA), which localizes to the lagging edge before other proteins and becomes more tightly restricted as cells polarize; additionally, it accumulates in the cleavage furrow during cytokinesis. CynA protein that is tightly localized, or "clustered," to the cell rear is immobile, but when polarity is disrupted, it disperses throughout the membrane and responds to uniform chemoattractant stimulation by transiently localizing to the cytosol. These behaviors require a pleckstrin homology-domain membrane tether and a WD40 clustering domain, which can also direct other membrane proteins to the back. Fragments of CynA lacking the pleckstrin homology domain, which are normally found in the cytosol, localize to the lagging edge membrane when coexpressed with full-length protein, showing that CynA clustering is mediated by oligomerization. Cells lacking CynA have aberrant lateral protrusions, altered leading-edge morphology, and decreased directional persistence, whereas those overexpressing the protein display exaggerated features of polarity. Consistently, actin polymerization is inhibited at sites of CynA accumulation, thereby restricting protrusions to the opposite edge. We suggest that the mutual antagonism between CynA and regions of responsiveness creates a positive feedback loop that restricts CynA to the rear and contributes to the establishment of the cell



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"We are like dwarfs on the shoulders of giants, so that we can see more than them and more distant things, certainly not to the keenness of vision or the height of our body, but because we are raised and taken up by the stature of giants (*Bernardo di Chartres, 1159*)"

The Skeletal Diseases Lab (SDL) is located on the first floor of Coppito 2 building, rooms B.2.33/B.2.36. It is a very young lab both for its recent birth, and because of the people who work in (average age <30 years), even if the PI, Prof. Nadia Rucci is an experienced scientist who's been teaming up with prof. Anna Teti.

The other people working in the SDL are:

Alfredo Cappariello (Postdoc), Marco Ponzetti (MSc student), Riccardo Paone (MSc student), Cristian Albergo (undergrad) and Annamaria Tisi (undergrad). We also host an English student from the University of Manchester, Alexander Loftus, (European "Erasmus" scholarship).

Current lines of research of the Skeletal Diseases Lab are as follows:

Study of the molecular mechanisms regulating the development of osteotropic cancers (i.e. bone metastases and osteosarcoma) and identification of new therapeutic approaches;

Study of the effects of mechanical unloading on bone tissue and identification of new biomarkers; Identification of new therapeutic targets for the treatment of osteoporosis; Identification of new experimental therapies for the treatment of osteopetrosis.

Main expertise of the Skeletal Diseases Lab: Morphology, histology and immunohistochemical analyses; Osteoblast and osteoclast primary cultures, tumour cell line (breast cancer, osteosarcoma) cultures; Cell biology and related

techniques (stable transfection, proliferation and apoptosis assays, scratch healing assay, migration and invasion assays, angiogenesis assays, CFU on soft agar); Molecular biology techniques (RNA/Protein analyses, Real time RT-PCR, Western blotting, in vivo crosslinking). In vivo animal models of cancer by xeno- and allograft of tumour cells, including: Subcutaneous injection Intratibial/paratibial injection of breast cancer and osteosarcoma cells; Orthotopic injection of breast cancer cells; Intracardiac injection of osteotropic tumour cells to obtain bone and visceral metastases. In vivo animal models of osteoporosis, including hindlimbs suspension, Botox injection to hindlimb muscle, ovariectomized mice. Main techniques to evaluate *in vivo* tumour growth, *in itinere* and/or *post mortem*, including: Bioluminescence Reporter Imaging to evaluate tumour burden; X-ray, microCT analyses, Serum analysis of markers of bone turnover, inflammation, and organ disease

Selected Publications: Rucci N, Capulli M, Olstad OK, Önnarfjord P, Tillgren V, Gautvik KM, Heinegård D, Teti A. The $\alpha 2\beta 1$ binding domain of chondroadherin inhibits breast cancer-induced bone metastases and impairs primary tumour growth: a preclinical study. **Cancer Lett** 358:67-75; 2015.

Rucci N, Capulli M, Piperni SG, Cappariello A, Lau P, Frings-Meuthen P, Heer M, Teti A. Lipocalin 2: a new mechanoresponding gene regulating bone homeostasis. **J Bone Miner Res** 30:357-368;2015.

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Conferences

Meeting: “ 45th Annual ESDR Meeting “
Organised by: European Society of Dermatology
Where Rotterdam, The Netherlands
When 9-12 September 2015
Contacts: <http://www.esdr2015.org/>

Course: «Corso teorico pratico: Approcci bioinformatici per l'analisi di espressione genica»
Organised by: Associazione Italiana di Colture Cellulari (AICC) and Istituto Ortopedico Rizzoli, Bologna
Where: Istituto Ortopedico Rizzoli, Centro Ricerca di Codivilla-Putti, Sala Anfiteatro Bologna
When: September 16-18, 2015
Contacts: Dr Evelina F. Sciandra, mail: evelinafiorenza.sciandra@ior.it Tel: 051/636.6937
Notes: Registration only for AICC members

Events

Notte Europea dei Ricercatori “Sharper 2015” L'Aquila, 25 settembre 2015



University of L'Aquila completed the international project

Prof Teti research group. Asterisks indicate the INTERBONE fellows

INTERBONE supported by the



European Commission

The European Commission funded project INTERBON, coordinated by Prof Anna Maria Teti and involving the University of L'Aquila Department of Biotechnological and Applied Clinical Sciences, has just been completed. The project integrated a staff exchange programme between five Countries (Italy, Netherlands, Brazil, India and the United States) to perform collaborative studies on the mechanisms underlying the interactions between bone and blood vessels, the relationship between bone and leukemia and the bone regeneration properties of new biomaterials. The University of L'Aquila has hosted five scientists from India and Brazil and has sent five scientists to the United States, Brazil and India. The scientific programme has been successfully fulfilled, allowing the training of young investigators on essential functions of bone in health and disease. "We are very happy for the positive outcome of the project", Prof Teti says, "confirming the high competitiveness of the University of L'Aquila in the international scientific panorama. This is an important challenge for our students and young investigators and a success for our University as a whole".

Dr. Mattia Capulli (Prof Teti research group) has been elected into the Young Investigator Committee of the International Bone and Mineral Society.

Scientist Jailed for faking data

<http://www.iflscience.com/health-and-medicine/4-year-jail-sentence-researcher-who-faked-hiv-vaccine-trial-data>

DISCAB and the ERASMUS Community

My name is Ronak Arjan and I am an undergraduate student from The University of Manchester.



I am here in L'Aquila under the Erasmus+ programme for traineeships. This

programme provides financial support to undergraduate students to go abroad and obtain work experience in your field of interest within the European Union

The Lab lead by Professor Anna Teti is full of passionate people who love what they do. They are always willing to help and explain things, which creates a very good learning environment. I have learnt a wide range of techniques and gained valuable skills that will help my future career. Specific techniques I have learnt here are immunofluorescence, osteoblasts cultures, immunohistochemistry and MACS magnetic bead cell sorting just to name a few.

The lab provides you with everything you need to achieve your goals and your progress is tracked during lab meetings. Furthermore, we attend a weekly journal club and also seminars to discuss, stimulate and exchange scientific ideas.

I have thoroughly enjoyed my 1 year in L'Aquila. The region of Abruzzo has beautiful mountains, caves and lakes. L'Aquila itself is a wonderful city full of good food and bars. I would recommend the experience for somebody who enjoys nature and wants to further their development to become a top level scientist.

One thing I will really miss is the ice cream in L'Aquila and I wish I could take enough back to England to last me for another year!

DISCAB "Poster Week"

A Celebration of DICAB Research

Great success for the "Poster Week" initiative organized by Dr. Francesco Masedu (Research committee member) from the 22nd to the 29th June. Posters were displayed illustrating current research projects within our vibrant DISCAB research community, providing an important opportunity for the informal yet structured communication and good presentation practice for junior DISCAB members. The quantity of Posters presented was good and quality high. In general, it is fair to say that this initiative was an important and successful experience and will be repeated in due course.

Fondazione Jérôme Lejeune – sovvenzioni per la ricerca

Il Comitato Scientifico della Fondazione Jérôme Lejeune invita i ricercatori a presentare progetti di ricerca finalizzati alla scoperta della fisiopatologia delle disabilità intellettive dei pazienti affetti da malattie genetiche, in particolare dalla trisomia 21 (sindrome di Down) e da altre anomalie rare come X fragile, Cri du Chat, Rett, Williams-Beuren, Prader-Willi, Angelman e altre sindromi, escluso l'autismo. <http://www.fondationlejeune.org/en/our-missions-and-actions/research/apply-for-a-grant-obtain-funding#sthash.vKlIZgmo.dpuf>

Premio 2015 per le migliori tesi di laurea di specializzazione sulla sindrome di Pitt-Hopkins

L'Associazione Italiana Sindrome di Pitt-Hopkins – Insieme di più – ONLUS () istituisce un totale di 5 premi per le migliori tesi di laurea o di specializzazione sul tema della sindrome di Pitt-Hopkins, discusse nel periodo **ottobre 2013-novembre 2015**. L'iniziativa ha lo scopo di favorire la conoscenza sulla sindrome di Pitt-Hopkins, di ottimizzarne l'assistenza medica e neuropsicologia e di incoraggiare la ricerca. L'importo del premio per l'anno 2015 è di € 500,00. Possono concorrere i laureati e gli specialisti che abbiano conseguito il titolo di laurea o di specializzazione da non più di anni 2 alla data di chiusura del bando. Coloro che intendano concorrere dovranno inviare, entro il **15 Novembre 2015**, a mezzo raccomandata A.R., domanda di ammissione in carta libera diretta al Coordinatore del Comitato Scientifico, Prof.ssa Marcella Zollino - Istituto di Genetica Medica, Università Cattolica Sacro Cuore, Policlinico A. Gemelli, L.go F. Vito, 1 00168 Roma. **Per maggiori informazioni** : <http://www.aisph.it/it/>

Bando AFM Telethon

AFM Telethon pubblica diversi bandi per il finanziamento della ricerca. È stato recentemente pubblicato un invito a presentare lettere di intenti per progetti di ricerca sull'atrofia muscolare spinale e collagene VI.

Per maggiori informazioni <http://www.afm-telethon.com/research/calls-for-proposals/current-calls-for-proposals.html>

Premio scientifico 2015 Care-for-rare

La Fondazione Care-for-Rare mette in palio due premi scientifici all'anno per offrire ai giovani ricercatori l'opportunità di avviare un progetto di ricerca sulle malattie rare. Il Premio Dott. Holger Müller, del valore di 5.000 euro, viene assegnato a singoli ricercatori o gruppi di ricerca che hanno pubblicato uno studio di rilevante interesse nel campo delle malattie rare nel corso dell'anno precedente. **Per maggiori informazioni** <http://www.care-for-rare.org/en/awards>

Premio per l'attività di ricerca sulla ceroidolipofusinosi neuronale

La Fondazione ha annunciato la sesta edizione del premio per l'attività di ricerca nel campo della ceroidolipofusinosi neuronale (CLN). I ricercatori di base e clinici di tutto il mondo sono invitati a presentare proposte di progetti innovativi che siano clinicamente orientati o che coprano gli aspetti traslazionali della biologia del gene CLN3 e che possano contribuire a trovare una cura per la CLN giovanile. Particolare attenzione sarà posta nei confronti dei contributi provenienti da ricercatori che lavorano nel campo di altre malattie da accumulo lisosomiale, della biologia cellulare endolisosomiale e delle malattie neurodegenerative. Insieme con la comunità di ricerca, l'obiettivo di questa iniziativa è di promuovere il progresso di nuove prospettive terapeutiche in grado di aiutare i pazienti affetti da CLN giovanile. Il premio, del valore di 50.000€, servirà a finanziare una borsa di studio post-dottorato della durata di un anno destinata a giovani ricercatori del mondo accademico e dell'industria. **Scadenza: 31.10.2015**

The Endocrine Fellows Foundation (EFF) grant Cycle 2-2015, the Fall Cycle,! Two research grant opportunities.

The first is for fellows with one to two full years remaining in their fellowship. The second is for Young Investigators. This would be for any individual who has completed their fellowship within the past two years and is looking to complete further research. To submit your grant application, go to <http://endocrinefellows.org/grants/> questions: info@endocrinefellows.org. Application deadline **Friday, August 7, 2015**

Bando ACRI "Young Investigator Training Program" open to young investigators to work for one month in Italian research institutes that adhere to the programme applications must be made before 15/09/2015

Job Opportunities

For further information for the following worldwide academic vacancies in pharmacy and biomedical sciences schools go to the Biopharmo site at: Biopharmo.com

Belgium: Full time scientific assistant: Experienced epidemiologist University of Antwerp

Canada: Research Chairs in Health Care Delivery North York General Hospital

Tier 1 Canada Research Chair in Biomedical Technology The Faculty of Applied Sciences Simon Fraser University

China: Lecturers (Education) in Pharmaceutical Sciences China Medical University - Queen's University Joint College (CQC), Shenyang, China Academic Vacancies in Psychology School of Psychology at Beijing Normal University

Colombia: Professor of Psychology The Department of Psychology at Universidad de los Andes Colombia

Denmark: Professor in Pharmacology Aarhus University

Hong Kong: Tenure-track Professor in the School of Nursing The University of Hong Kong

Tenure-track Associate Professor/Assistant Professor (research-based) in the School of Nursing The University of Hong Kong

Associate Professor of Nursing Practice in the School of Nursing The University of Hong Kong

Ireland: M.Sc. in Immunology, Trinity College Dublin (TCD), Ireland NEW!

Israel: Post-doctorate fellows in Bioinformatics University of Haifa

New Zealand: Lecturer or Senior Lecturer in Cross-cultural Psychology School of Psychology Victoria University of Wellington, New Zealand

Qatar: Professor (Assistant/Associate/Full Professor) — Pharmacology Qatar University

Saudi Arabia: Professor of Medicine College of Medicine Dar Aluloom University NEW!

Lecturer/Assistant/Associate/Full Professor Computer Science, Information Systems, Information Technology King Saud Bin Abdulaziz University for Health Sciences Saudi Arabia

Spain: Full Professor, Tenure Track (2+4) of Human Anatomy The University of Navarra

Sweden: Clinical Professors with different specializations Örebro University in Sweden

Switzerland: Post-Doctoral Student in Nursing The Institute of Nursing Science (INS) at the University of Basel

Doctoral Student / Research Assistant in Nursing The Institute of Nursing Science (INS) at the University of Basel Professor in

Osteopathy (full time position: 100%) The School of Health Sciences, Fribourg (HEdS-FR) Switzerland Doctoral student /

Research assistant to join the BRIGHT study team The Institute of Nursing Science at the University of Basel

Research assistants / doctoral students The Institute of Nursing Science University of Basel

Trinidad and Tobago: Senior Lecturer/Lecturer in Veterinary Anatomy, Histology and Embryology The University of the West Indies St. Augustine Trinidad and Tobago, West Indies

Senior Lecturer/Lecturer in Pharmacology The University of the West Indies St. Augustine Trinidad and Tobago, West Indies

Senior Lecturer/Lecturer in Molecular Biology/Chemical Pathology/Clinical Chemistry The University of the West Indies St.

Augustine Trinidad and Tobago, West Indies

Director of School of Pharmacy The University of the West Indies St. Augustine Trinidad and Tobago, West Indies

Senior Lecturer/Lecturer in Biostatistics The University of the West Indies St. Augustine Trinidad and Tobago, West Indies

Lecturer in Radiology The University of the West Indies St. Augustine Trinidad and Tobago, West Indies

Lecturer in Psychiatry The University of the West Indies St. Augustine Trinidad and Tobago, West Indies

Lecturer in Paediatrics The University of the West Indies St. Augustine Trinidad and Tobago, West Indies

Senior Lecturer/Lecturer Adult/Internal Medicine The University of the West Indies St. Augustine Trinidad and Tobago, West Indies

United States: Lecturer - Biostatistics University of California

Postdoctoral Scholars in Pharmaceutical Sciences University of California, Irvine

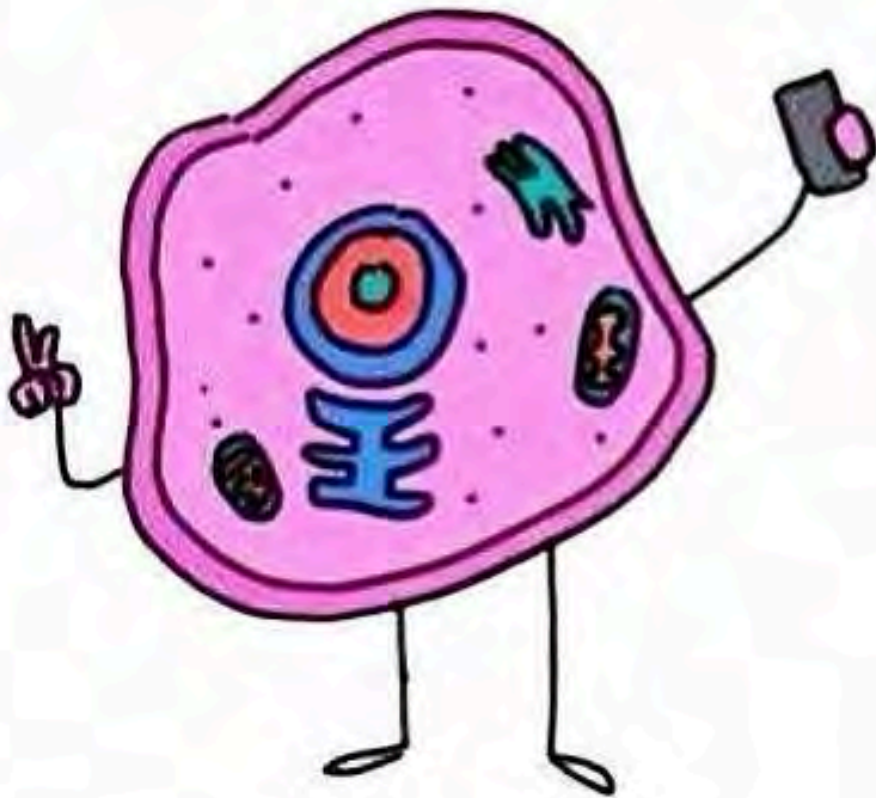
Lecturer pool for Pharmaceutical Sciences University of California, Irvine

Postdoctoral Scholars in Biomedical Engineering University of California, Irvine

Postdoctoral Scholars in Laboratory of Fluorescence Dynamics University of California, Irvine

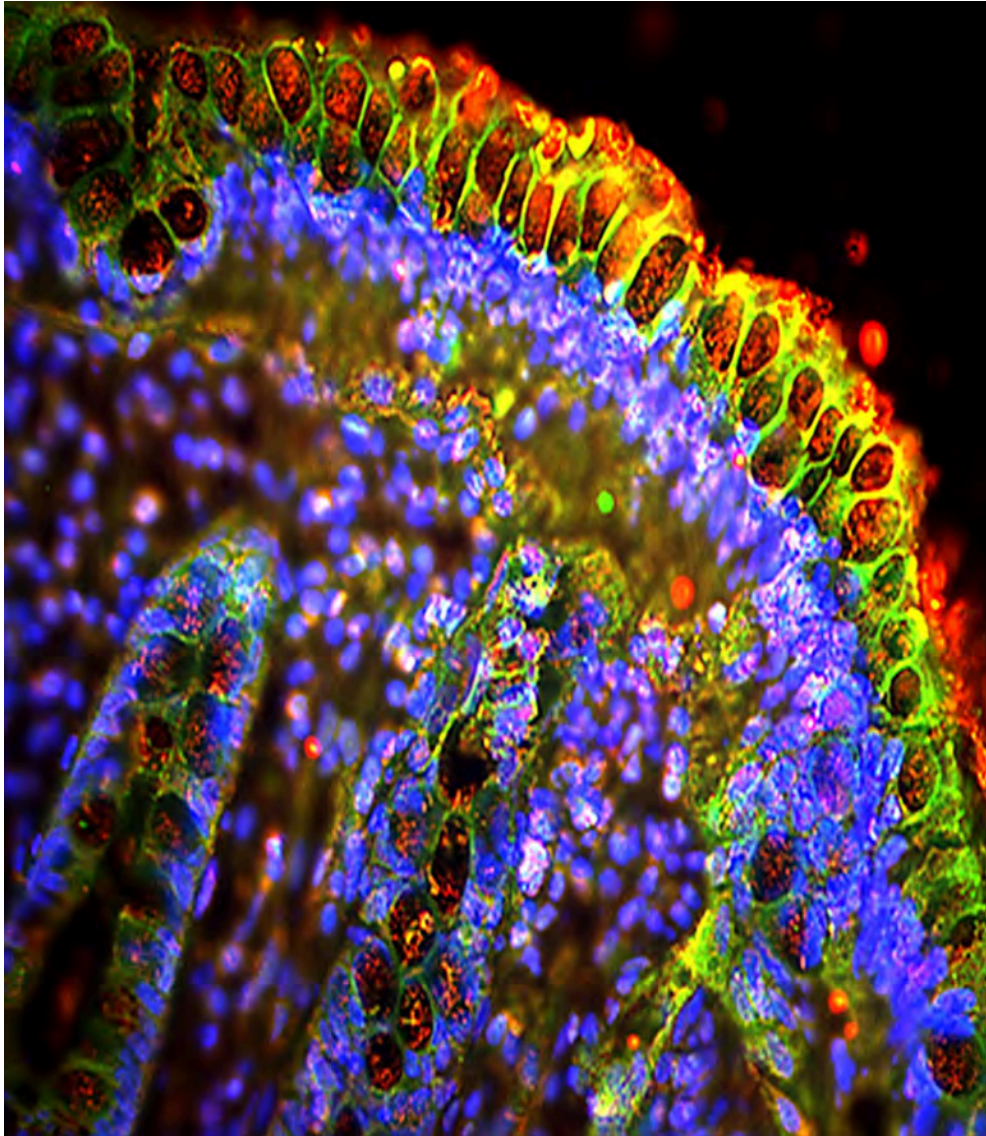
Postdoctoral Scholars for Department of Biomedical Engineering University of California, Irvine

Don't forget to send information relevant to this publication to discabresearchnews@gmail.com



Cell-fie

The single IgG IL-1-related receptor (Sigirr) is expressed on the surface of intestinal cells lining the colon. The receptor regulates the inflammatory response which can affect growth of commensal bacteria in the gut.



The single IgG IL-1-related receptor controls TLR responses in differentiated human intestinal epithelial cells.

Khan MA, et al.,

J Immunol. 2010 184(5):2305-13. doi: 10.4049/jimmunol.0900021.