Università degli Studi dell'Aquila
Dipartimento di
Scienze Cliniche Applicate e Biotecnologiche
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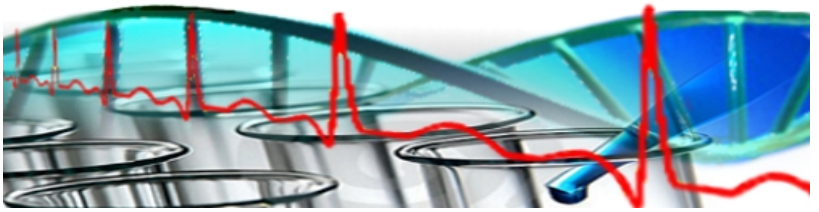
DISCAB Research News



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Inaugural Editorial

On behalf of myself (Professor Andrew R. Mackay) and the DISCAB Research News team: Drs. Lucia Cappabianca; Mattia Capulli; Cristina Pelligrini; and Andrea Ianni, I am delighted to announce the publication of this inaugural issue of DISCAB Research News.

This publication is a natural outgrowth of the need to improve research in our department in order to better confront the obvious changes and challenges that face our academic research community. We feel that a news letter dedicated to departmental research would be an ideal vehicle to build on recent departmental initiatives, as well as to capture the diversity of scholarly research in our ever more vibrant DISCAB community.

The team decided that the Newsletter should be published in pdf format and sent individually via e.mail, with back-issues deposited in the DISCAB web site. We will endeavour to publish a monthly issue of DISCAB Research News, with a selection of articles focusing on topics relevant to research in the DISCAB community.

The inaugural issue is divided into the following sections: Recent research breakthrough, DISCAB Research groups; recent DISCAB publications; upcoming Congresses, Grants and Job opportunities; General news and views; and last but not least, a humorous section.

I wish to thank the DISCAB News team, who have wholeheartedly supported the birth of this inaugural issue, and also members of the DISCAB Research committee for enthusiastic support and material.

I would also like to take this opportunity to enlist your support for future DISCAB Research News issues. The timely publication of future issues will depend upon your contributions and, in such, will represent a true reflection of the pride, dedication and enthusiasm with which we all hold our research activity.

Please send all contributions to the DISCAB Research News team at: discabresearchnews@gmail.com

Sincerely, Andrew R. Mackay

*Asthma breakthrough

Calcium-sensing receptor antagonists abrogate airway hyperresponsiveness and inflammation in allergic asthma. Yarova PL et al., Sci Transl Med 7(284), 2015

Abstract
Airway hyperresponsiveness and inflammation are fundamental hallmarks of allergic asthma that are accompanied by increases in certain polycations, such as eosinophil cationic protein. Levels of these cations in body fluids correlate with asthma severity. We show that polycations and elevated extracellular calcium activate the human recombinant and native calcium-sensing receptor (CaSR), leading to intracellular calcium mobilization, cyclic adenosine monophosphate breakdown, and p38 mitogen-activated protein kinase phosphorylation in airway smooth muscle (ASM) cells. These effects can be prevented by CaSR antagonists, termed calcilytics. Moreover, asthmatic patients and allergen-sensitized mice expressed more CaSR in ASMs than did their healthy counterparts. Indeed, polycations induced hyperreactivity in mouse bronchi, and this effect was prevented by calcilytics and absent in mice with CaSR ablation from ASM. Calcilytics also reduced airway hyperresponsiveness and inflammation in allergen-sensitized mice in vivo. These data show that a functional CaSR is up-regulated in asthmatic ASM and targeted by locally produced polycations to induce hyperresponsiveness and inflammation. Thus, calcilytics may represent effective asthma therapeutics.

*Brain plasticity restored in older mice

Inhibitory Neuron Transplantation into Adult Visual Cortex Creates a New Critical Period that Rescues Impaired Vision. Davies M et al., Neuron 86 (4), 1055-1066, 2015

Abstract
The maturation of inhibitory circuits in juvenile visual cortex triggers a critical period in the development of the visual system. Although several manipulations of inhibition can alter the timing of the critical period, none have demonstrated the creation of a new critical period in adulthood. We developed a transplantation method to reactivate critical period plasticity in the adult visual cortex. Transplanted embryonic inhibitory neurons from the medial ganglionic eminence reinstate ocular dominance plasticity in adult recipients. Transplanted inhibitory cells develop cell-type-appropriate molecular characteristics and visually evoked responses. In adult mice impaired by deprivation during the juvenile critical period, transplantation also recovers both visual cortical responses and performance on a behavioral test of visual acuity. Plasticity and recovery are induced when the critical period would have occurred in the donor animal. These results reveal that the focal reactivation of visual cortical plasticity using inhibitory cell transplantation creates a new critical period that restores visual perception after childhood deprivation.

*3-D technology detects 40 percent more breast cancers than mammography

Performance of one-view breast tomosynthesis as a stand-alone breast cancer screening modality: results from the Malmö Breast Tomosynthesis Screening Trial, a population-based study. Lang K et al., Eur Radiol DOI 10.1007/s00330-015-3803-3

Abstract
Objective To assess the performance of one-view digital breast tomosynthesis (DBT) in breast cancer screening. Methods The Malmö Breast Tomosynthesis Screening Trial is a prospective population-based one-arm study with a planned inclusion of 15000 participants; a random sample of women aged 40–74 years eligible for the screening programme. This is an explorative analysis of the first half of the study population (n = 7500). Participants underwent one-view DBT and two-view digital mammography (DM), with independent dou- ble reading and scoring. Primary outcome measures were de- tection rate, recall rate and positive predictive value (PPV). McNemar's test with 95 % confidence intervals was used. Results Breast cancer was found in sixty-eight women. Of these, 46 cases were detected by both modalities, 21 by DBT alone and one by DM alone. The detection rate for one-view DBT was 8.9/1000 screens (95 % CI 6.9 to 11.3) and 6.3/1000 screens (4.6 to 8.3) for two-view DM ($p < 0.0001$). The recall rate after arbitration was 3.8 % (3.3 to 4.2) for DBT and 2.6 % (2.3 to 3.0) for DM ($p<0.0001$). The PPV was 24 % for both DBT and DM.

*Ubiquitin system produces a protein that greatly restricts the development of cancerous tumors

KPC1-mediated ubiquitination and proteasomal processing of NF-κB1 p105 to p50 restricts tumor growth. Kravtsova-Ivantsiv Y, et al. Call 161(2): 333-347, 2015

Abstract
NF-κB is a key transcriptional regulator involved in inflammation and cell proliferation, survival, and transformation. Several key steps in its activation are mediated by the ubiquitin (Ub) system. One uncharacterized step is limited proteasomal processing of the NF-κB1 precursor p105 to the p50 active subunit. Here, we identify KPC1 as the Ub ligase (E3) that binds to the ankyrin repeats domain of p105, ubiquitinates it, and mediates its processing both under basal conditions and following signaling. Overexpression of KPC1 inhibits tumor growth likely mediated via excessive generation of p50. Also, overabundance of p50 downregulates p65, suggesting that a p50-p50 homodimer may modulate transcription in place of the tumorigenic p50-p65. Transcript analysis reveals increased expression of genes associated with tumor-suppressive signals. Overall, KPC1 regulation of NF-κB1 processing appears to constitute an important balancing step among the stimulatory and inhibitory activities of the transcription factor in cell growth control.

*Removing mutant p53 significantly regresses tumors, improves cancer survival

Improving survival by exploiting tumour dependence on stabilized mutant p53 for treatment. Alexandrova EM et al. *Nature*, 2015; DOI: 10.1038/nature14430

Abstract

Missense mutations in p53 generate aberrant proteins with abrogated tumour suppressor functions that can also acquire oncogenic gain-of-function activities that promote malignant progression, invasion, metastasis and chemoresistance1, 2, 3, 4, 5. Mutant p53 (mutp53) proteins undergo massive constitutive stabilization specifically in tumours, which is the key requisite for the acquisition of gain-of-functions activities6, 7, 8. Although currently 11 million patients worldwide live with tumours expressing highly stabilized mutp53, it is unknown whether mutp53 is a therapeutic target *in vivo*. Here we use a novel mutp53 mouse model expressing an inactivatable R248Q hotspot mutation (floxQ) to show that tumours depend on sustained mutp53 expression. Upon tamoxifen-induced mutp53 ablation, allotransplanted and autochthonous tumours curb their growth, thus extending animal survival by 37%, and advanced tumours undergo apoptosis and tumour regression or stagnation. The HSP90/HDAC6 chaperone machinery, which is significantly upregulated in cancer compared with normal tissues, is a major determinant of mutp53 stabilization9, 10, 11, 12. We show that long-term HSP90 inhibition significantly extends the survival of mutp53 Q/− (R248Q allele2) and H/H (R172H allele3) mice by 59% and 48%, respectively, but not their corresponding $p53^{-/-}$ littermates. This mutp53-dependent drug effect occurs in H/H mice treated with 17DMAG+SAHA and in H/H and Q/− mice treated with the potent Hsp90 inhibitor ganetespib. Notably, drug activity correlates with induction of mutp53 degradation, tumour apoptosis and prevention of T-cell lymphomagenesis. These proof-of-principle data identify mutp53 as an actionable cancer-specific drug target.

***Breast Cancer metastasis blocker**

CCL2-induced chemokine cascade promotes breast cancer metastasis by enhancing retention of metastasis-associated macrophages

Kitamura T et al., J. Exp. Med 2015 June 8 doi: 10.1084/jem.20141836.

ABSTRACT

Pulmonary metastasis of breast cancer cells is promoted by a distinct population of macrophages, metastasis-associated macrophages (MAMs), which originate from inflammatory monocytes (IMs) recruited by the CC-chemokine ligand 2 (CCL2). We demonstrate here that, through activation of the CCL2 receptor CCR2, the recruited MAMs secrete another chemokine ligand CCL3. Genetic deletion of CCL3 or its receptor CCR1 in macrophages reduces the number of lung metastasis foci, as well as the number of MAMs accumulated in tumor-challenged lung in mice. Adoptive transfer of WT IMs increases the reduced number of lung metastasis foci in *Ccl3* deficient mice. Mechanistically, *Ccr1* deficiency prevents MAM retention in the lung by reducing MAM–cancer cell interactions. These findings collectively indicate that the CCL2-triggered chemokine cascade in macrophages promotes metastatic seeding of breast cancer cells thereby amplifying the pathology already extant in the system. These data suggest that inhibition of CCR1, the distal part of this signaling relay, may have a therapeutic impact in metastatic disease with lower toxicity than blocking upstream targets.

* Breakthrough in Autophagy research

Regulation of endoplasmic reticulum turnover by selective autophagy

Khaminets A et al., *Nature* (2015) doi:10.1038/nature14498.

ABSTRACT

The endoplasmic reticulum (ER) is the largest intracellular endomembrane system, enabling protein and lipid synthesis, ion homeostasis, quality control of newly synthesized proteins and organelle communication. Constant ER turnover and modulation is needed to meet different cellular requirements and autophagy has an important role in this process. However, its underlying regulatory mechanisms remain unexplained. Here we show that members of the FAM134 reticulon protein family are ER-resident receptors that bind to autophagy modifiers LC3 and GABARAP, and facilitate ER degradation by autophagy ('ER-phagy'). Downregulation of FAM134B protein in human cells causes an expansion of the ER, while FAM134B overexpression results in ER fragmentation and lysosomal degradation. Mutant FAM134B proteins that cause sensory neuropathy in humans are unable to act as ER-phagy receptors. Consistently, disruption of *Fam134b* in mice causes expansion of the ER, inhibits ER turnover, sensitizes cells to stress-induced apoptotic cell death and leads to degeneration of sensory neurons. Therefore, selective ER-phagy via FAM134 proteins is indispensable for mammalian cell homeostasis and controls ER morphology and turnover in mice and humans.

In this inaugural Issue of "DISCAB Research News", we introduce the Experimental Pathology Research Group", as an initial example and template for other DISCAB research groups, who we cordially invite to submit similar descriptions for publication in future issues. Through this endeavour, we aim to foster a more complete understanding of research performed in our department in order to stimulate interest, communication and eventual collaboration.

The "Experimental Pathology" research Group, located on the first floor of Coppito II (A2 corridor Labs A2.9 and A2.10), is currently comprised of doctoral student Dott. Luciana Gneo, post-doctoral researcher Dr. Pierdomenico Ruggeri, Research scientist Dr. Lucia Cappabianca and Professors Antonietta Farina and Andrew R. Mackay. Founded in 1991 by Prof's Farina and Mackay in Collemaggio as a direct spin-off of their respective experiences in Molecular biological Cancer research at the National Cancer Institute (NIH, USA), the group focuses on basic molecular cancer research into mechanisms that regulate tumour progression and has led to: better understanding of how the tumour microenvironment regulates tumour progression; characterisation of novel transcriptional and post-transcriptional mechanisms that regulate metastasis associated matrix metalloproteinases, tissue inhibitor of metalloproteinases and autotaxin; identified protective roles for MMPs tumour progression highlighting the potential detrimental effects of broad range MMP inhibitors in cancer treatment; and identified a redox-regulated MMP-dependent mechanism for malignant cancer cell behaviour and angiogenesis, studies that highlight the complexity of matrix metalloproteinase and tissue inhibitors of metalloproteinase involvement in malignant tumour behaviour. Recently, this group identified a novel oncoprotein involved in neuroblastomas progression. This novel oncoprotein, a developmental and stress-regulated TrkAIII splice variant of the TrkA NGF receptor, is expressed by advanced stage metastatic neuroblastomas, associates with disease progression and post therapeutic disease relapse and exhibits oncogenic activity in neuroblastoma models. Recent advances have revealed that TrkAIII promotes an intracellular alternative to classical cell surface receptor tyrosine kinase oncogenic signaling and exerts oncogenic activity through Akt/NF-kB cell survival signaling, which also results in chemo-resistance; regulates angiogenesis by altering the equilibrium between VEGF/MMP-9 and thrombospondin; promotes centrosome amplification resulting in genetic instability; promotes tumour stem cell-like behaviour; results in a protective endoplasmic reticulum stress response and protects mitochondrial from free radical ROS-mediated death by increasing mitochondrial SOD-2 expression. The group is also developing therapeutic strategies to counteract the oncogenic affects of TrkAIII, including development of TrkAIII specific siRNA and PNA inhibitors. The group boasts an array of cellular biological (cell culture, transient and stable cell transfection; cell death, apoptosis, proliferation, invasion and angiogenesis assays); biochemical (MMPs and TIMPs purification; recombinant bacteria, insect and mammalian protein production; rabbit polyclonal antibody production; enzymatic assays, ELISA, immunoprecipitation, Western blotting) and molecular biological (DNA recombination and vector construction; DNA sequencing; regular and real time RT-PCR, in vivo and in vitro transcription assays, chromatin immunoprecipitation, electrophoretic mobility assays; Northern & Southern blotting) techniques.

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Selected Publications

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6. Farina AR, Cappabianca L, Ruggeri, PD., et al., 2012 Alternative TrkA splicing and neuroblastoma, Neuroblastoma – Present and Future, Prof Hiroyuki Shimada (Ed.), ISBN: 978-953-307-016-2, InTech.
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Conferences

Congress: " Comunicare la scienza"
Organised by. Associazione Italiana di Colture Cellulari (AICC)
Where: Rome il 9 giugno or Naples il 19 giugno
When: June 9, 2015 (in Rome) or June 19, 2015 (in Naples)
Contacts: http://www.onlus-aicc.org/eventi/
Notes: Registration only for AICC members

Congress "Alla ricerca delle evidenze nei disturbi dello spettro autistico "
Organised by: ASL1 Avezzano-L'Aquila-Sulmona and University of L'Aquila-DISCAB
Where: L'Aquila; Room "Alan Turing" (Blocco zero), Polo Universitario Coppito
When: June 19, 2015
Contacts: Settore Formazione ASL n.1- tel. 0862 368783-formazione@asl1abruzzo.it
Notes: Registration free

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

General DISCAB News & Views

Our congratulations go to Professor Anna Teti, who has been elected Vice President of the International Bone and Mineral Society

A Departmenal "Poster Week" will be held in the the Atrium of Coppito II Department from the 22 to 29 of June, 2015. This event is designed to promote receiprocal interest in departmental research and to provide junior researchers with an opportunity to fine tune their scientific presentation skills within an informal setting. For further information contact Dr. Francesco Masedu at:
francesco.masedu@cc.univaq.it

The European Union rejects a plea to eliminate animal research across Europe as it would harm biomedical research
http://news.sciencemag.org/europe/2015/06/european-union-rejects-plea-end-animal-research

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

Grants

The Doris Duke Charitable Foundation has announced a new Institutional Grant Opportunity, *2015 Fund to Retain Clinical Scientists*. The fund will provide funds to early-career physician scientists working on clinical research projects and facing extra-professional demands of caregiving. Letters of intent are due **June 15, 2015**. For more information go to: http://www.ddcf.org/Programs/Medical-Research/Goals-and-Strategies/Build-the-Clinical-Research-Career-Ladder/Fund-to-Retain-Clinical-Scientists/

Bando ACRI "Young Investigator Training Program" destinato a giovani ricercatori che, per un mese, lavoreranno presso gli enti di ricerca italiani che aderiranno all'iniziativa. 15/09/2015 : Termine per la presentazione delle domande. For further information go to: http://www.acri.it/PublicFondazioniOnline/Detail/632

Studio sull'innovazione frugale e la riprogettazione delle tecniche tradizionali. Studio sul concetto di innovazione frugale da un punto di vista industriale. Valutazione del potenziale di innovazione frugale per la competitività e lo sviluppo economico dell'Europa nell'ambito delle politiche europee (in materia di ricerca e innovazione, industria, regionali ecc.). Analisi delle varie opzioni di strategie pubbliche e private per la creazione di posti di lavoro e la crescita. 26/06/2015 : Termine per la presentazione delle offerte

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. For further information go to: http://www.care-for-rare.org/en/awards

Borsa di studio per dottorato di ricerca della Fondazione Kindness for Kids. Questa borsa di studio, finanzia un dottorato di ricerca che utilizza esperimenti in vitro per sviluppare nuovi trattamenti per le malattie rare pediatriche. La domanda deve essere inviata via email in inglese come allegato PDF entro il 15 giugno 2015 alla j.barske@kindness-for-kids.de

AFM Telethon have published a call for proposals for Spinal Muscular Atrophy and Collagen VI Call for Projects. For further information go to: http://www.afm-telethon.com/research/calls-for-proposals/current-calls-for-proposals.html

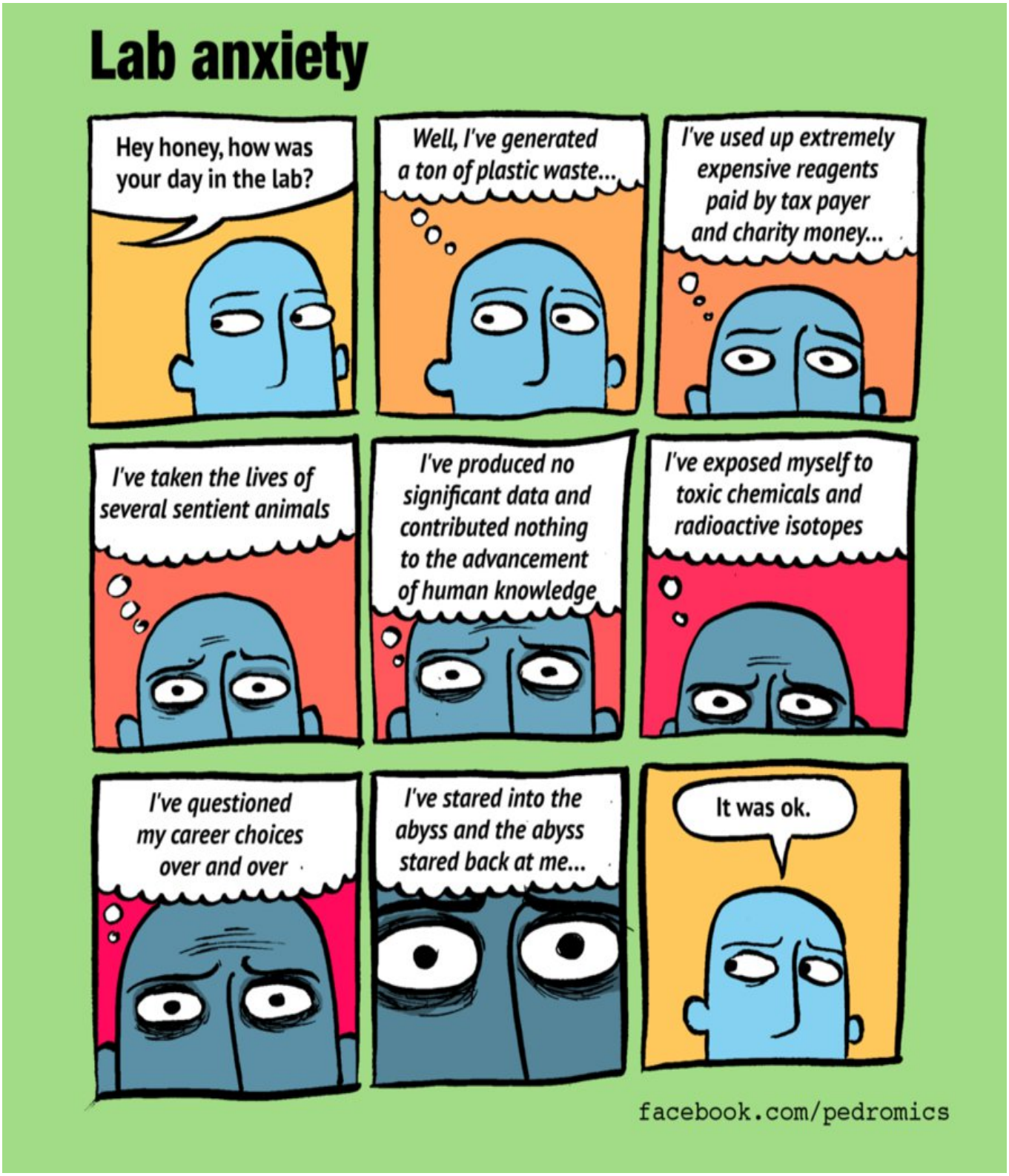
Neuronal Ceroid Lipofuscinosis (NCL) Research Award
NCL invite medical and basic science researchers worldwide to submit innovative clinically oriented or translational project proposals focused upon CLN3 biology, which contribute to finding a cure for juvenile NCL. Submissions are particularly encouraged from scientists working in related biomedical areas such as other lysosomal storage diseases, endolysosomal cell biology and neurodegenerative disorders. The grant (50,000 euros) serves as seed money supporting a one year postdoctoral fellowship to help young scientists progressing CLN3 research in academia or industry. Deadline: October 31, 2015. For further information go to: http://www.neuron-eranet.eu/en/592.php

Call 4 Proposals (2015): Research Osteogenesis Imperfecta (OI)
The aim of this call is to (co) fund projects that will generate better treatment of Osteogenesis Imperfecta. Researchers responding to this call can come from any country. A wide range of treatment or research strategies will be considered. No area will be excluded as long as the quality of life of people with OI can be improved in a tangible and sustainable manner. All disciplines that contribute to the wellbeing of people with OI are invited to join. Creation of alliances and partnerships across national boundaries and medical institutions are explicitly welcomed, especially if they include collaboration with a partner form The Netherlands. Application deadline: 15 July 2015for further information go to: http://www.care4brittlebones.org/nl/onderzoek-menu/call4proposals-nl-2015-menu

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


Lab anxiety
Hey honey, how was your day in the lab?
Well, I've generated a ton of plastic waste...
I've used up extremely expensive reagents paid by tax payer and charity money...
I've taken the lives of several sentient animals
I've produced no significant data and contributed nothing to the advancement of human knowledge
I've exposed myself to toxic chemicals and radioactive isotopes
I've questioned my career choices over and over
I've stared into the abyss and the abyss stared back at me...
It was ok.
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