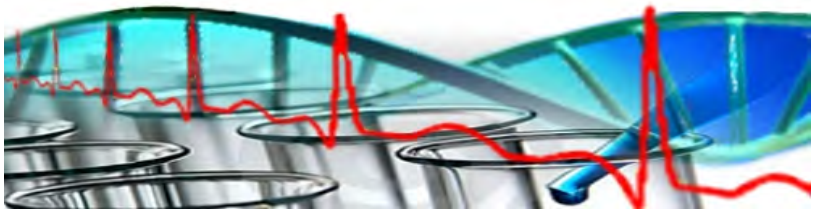
Università degli Studi dell'Aquila
Dipartimento di
Scienze Cliniche Applicate e Biotecnologiche
Nam et ipsa scientia potestas est

DISCAB Research News



Newsletter February, 2016 Issue 6 page 1

Contents

The DISCAB Research news team hope you all had a great Christmas and didn't put on too much weight.

In this sixth issue of DISCAB Research News, the first of 2016, we report exceptional advances in Schizophrenia, Diabetes and superbug resistance research.

In the DISCAB research section, we introduce the research group of Prof. Anna Teti and list recent publications by DISCAB members.

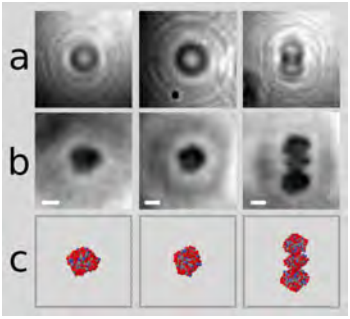
In the News and Views section, we highlight a novel earthquake early warning system to be developed in the USA and another Nature report on potential scientific fraud in Italy.

We hope that you enjoy this edition and remind you that we are what you make us. Therefore, please send us your information and ideas so that we can continue to improve this journal

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

***How to image a single protein**

Jean-Nicolas Longchamp et al.,



http://arxiv.org/abs/1512.08958

Imaging a single protein has been a long-standing dream for advancing structural biology and with this various fields in natural science. In particular, revealing the distinct conformations of an individual protein is of outermost importance. To do so, one needs to master and combine three requirements. At first, a method for isolating individual proteins for further inspection has to be at hand; quite the opposite to the current challenge of assembling proteins into a crystal for X-ray analysis1,2. Furthermore, technologies are required for keeping a single protein fixed in space long enough to accumulate sufficient structural information from a scattering experiment. Last but not least, gentle radiation with a wavelength small enough to uncover structural details while ensuring that radiation damage does not decompose the protein during observation as it is available by low-energy electron holography3 is vital for imaging. Here we show that soft-landing electrospray beam deposition4,5 allows for specific selection and sound deposition5 of individual proteins and protein complexes onto ultraclean freestanding graphene6 in an ultra-high vacuum environment. Due to the fact that graphene is transparent for low-energy electrons7 and since the latter do not damage biological molecules8,9, we were able to acquire high signal-to-noise ratio electron holograms of individual proteins (Cytochrome C and BSA) as well as of protein complexes (haemoglobin). The numerical hologram reconstructions reveal the overall shape of single proteins. With this, images of individual folded proteins and protein complexes, not being the result of an averaging process, have been obtained for the first time.

*** The Happiness Gene**

A genetic component to National Differences in Happiness

Minkov M and Bond H

J Happiness Stud
DOI 10.1007/s10902-015-9712-y

Abstract National differences in subjective well-being (SWB) have been attributed to socio economic, climatic, and genetic factors. We focus on one particular facet of SWB happiness or positive affect—measured by the nationally representative World Values Survey (WVS). We find that national percentages of very happy people across the three latest WVS waves (2000–2004, 2005–2009, 2010–2014) are consistently and highly correlated with national prevalence of the rs324420 A allele in the FAAH gene, involved in the hydrolysis of anandamide, a substance that reportedly enhances sensory pleasure and helps reduce pain. Climatic differences are also significantly associated with national differences in happiness, whereas economic wealth, recent economic growth, rule of law, pathogen prevalence, and the distribution of short versus long alleles in the serotonin transporter gene SLC6A4 are not significant predictors of national happiness.

*** The War of The Worlds**

Nanoparticles kill superbugs-Photoexcited quantum dots for killing multidrug-resistant bacteria

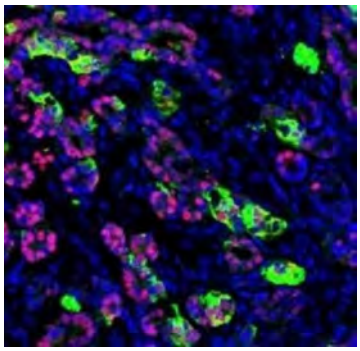
Colleen M. Courtney, CM et al.,
Nature Materials 2016 doi:10.1038/nmat4542

Multidrug-resistant bacterial infections are an ever-growing threat because of the shrinking

arsenal of efficacious antibiotics. Metal nanoparticles can induce cell death, yet the toxicity effect is typically nonspecific. Here, we show that photoexcited quantum dots (QDs) can kill a wide range of multidrug-resistant bacterial clinical isolates, including methicillin-resistant *Staphylococcus aureus*, carbapenem-resistant *Escherichia coli*, and extended-spectrum β-lactamase-producing *Klebsiella pneumoniae* and *Salmonella typhimurium*. The killing effect is independent of material and controlled by the redox potentials of the photogenerated charge carriers, which selectively alter the cellular redox state. We also show that the QDs can be tailored to kill 92% of bacterial cells in a monoculture, and in a co-culture of *E. coli* and HEK 293T cells, while leaving the mammalian cells intact, or to increase bacterial proliferation. Photoexcited QDs could be used in the study of the effect of redox states on living systems, and lead to clinical phototherapy for the treatment of infections.

***A breakthrough in Diabetes research**
"How to make a silk purse out of a Sow's ear"

Human Pancreatic beta-like cells converted from fibroblasts



Zu S et al., Nature communications, 2016
doi:10.1038/ncomms10080

Pancreatic beta cells are of great interest for biomedical research and regenerative medicine.Here we show the conversion of human fibroblasts towards an endodermal cell fate byemploying non-integrative episomal reprogramming factors in combination with specificgrowth factors and chemical compounds. On initial culture, converted definitive endodermal progenitor cells (cDE cells) are specified into posterior foregut-like progenitor cells (cPF cells). The cPF cells and their derivatives, pancreatic endodermal progenitor cells (cPE cells), can be greatly expanded. A screening approach identified chemical compounds that promote the differentiation and maturation of cPE cells into functional pancreatic beta-like cells (cPB cells) in vitro. Transplanted cPB cells exhibit glucose-stimulated insulin secretion in vivo and protect mice from chemically induced diabetes. In summary, our study has important implications for future strategies aimed at generating high numbers of functional beta cells, which may help restoring normoglycemia in patients suffering from diabetes.

***Internet the double edged sword**
The spreading of misinformation on line

Del Vicario M et al., PNAS 2016
doi:10.1073/pnas.1517441113

Thewide availability of user-provided content in online socialmedia facilitates the aggregation of people around common interests, worldviews, and narratives. However, theWorld WideWeb (WWW) also allows for the rapid dissemination of unsubstantiated rumors and conspiracy theories that often elicit rapid, large, but naive social responses such as the recent case of Jade Helm where a simple military exercise turned out to be perceived as the beginning of a new civil war in the United States. In this work, we address the determinants governing misinformation spreading through a thorough quantitative analysis. In particular, we focus on how Facebook users consume information related to two distinct narratives: scientific and conspiracy news. We find that, although consumers of scientific and conspiracy stories present similar consumption patterns with respect to content, cascade dynamics differ. Selective exposure to content is the primary driver of content diffusion and generates the formation of homogeneous clusters, i.e., "echo chambers." Indeed, homogeneity appears to be the primary driver for the diffusion of contents and each echo chamber has its own cascade dynamics. Finally, we introduce a data-driven percolation model mimicking rumor spreading and we show that homogeneity and polarization are the main determinants for predicting cascades' size.

***The Psychedelic Renaissance**
Psychedelic Studies Group -Yale University

Taub B. http://www.iflscience.com/brain/psychedelic-studies-group-launched-yale-university

Academics at Yale University have founded a study group focusing on the use of psychedelic substances in the field of psychiatry and psychotherapy.

The potential of such substances for helping scientists to explore the human mind and treat psychological disorders was first investigated in the 1950s, following the emergence of LSD. Initial theories about how psychedelics worked followed the so-called psychotomimetic model, which held that ingesting these substances induced temporary psychosis, enabling scientists to observe this phenomenon in a controlled way.

This line of investigation was later abandoned when it became apparent that the effects of these substances did not in fact match the effects of psychosis, although some psychotherapists began to report that the use of psychedelic drugs facilitated many types of therapy.

In light of this, some scientists began experimenting with chemicals such as LSD, MDMA, psilocybin (the psychoactive chemical found in hallucinogenic mushrooms), and DMT to treat a number of conditions ranging from anxiety to addiction, yet most of this research ended once these substances were outlawed by most western countries.

Recently, however, psychedelic science has experienced something of a resurgence, with a number of academic institutions receiving permission to conduct trials using psychoactive drugs. For instance, research into the anti-depressant potential of psilocybin is currently underway at Imperial College London, while Swiss scientists recently published a paper on the ability of LSD to help terminal patients overcome death-related anxiety. Elsewhere, trails involving the use of MDMA to treat post-traumatic stress disorder among war veterans are also in the pipeline.

The YPPG has been set up by a collection of residents, fellows, graduate students, clinical practitioners, and faculty members at Yale as a platform to discuss past and ongoing research into psychedelics. Prominent researchers in the field of psychedelics will be invited to talk from around the world, in an attempt to combine and consolidate the expertise of those at the forefront of this exciting area of science.

In establishing the group, the organizers hope to help guide future research into psychedelic substances by critically engaging with key questions about the true effect of these drugs and what clinical implications they may have.

***From single cell to Gentleman**

Evolution of an ancient protein function involved in organized multi-cellularity in animals

Anderson DP et al., eLife 2016. Doi:10.7554/eLife.10147

To form and maintain organized tissues, multicellular organisms orient their mitotic spindles relative to neighboring cells. A molecular complex scaffolded by the GK protein-interaction domain (GKPID) mediates spindle orientation in diverse animal taxa by linking microtubule motor proteins to a marker protein on the cell cortex localized by external cues. Here we illuminate how this complex evolved and commandeered control of spindle orientation from a more ancient mechanism. The complex was assembled through a series of molecular exploitation events, one of which – the evolution of GKPID's capacity to bind the cortical marker protein – can be recapitulated by reintroducing a single historical substitution into the reconstructed ancestral GKPID. This change revealed and repurposed an ancient molecular surface that previously had a radically different function. We show how the physical simplicity of this binding interface enabled the evolution of a new protein function now essential to the biological complexity of many animals.

***Cool Idea -Sponges to trap metastatic breast cancer**

In vivo capture and label-free detection of early metastatic disease

Azarin SM et al., Nature Communications 2015
Doi:10.1038/ncomms9094

Breast cancer is a leading cause of death for women, with mortality resulting from metastasis. Metastases are often detected once tumour cells affect the function of solid organs, with a high disease burden limiting effective treatment. Here we report a method for the early detection of metastasis using an implanted scaffold to recruit and capture metastatic cells *in vivo*, which achieves high cell densities and reduces the tumour burden within solid organs 10-fold. Recruitment is associated with infiltration of immune cells, which include $Gr1^{hi}CD11b+$ cells. We identify metastatic cells in the scaffold through a label-free detection system using inverse spectroscopic optical coherence tomography, which identifies changes to nanoscale tissue architecture associated with the presence of tumour cells. For patients at risk of recurrence, scaffold implantation following completion of primary therapy has the potential to identify metastatic disease at the earliest stage, enabling initiation of therapy while the disease burden is low.

***Fantastic breakthrough in Schizophrenia Research**

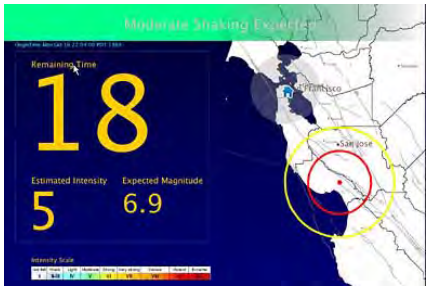
Schizophrenia risk from complex variation of complement component 4

Sekar A et al., Nature 2016; 530: 177
Doi::10.1038/nature16549

Schizophrenia is a heritable brain illness with unknown pathogenic mechanisms. Schizophrenia's strongest genetic association at a population level involves variation in the major histocompatibility complex (MHC) locus, but the genes and molecular mechanisms accounting for this have been challenging to identify. Here we show that this association arises in part from many structurally diverse alleles of the complement component 4 (C4) genes. We found that these alleles generated widely varying levels of C4A and C4B expression in the brain, with each common C4 allele associating with schizophrenia in proportion to its tendency to generate greater expression of C4A. Human C4 protein localized to neuronal synapses, dendrites, axons, and cell bodies. In mice, C4 mediated synapse elimination during postnatal development. These results implicate excessive complement activity in the development of schizophrenia and may help explain the reduced numbers of synapses in the brains of individuals with schizophrenia.

*One to keep your eye on.

Early Earthquake Warning system to be developed



The United States Geological Survey (USGS) along with a coalition of university partners are developing and testing an earthquake early warning system called ShakeAlert for the west coast of the United States. The work is being funded by the Gordon and Betty Moore Foundation and the USGS. The State of California is also a partner in this project through the Governor's Office of Emergency Services and the California Geological Survey.

Today, the technology exists to detect earthquakes, so quickly, that an alert can reach some areas before strong shaking arrives. The purpose of an EEW system is to identify and characterize an earthquake a few seconds after it begins, calculate the likely intensity of ground shaking that will result, and deliver warnings to people and infrastructure in harm's way. This can be done by detecting the first energy to radiate from an earthquake, the P-wave energy, which rarely causes damage. Using P-wave information, we first estimate the location and the magnitude of the earthquake. Then, the anticipated ground shaking across the region to be affected is estimated and a warning is provided to local populations. The method can provide warning before the S-wave arrives, bringing the strong shaking that usually causes most of the damage.
Studies of earthquake early warning methods in California have shown that the warning time would range from a few seconds to a few tens of seconds, depending on the distance to the epicenter of the earthquake. For very large events like those expected on the San Andreas fault zone or the Cascadia subduction zone the warning time could be much longer because the affected area is much larger. ShakeAlert can give enough time to slow and stop trains and taxiing planes, to prevent cars from entering bridges and tunnels, to move away from dangerous machines or chemicals in work environments and to take cover under a desk, or to automatically shut down and isolate industrial systems. Taking such actions before shaking starts can reduce damage and casualties during an earthquake. It can also prevent cascading failures in the aftermath of an event. For example, isolating utilities before shaking starts can reduce the number of fire initiations.
Status The ShakeAlert EEW system has been developed for the West Coast within the existing operational environments of three ANSS regional seismic networks in southern California (Southern California Seismic Network, SCSN), northern California (Northern California Seismic System, NCSS), and the Pacific Northwest (Pacific Northwest Seismic Network, PNSN). This enables USGS and ANSS to leverage their substantial investment in sensor networks, data telemetry systems, data processing centers, and software for earthquake monitoring activities residing in these network centers. The ShakeAlert system has been sending live alerts to test users since January of 2012.
System Goal To issue public warnings of potentially damaging earthquakes and provide warning parameter data to government agencies and private users on a region-by-region basis, as soon as the ShakeAlert system, its products, and its parametric data meet minimum quality and reliability standards in those geographic regions. Product availability will expand geographically via regional seismic networks, such that ShakeAlert products and warnings become available for all regions with dense seismic instrumentation.

Italian papers on genetically modified crops under investigation

Nature **529,** 268–269 (21 January 2016)
doi:10.1038/nature.2016.19183

GM soya bean has passed numerous safety tests.
Papers that describe harmful effects to animals fed genetically modified (GM) crops are under scrutiny for alleged data manipulation. The leaked findings of an ongoing investigation at the University of Naples in Italy suggest that images in the papers may have been intentionally altered. The leader of the lab that carried out the work there says that there is no substance to this claim.

The Bone Biopathology Laboratory is headed by Prof Anna Maria Teti and it is composed by 10 members from 3 different nationalities (Italy, India and UK) and numerous visiting students and scientists that contribute to an international environment.

The group has a long-standing expertise in bone cell biology and pathophysiology, and investigates the mechanisms inducing bone diseases, including osteoporosis, bone metastasis and rare genetic syndromes. The team performs in vitro and in vivo studies using various approaches, ranging from state-of-art microscopy to RNA deep sequencing and large-scale analysis, cell and molecular biology, histology and histopathology, histo/cytochemistry, immunohisto/cytochemistry, histomorphometry, X-ray analysis, micro computed tomography, bioluminescence, indentation studies. Mouse models of rare genetic bone diseases, such as osteopetrosis, have been generated by the group, and mouse models of common bone diseases, such as osteoporosis and bone malignancies, are routinely used in the laboratory. The team is also specialized in studies on disuse osteoporosis and is equipped to perform studies in simulated microgravity conditions using tri-dimensional cultures. The team has long-standing international collaborations with groups in USA, Norway, Germany, France, UK, India, Brazil, Australia and South Africa. It has participated in FP6 projects MetaBre (as coordinator) and OSTEOGENE (as deputy coordinator) and in FP7 project INTERBONE (as coordinator), and is currently involved in FP7 project SYBIL (as vice-coordinator) and in Horizon 2020 project RUBICON (as coordinator). The group is also supported by the Italian charities, Telethon and AIRC.

Prof Teti and her collaborators are internationally recognised in the field of bone research. Prof Teti has held senior position of responsibility in the European Calcified Tissue Society (treasurer), in the International Bone and Mineral Society (vice-president) and in the American Society for Bone and Mineral Research (ASBMR 2017 programme co-chair). Dr Mattia Capulli and Dr Antonio Maurizi have received international training at the Columbia University in New York (USA) under the mentoring of Prof Gerard Karsenty and Stavroula Kousteni. Dr Capulli is member of the International Federation of Bone and Mineral Research young investigator committee and has received numerous young investigator awards and travel grants for oral presentations at international congresses. His research has also been supported by the European Calcified Tissue Society. For information contact: bonesecr@univaq.it

Patent

- Small interfering rna (sirna) for the therapy of type 2 (ado2) autosomal dominant osteopetrosis caused by clcn7 (ado2 clcn7-dependent) gene mutation. WO 2015177743 A1

Selected publications

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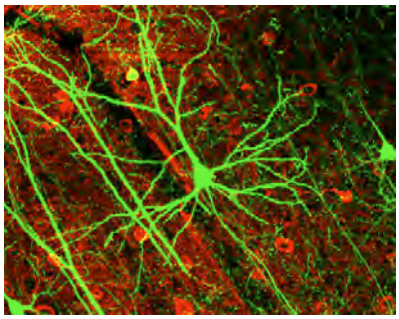
Cholinergic excitation from the pedunculopontine tegmental nucleus to the dentate nucleus in the rat.



Vitale F, Mattei C, Capozzo A, Pietrantoni I, Mazzone P, Scarnati E. Neuroscience. 2016; 317:12-22. doi: 10.1016/j.neuroscience.2015.12.055. PMID: 26762800

Abstract: In spite of the existence of pedunculopontine tegmental nucleus (PPTg) projections to cerebellar nuclei, their nature and functional role is unknown. These fibers may play a crucial role in postural control and may be involved in the beneficial effects induced by deep-brain stimulation (DBS) of brainstem structures in motor disorders. We investigated the effects of PPTg microstimulation on single-unit activity of dentate, fastigial and interpositus nuclei. The effects of PPTg stimulation were also studied in rats whose PPTg neurons were destroyed by ibotenic acid and subsequently subjected to iontophoretically applied cholinergic antagonists. The main response recorded in cerebellar nuclei was a short-latency (1.5-2ms) and brief (13-15ms) orthodromic activation. The dentate nucleus was the most responsive to PPTg stimulation. The destruction of PPTg cells reduced the occurrence of PPTg-evoked activation of dentate neurons, suggesting that the effect was due to stimulation of cell bodies and not due to fibers passing through or close to the PPTg. Application of cholinergic antagonists reduced or eliminated the PPTg-evoked response recorded in the dentate nucleus. The results show that excitation is exerted by the PPTg on the cerebellar nuclei, in particular on the dentate nucleus. Taken together with the reduction of nicotinamide adenine dinucleotide phosphate-diaphorase-positive neurons in lesioned animals, the iontophoretic experiments suggest that the activation of dentate neurons is due to cholinergic fibers. These data help to explain the effects of DBS of the PPTg on axial motor disabilities in neurodegenerative disorders.

Gravina GL, Mancini A, Sanita P, Vitale F, Marampon F, Ventura L, Landesman Y, McCauley D, Kauffman M, Shacham S, Festuccia C. Erratum to: KPT-330, a potent and selective exportin-1 (XPO-1) inhibitor, shows antitumor effects modulating the expression of cyclin D1 and survivin in prostate cancer models. BMC Cancer. 2016 16: 8. doi: 10.1186/s12885-015-2046-7. PMID: 26753765

An Innovative Model of a Home-Like Environment for People in Vegetative and Minimally Conscious States.

Zylberman R, Carolei A, Sacco S, Mallia P, Pistoia F. Neurohospitalist. 2016;6: 14-9. doi: 10.1177/1941874415596747. PMID: 26753053

BACKGROUND AND PURPOSE: Many forms of assisted living have been proposed for people who have a loss of autonomy in activities of daily living. Despite the increasing prevalence of vegetative and minimally conscious states, no dedicated residential accommodation has been implemented for patients with chronic disorders of consciousness (DOCs). **METHODS:** This is a descriptive study addressing an innovative model of in-house assistance, named Casa Iride, which has recently been implemented in the attempt to ensure health, safety, and well-being for people with DOCs and their families. **RESULTS:** Our findings show that Casa Iride enables severely disabled individuals to live with dignity within a customized domestic environment. At the same time, it provides support for caregivers from both a practical and a psychological point of view. **CONCLUSIONS:** The results so far indicate a virtuous cycle that brings health, social, psychological, ethical, and economic advantages: the individuals receive all the assistance needed; the families share a place with other people with similar challenges, become more aware of their situation, and learn to cope with it and to maintain their productivity at work; and the care flow of patients through intensive care units and intensive rehabilitation wards is not delayed by a lack of post discharge services.

Evidence of estrogen modulation on memory processes for emotional content in healthy young women.

Pompili A, Arnone B, D'Amico M, Federico P, Gasbarri A.
Psychoneuroendocrinology. 2015;65:94-101. doi:10.1016/j.psyneuen.2015.12.013. PMID: 26731574

PURPOSE: It is well accepted that emotional content can affect memory, interacting with the encoding and consolidation processes. The aim of the present study was to verify the effects of estrogens in the interplay of cognition and emotion. **METHODS:** Images from the International Affective Pictures System, based on valence (pleasant, unpleasant and neutral), maintaining arousal constant, were viewed passively by two groups of young women in different cycle phases: a periovulatory group (PO), characterized by high level of estrogens and low level of progesterone, and an early follicular group (EF), characterized by low levels of both estrogens and progesterone. The electrophysiological responses to images were measured, and P300 peak was considered. One week later, long-term memory was tested by means of free recall. **FINDINGS:** Intra-group analysis displayed that PO woman had significantly better memory for positive images, while EF women showed significantly better memory for negative images. The comparison between groups revealed that women in the PO phase had better memory performance for positive pictures than women in the EF phase, while no significant differences were found for negative and neutral pictures. According to the free recall results, the subjects in the PO group showed greater P300 amplitude, and shorter latency, for pleasant images compared with women in the EF group. **CONCLUSION:** Our results showed that the physiological hormonal fluctuation of estrogens during the menstrual cycle can influence memory, at the time of encoding, during the processing of emotional information.

MicroRNA expression analysis in high fat diet-induced NAFLD-NASH-HCC progression: study on C57BL/6J mice.

Tessitore A, Cicciarelli G, Del Vecchio F, Gaggiano A, Verzella D, Fischietti M, Mastroiaco V, Vetuschi A, Sferra R, Barnabei R, Capece D, Zazzeroni F, Alesse E.
BMC Cancer. 2016; 16:3. doi: 10.1186/s12885-015-2007-1. PMID: 26728044

BACKGROUND: Hepatocellular carcinoma (HCC) is the most common malignant tumor of the liver. Non-alcoholic fatty liver disease (NAFLD) is a frequent chronic liver disorder in developed countries. NAFLD can progress through the more severe non alcoholic steatohepatitis (NASH), cirrhosis and, lastly, HCC. Genetic and epigenetic alterations of coding genes as well as deregulation of microRNAs (miRNAs) activity play a role in HCC development. In this study, the C57BL/6J mouse model was long term high-fat (HF) or low-fat (LF) diet fed, in order to analyze molecular mechanisms responsible for the hepatic damage progression. **METHODS:** Mice were HF or LF diet fed for different time points, then plasma and hepatic tissues were collected. Histological and clinical chemistry assays were performed to assess the progression of liver disease. MicroRNAs' differential expression was evaluated on pooled RNAs from tissues, and some miRNAs showing dysregulation were further analyzed at the individual level. **RESULTS:** Cholesterol, low and high density lipoproteins, triglycerides and alanine aminotransferase increase was detected in HF mice. Gross anatomical examination revealed hepatomegaly in HF livers, and histological analysis highlighted different degrees and levels of steatosis, inflammatory infiltrate and fibrosis in HF and LF animals, demonstrating the progression from NAFLD through NASH. Macroscopic nodules, showing typical neoplastic features, were observed in 20 % of HF diet fed mice. Fifteen miRNAs differentially expressed in HF with respect to LF hepatic tissues during the progression of liver damage, and in tumors with respect to HF non tumor liver specimens were identified. Among them, miR-340-5p, miR-484, miR-574-3p, miR-720, whose expression was never described in NAFLD, NASH and HCC tissues, and miR-125a-5p and miR-182, which showed early and significant dysregulation in the

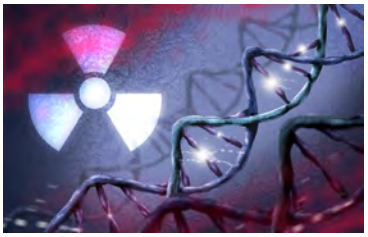
sequential hepatic damage process. **CONCLUSIONS:** In this study, fifteen microRNAs which were modulated in hepatic tissues and in tumors during the transition NAFLD-NASH-HCC are reported. Besides some already described, new and early dysregulated miRNAs were identified. Functional analyses are needed to validate the results here obtained, and to better define the role of these molecules in the progression of the hepatic disease.

Tailoring the dosing schedule of nab-paclitaxel in metastatic breast cancer according to patient and disease characteristics: Recommen-dations from a panel of experts.

Arpino G, Marmé F, Cortés J, Ricevuto E, Leonard R, Llombart-Cussac A. Crit Rev Oncol Hematol. 2015; pii: S1040-8428(15)30056-1. doi:10.1016/j.critrevonc. 2015.10.007.

Abstract: The choice of chemotherapy for patients with metastatic breast cancer (MBC) depends on disease- and patient-related factors, but there is little guidance on dosing modifications for patients unable to receive the licensed dose. Nab-paclitaxel is a solvent-free form of paclitaxel that uses albumin as a drug carrier and exploits endogenous albumin transport pathways to achieve enhanced drug targeting and tumour penetration with reduced toxicity. It is approved for use at a dose of 260mg/m(2) every three weeks in adults who have failed first-line treatment for MBC and for whom standard anthracycline-based therapy is not indicated. Emerging data suggest that weekly dosing schedules of nab-paclitaxel may provide clinical benefit in some patients, but the utility of these alternative dosing schedules remains unclear. A panel of breast cancer experts convened to review available literature for nab-paclitaxel in MBC and, taking into account their clinical experience, recommended that alternative dosing schedules may be considered according to the aggressiveness of disease and patient condition as follows: 125mg/m(2) QW 3/4 (aggressive disease and fit), 100mg/m(2) QW 3/4 (aggressive or indolent disease and unfit). All dosing schedules were considered acceptable for fit patients with indolent disease. These recommendations are based on current evidence, and emerging data from ongoing trials may reinforce or modify the recommendations provided.

Cyclin D1 silencing suppresses tumorigenicity, impairs DNA double strand break repair and thus radiosensitizes androgenindependent prostate cancer cells to DNA damage.



Marampon F, Gravina GL, Ju X, Vetuschi A, Sferra R, Casimiro MC, Pompili S, Festuccia C, Colapietro A, Gaudio E, Di Cesare E, Tombolini V, Pestell RG. Oncotarget. 2015; doi: 10.18632/oncotarget. 6579.

Abstract: Patients with hormone-resistant prostate cancer (PCa) have higher biochemical failure rates following radiation therapy (RT). Cyclin D1 deregulated expression in PCa is associated with a more aggressive disease: however its role in radioresistance has not been determined. Cyclin D1 levels in the androgen-independent PC3 and 22Rv1 PCa cells were stably inhibited by infecting with cyclin D1-shRNA. Tumorigenicity and radiosensitivity were investigated using in vitro and in vivo experimental assays. Cyclin D1 silencing interfered with PCa oncogenic phenotype by inducing growth arrest in the G1 phase of cell cycle and reducing soft agar colony formation, migration, invasion in vitro and tumor formation and neo-angiogenesis in vivo. Depletion of cyclin D1 significantly radiosensitizes PCa cells by increasing the RT-induced DNA damages by affecting the NHEJ and HR pathways responsible of the DNA double-strand break repair. Following treatment of cells with RT the abundance of a biomarker of DNA damage, γ-H2AX, was dramatically increased in sh-cyclin D1 treated cells compared to shRNA control. Concordant with these observations DNA-PKcs-activation and RAD51-accumulation, part of the DNA double-strand break repair machinery, were reduced in shRNA-cyclin D1 treated cells compared to shRNA control. We further demonstrate the physical interaction between CCND1 with activated-ATM, -DNA-PKcs and RAD51 is enhanced by RT. Finally, siRNA-mediated silencing experiments indicated DNA-PKcs and RAD51 are downstream targets of

CCND1-mediated PCa cells radioresistance. In summary, these observations suggest that CCND1 is a key mediator of PCa radioresistance and could represent a potential target for radioresistent hormone-resistant PCa.

Dysbindin-1 modifies signaling and cellular localization of recombinant, human D3 and D2 receptors.

Schmieg N, Rocchi C, Romeo S, Maggio R, Millan MJ, Mannoury la Cour C.
J Neurochem. 2015; doi: 10.1111/jnc.13501. PMID: 26685100

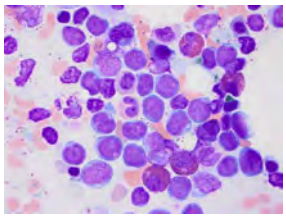
Abstract: Dystrobrevin binding protein-1 (dysbindin-1), a candidate gene for schizophrenia, modulates cognition, synaptic plasticity and frontocortical circuitry and interacts with glutamatergic and dopaminergic transmission. Loss of dysbindin-1 modifies cellular trafficking of dopamine D2 receptors to increase cell surface expression, but its influence upon signaling has never been characterized. Further, the effects of dysbindin-1 upon closely-related D3 receptors remain unexplored. Hence, we examined the impact of dysbindin-1 (isoform A) co-expression on the localization and coupling of human D2L and D3 receptors stably expressed in CHO or SH-SY5Y cells lacking endogenous dysbindin-1. Dysbindin-1 co-transfection decreased cell surface expression of both D3 and D2L receptors. Further, while their affinity for DA was unchanged, dysbindin-1 reduced the magnitude and potency of DA-induced adenylate cylase recruitment/cAMP production. Dysbindin-1 also blunted the amplitude of DA-induced phosphorylation of ERK1/2 and Akt at both D2L and D3 receptors without, in contrast to cAMP, affecting the potency of DA. Interference with calveolin/clathrin-mediated processes of internalization prevented the modification by dysbindin-1 of ERK1/2 and adenylyl cyclase stimulation at D2L and D3 receptors. Finally, underpinning the specificity of the influence of dysbindin-1 on D2L and D3 receptors, dysbindin-1 did not modify recruitment of adenylyl cyclase by D1 receptors. Theseobservations demonstrate that dysbindin-1 influences cell surface expression of D3 in addition to D2L receptors, and that it modulates activation of their signaling pathways. Accordingly, both a deficiency and an excess of dysbindin-1 may be disruptive for dopaminergic transmission, supporting its link to schizophrenia and other CNS disorders. This article is protected by copyright. All rights reserved.

Safety and efficacy of intra-articular anti-tumor necrosis factor α agents compared to corticosteroids in a treat-to-target strategy in patients with inflammatory arthritis and monoarthritis flare.

Carubbi F, Zugaro L, Cipriani P, Conchiglia A, Gregori L, Danniballe C, Letizia Pistoia M, Liakouli V, Ruscitti P, Ciccia F, Triolo G,, Masciocchi C, Giacomelli R.
Int J Immunopathol Pharmacol. 2015; pii: 0394632015593220. PMID: 26684633

Abstract: The aim of this study was to assess safety and efficacy of ultrasonography (US)-guided intra-articular injections using tumor necrosis factor (TNF) blockers compared to corticosteroids in rheumatoid arthritis (RA) or psoriatic arthritis (PsA) patients, experiencing refractory monoarthritis despite the current systemic therapy. Eighty-two patients were randomized to receive three intra-articular injections monthly of either corticosteroid or TNF blockers. Primary endpoints were the safety and an improvement greater than 20% for visual analogic scales of involved joint pain in patients injected with anti-TNFα. Further clinical, US, and magnetic resonance imaging (MRI) evaluations were considered secondary endpoints. Intra-articular TNF blockers are a safe strategy, determining a significant reduction of patient and physician reported clinical outcomes and US/MRI scores, in RA and PsA patients, when compared to intra-articular injections of corticosteroids. US guidance excluded the possibility to inject the drug in the wrong site, maximizing local effects, reducing systemic effects, and increasing the safety of the procedure. Patients with inflammatory monoarthritis could be successfully treated with US-guided intra-articular TNF blockers that are a safe and well tolerated procedure, to achieve a longstanding clinical and radiological good clinical response and/or disease remission.

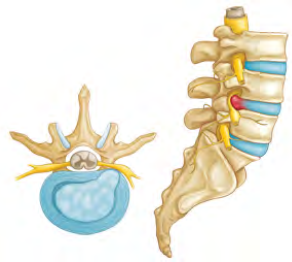
Normal hematopoiesis and lack of β-catenin activation in osteoblasts of patients and mice harboring Lrp5 gain-of-function mutations.



Galán-Díez M, Isa A, Ponzetti M, Nielsen MF, Kassem M, Kousteni S.
Biochim Biophys Acta. 2016 Mar;1863(3):490-8. doi: 10.1016/j.bbamcr.2015.11.037. Epub 2015; PMID: 26681532

Abstract: Osteoblasts are emerging regulators of myeloid malignancies since genetic alterations in them, such as constitutive activation of β-catenin, instigate their appearance. The LDL receptor-related protein 5 (LRP5), initially proposed to be a co-receptor for Wnt proteins, in fact favors bone formation by suppressing gut-serotonin synthesis. This function of Lrp5 occurring in the gut is independent of β-catenin activation in osteoblasts. However, it is unknown whether Lrp5 can act directly in osteoblast to influence other functions that require β-catenin signaling, particularly, the deregulation of hematopoiesis and leukemogenic properties of β-catenin activation in osteoblasts, that lead to development of acute myeloid leukemia (AML). Using mice with gain-of-function (GOF) Lrp5 alleles (Lrp5(A214V)) that recapitulate the human high bone mass (HBM) phenotype, as well as patients with the T253I HBM Lrp5 mutation, we show here that Lrp5 GOF mutations in both humans and mice do not activate β-catenin signaling in osteoblasts. Consistent with a lack of β-catenin activation in their osteoblasts, Lrp5(A214V) mice have normal trilinear hematopoiesis. In contrast to leukemic mice with constitutive activation of β-catenin in osteoblasts (Ctnnb1(CAosb)), accumulation of early myeloid progenitors, a characteristic of AML, myeloid-blasts in blood, and segmented neutrophils or dysplastic megakaryocytes in the bone marrow, are not observed in Lrp5(A214V) mice. Likewise, peripheral blood count analysis in HBM patients showed normal hematopoiesis, normal percentage of myeloid cells, and lack of anemia. We conclude that Lrp5 GOF mutations do not activate β-catenin signaling in osteoblasts. As a result, myeloid lineage differentiation is normal in HBM patients and mice. This article is part of a Special Issue entitled: Tumor Microenvironment Regulation of Cancer Cell Survival, Metastasis, Inflammation, and Immune Surveillance.

Indications and efficacy of O2-O3 intradiscal versus steroid intraforaminal injection in different types of disco vertebral pathologies: a prospective randomized double-blind trial with 517 patients.

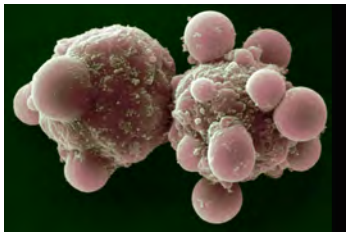


Perri M, Marsecano C, Varrassi M, Giordano AV, Splendiani A, Di Cesare E, Masciocchi C, Gallucci M.
Radiol Med. 2015; PMID: 26676838

OBJECTIVE: The aim of this study was to prospectively evaluate the clinical efficacy of perigangliar steroid and local anesthetic with intradiscal O2-O3 injection versus steroid and local anesthetic intraforaminal injection in different types of herniation and grade of disc degeneration. **MATERIALS AND METHODS:** A total of 517 patients were randomly assigned to two groups. Control Group (159 men, 101 women; age range 25-89 years) underwent steroid and local anesthetic intraforaminal injection. Study Group (163 men, 94 women; age range 22-92 years) underwent the same treatment with addiction of O2-O3 intradiscal injection. Procedures were performed under computed tomographic guidance. Visual Analog Scale Questionnaire was administered before treatment and at intervals, the last at 6-month follow-up. Results were compared with Kruskal-Wallis and t test. **RESULTS:** After 6 months, O2-O3 discolysis was successful in 106 (41.24 %) Study Group patients with extrusions compared with 9 Control Group patients (3.5 %) ($P < 0.001$). In 89 (34.6 %) Study Group patients with protrusions, success rate was statistically significant compared with 5 Control Group patients (1.9 %). Significant difference was detected in the presence of Grade I, II, III of Degenerated Disc in 185 of Study Group patients (68.4 %) compared with 4 Control Group patients (1.5 %). **CONCLUSIONS:** The addition of O2-O3 discolysis is more effective at 6 months than perigangliar steroid and local anesthetic injection, especially in cases of herniated or protruded discs and with a Grade of Disc Degeneration from mild to moderate range.

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

NGF sensitizes TrkA SH-SY5Y neuroblastoma cells to TRAIL-induced apoptotsis



Ruggeri P, Cappabianca L, Farina AR, Gneo L and Mackay AR.
Cell Death Discovery 2016; 2, 16004;
doi:101038/ccdiscovery.2164.4

We report a novel pro-apoptotic function for nerve growth factor (NGF) and its tropomyosin-related kinase A (TrkA) receptor in sensitizing TRAIL (TNF-related apoptotis-inducing ligand)-resistant SH-SY5Y neuroblastoma (NB) cells to TRAIL-induced apoptosis, resulting in the abrogation of anchorage-independent tumourigenic growth in vitro. We show that the TRAIL-resistant SH-SY5Y phenotype is cFLIP (cellular FLICE-like inhibitory protein) dependent and not due to low-level functional TRAIL receptor or caspase expression or an inhibitory equilibrium between functional and decoy TRAIL receptors or B-cell lymphoma 2 (Bcl-2) and BH3-only (Bcl-2 homology domain 3-only) family proteins. NGF sensitization of SH-SY5Y cells to TRAIL-induced apoptosis was dependent upon TrkA expression, activation and subsequent sequestration of cFLIP. This reduces cFLIP recruitment to TRAIL-activated death receptors and increases the recruitment of caspase-8, leading to TRAIL-induced, caspase-dependent, type II apoptosis via the intrinsic mitochondrial pathway. This effect was temporary, inhibited within 6 h by nuclear factor-κ binding (NF-κB)-mediated increase in myeloid cell leukaemia-1 (Mcl-1) expression, abrogated by transient cFLIP or B-cell lymphoma-extra large (Bcl-xL) overexpression and optimized by NF-κB and Mcl-1 inhibitors. This novel mechanism adds an important pro-apoptotic immunological dimension to NGF/TrkA interaction that may not only help to explain the association between TrkA expression, better prognosis and spontaneous remission in NB, but also provides a novel potential pro-apoptotic therapeutic use for NGF, TRAIL and inhibitors of NF-κB and/or Mcl-1 in favourable and unfavourable NBs that express TrkA and exhibit cFLIP-mediated TRAIL resistance.

Congenital Central Hypoventilation Syndrome Family Network The Congenital Central Hypoventilation Syndrome (CCHS) pilot grant award represents a collaborative effort between the CCHS Family Network and the CCHS Foundation to encourage and support basic, clinical, translational, or epidemiological research to impact the lives of patients with CCHS. The grant provides up to $30,000 over 1 year for expenses related to the research project, which may include research laboratory supplies, equipment, publication charges for manuscripts that pertain directly to the funded project, and other research expenses. **Application Deadline: 29 February, 2016**

Kindness for Kids Health Care Award Kindness for kids will award a maximum of 40,000 euros for the implementation of a project that aims to directly improve the situation of children living with a rare disease through structural changes or with a new therapeutic approach in the area of physiotherapy and psychological care. For further information: http://www.kindness-for-kids.de/sites/default/files/images/Health%20Care%20Award%20Application%202016.pdf

The Jerome Lejeune Foundation If you are a researcher investigating intellectual disability from genetic origin appearing in early childhood, the Scientific Advisory Board of the Jerome Lejeune Foundation invites you to submit your research project aiming at deciphering the pathophysiology of the cognitive deficits of patients, especially those with trisomy 21 (Down syndrome) and other rare abnormalities such as fragile X, cri du chat, Rett, Williams-Beuren, Prader-Willi, Angelman, and other syndromes, excluding autism. Grants are offered for one or two year(s) within the range of EUR 20 000 per year. Clinical projects could benefit from more funding. **Deadline: 7 March, 2016** For further information: http://www.fondationlejeune.org/en/our-missions-and-actions/research/apply-for-a-grant-obtain-funding

The National Cancer Institute (NCI) has published three companion Funding Opportunity Announcements (FOAs) for Genomic Data Analysis Network Centers to support programs of the Center for Cancer Genomics (CCG). The FOAs are managed by CCG and solicit applications for a Processing Genomic Data Center, aVisualization Genomic Data Center, and a Specialized Genomic Data Center.

Progeria Research Foundation
The foundation is proving several grants such as Innovator Awards, Established Innovator Award, and Specialty Award. Details are provided on their website

AFM Telethon: Call for proposals
Several call for proposals are being made available by AFM Telethon. They have published a call for proposals for Spinal Muscular Atrophy and Collagen VI Call for Projects.

If you are a researcher investigating intellectual disability from genetic origin appearing in early childhood, the Scientific Advisory Board of the Jerome Lejeune Foundation invites you to submit your research project aiming at deciphering the pathophysiology of the cognitive deficits of patients, especially those with trisomy 21 (Down syndrome) and other rare abnormalities such as fragile X, cri du chat, Rett, Williams-Beuren, Prader-Willi, Angelman, and other syndromes, excluding autism. Grants are offered for one or two year(s) within the range of EUR 20 000 per year. Clinical projects could benefit from more funding. Deadline: 7 March, 2016

FONDAZIONE ANDREA E LIBI LORINI

OTTAVO PREMIO LORINI 2015
A RICERCATORI NEL SETTORE DELL'ONCOLOGIA E DELL'AIDS

La Fondazione Andrea e Libi Lorini, costituita il 15 luglio 1998 sulla base delle disposizioni testamentarie della Signora Libi Lorini, deceduta il 15 luglio 1997 a Milano, è stata riconosciuta dalla Regione Lombardia con decreto della Giunta Regionale 6 novembre 1998 n. 6/39316.
Scopo della Fondazione è quello "di provvedere all'elargizione annuale di borse di studio a giovani laureati in medicina, con ottimi risultati, presso un'Università Milanese che intendono specializzarsi in oncologia e/o nella cura dell'Aids negli Stati Uniti d'America e che abbiano svolto una tesi di laurea sperimentale".

Il Consiglio di Amministrazione, unitamente al Comitato Scientifico della Fondazione composto dai Professori Antonio Carrassi, Massimo Galli, Giovanni Staurenghi, Gianluca Vago, Umberto Veronesi e Paolo Vitti, ha deciso di affiancare all'attività principale di assegnazione delle borse di studio un'attività complementare a quella statutaria, istituendo un premio speciale, che è riservato a ricercatori i cui studi nel campo delle neoplasie e delle affezioni da AIDS abbiano portato a nuove conoscenze che potranno essere utili per lo sviluppo di approcci terapeutici e diagnostici innovativi.

Il Premio è destinato a ricercatori, di cittadinanza italiana, di età non superiore a 40 anni, che abbiano conseguito la laurea in Medicina e Chirurgia, Biotecnologie Mediche, Scienze Biologiche, Scienze Farmaceutiche e Farmacologiche, presso una qualsiasi Università italiana, pubblica o privata.

Gli interessati a partecipare al concorso dovranno inviare entro il **15 marzo 2016**, presso la sede della Fondazione, una copia per esteso del lavoro (pubblicato o accettato) accompagnata da (a) una copia del curriculum vitae e professionale completo dei dati anagrafici e del codice

fiscale; (b) una copia del certificato di laurea ed eventuali altri titoli; (c) un "abstract" del lavoro in lingua italiana riportante il contenuto della ricerca.
La documentazione dovrà pervenire in formato elettronico (MS-word, PDF) con autocertificazione di autenticità e su supporto cartaceo nella stesura estesa, all'indirizzo della Fondazione. E' opportuno preannunciare l'invio del materiale alla Fondazione telefonicamente o a mezzo fax o posta elettronica.
Nel caso di lavoro di gruppo il partecipante deve risultare come primo o ultimo autore nel lavoro presentato.
I lavori non dovranno essere stati pubblicati prima dell'anno 2012.

I lavori verranno esaminati da una Commissione costituita dal Consiglio di Amministrazione della Fondazione Andrea e Libi Lorini e dal suo Comitato Tecnico Scientifico.
Il premio – che potrà anche non essere assegnato ove i lavori presentati non venissero ritenuti adeguati – verrà attribuito ad insindacabile giudizio del Consiglio di Amministrazione, che effettuerà la selezione basandosi unicamente su criteri di carattere scientifico.

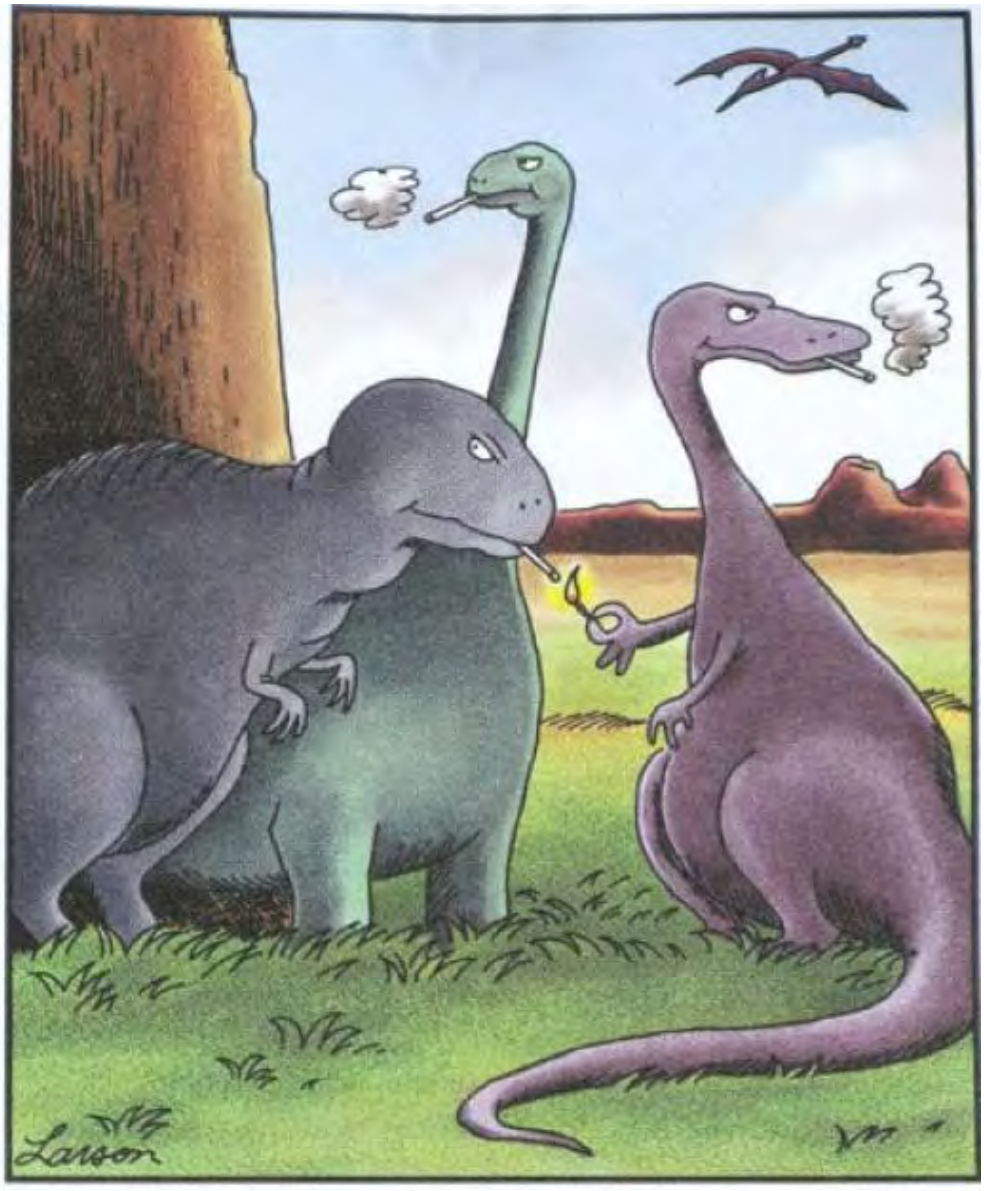
Il Premio consisterà nel versamento al vincitore dell'importo di Euro 40.000,00 (quarantamilaeuro) al lordo delle imposte che restano a carico del premiato e che dovranno essere liquidate a cura dello stesso.
La sua consegna verrà effettuata nel corso di un convegno, durante il quale l'interessato illustrerà il suo lavoro.

La partecipazione al concorso presuppone l'accettazione incondizionata di tutte le clausole del presente bando. La documentazione presentata non verrà restituita.

Ai sensi dell'art. 13 del Codice in materia di protezione dei dati personali (decreto legislativo 30 giugno 2003, n. 196), si informano i candidati che il trattamento dei dati da essi forniti in sede di partecipazione al concorso o comunque acquisiti a tal fine dalla Fondazione Andrea e Libi Lorini è finalizzato unicamente all'espletamento delle attività concorsuali ed avverrà a cura delle persone preposte al procedimento concorsuale, anche da parte della Commissione

esaminatrice, con l'utilizzo di procedure anche informatizzate, nei modi e nei limiti necessari per perseguire le predette finalità, direttamente o con eventuali comunicazioni a terzi. Il conferimento di tali dati è necessario per valutare i requisiti di partecipazione e il possesso di titoli, e la loro mancata indicazione può precludere tale valutazione. Ai candidati sono riconosciuti i diritti di cui all'art. 7 del citato Codice (decreto legislativo 196/2003) e, in particolare, il diritto di accedere ai propri dati personali, di chiederne la rettifica, l'aggiornamento e la cancellazione, se incompleti, erronei o raccolti in violazione della legge, nonché di opporsi al loro trattamento per motivi legittimi. Titolare del trattamento è la Fondazione Andrea e Libi Lorini, con sede a Milano in Via Silvio Pellico 12, nei confronti della quale possono essere fatti valere i diritti di cui sopra.

Per ogni ulteriore informazione si prega di contattare la Segreteria della Fondazione presso la sede, Telefono 02 8692700, Fax 02 867391, E-mail milano@fondazionelorini.it.



The real reason dinosaurs became extinct

Cellfie of the Day!

Developing nerve cells with nuclei in yellow. Credit:
Torsten Wittmann/University of California, San Francisco.