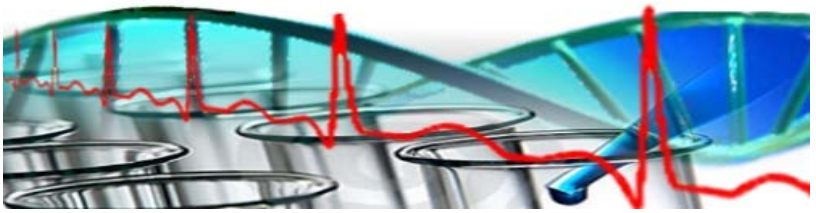
Università degli Studi dell'Aquila
Dipartimento di
Scienze Cliniche Applicate e Biotecnologiche
Nam et ipsa scientia potestas est

DISCAB Research News



Newsletter May, 2016 Issue 8 page 1

Contents

Welcome to the 8th edition of DISCAB Research News.

In this issue, we start with a truly space age "News and views" section, with Chinese claims that mammalian embryonal development is feasible in space and biotech company BioViva claims of a successful attempt to reverse the ageing process. We then drop back down to earth with current and more credible problems of the peer review publishing process, illustrated by the accelerated peer reviewing and publishing of articles concerning the Zika virus.

In the DISCAB research section we introduce "Visionlab-AQ", the research group headed by Professor Silvia Bisti and follow this with an ample "DISCAB research publications" section, comprising 13 new articles for this month.

In the "Research Breakthrough" section, we present a broad spectrum of articles that include: discovery of a novel mechanism to inhibit lymphangiogenesis, of relevance to organ transplantation, cancer metastasis and chronic inflammatory pathology; a new appraisal of the tree of life, in which bacteria take centre stage; an appraisal of the qualities of robotic soft tissue surgery; exposure the real dangers of medicine in the States; a comparison the effects of same sex and hetero sex parenting on child health; identification of age-related, normally cancer-associated, mutations to TP53 in apparently healthy individuals; novel breakthroughs in AML, prostate cancer and glioblastoma research; a novel use for psilocybin for the treatment of therapy-resistant depression; a skin cream that actually works; identification of a novel CCNF mutation that links neurodegeneration in ALS to that observed in frontotemporal dementia; the use of patient-derived xenograft tumourigenesis models in cancer therapy strategy decision-making.

Enjoy!

The DISCAB Research News Team

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

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Biotech Company Claims To Have Successfully Used Gene Therapy In Attempt To Reverse Aging

http://www.iflscience.com/health-and-medicine/biotech-company-claims-have-successfully-used-gene-therapy-attempt-revere-aging

April 25, 2016 | by Josh L Davis

photo credit: The telomeres, found at the end of chromosomes, have been implicated in aging. koya979/Shutterstock24.1K

In what they are claiming is a world first, biotech company BioViva has announced that they have used gene therapy to lengthen the caps on the end of DNA – known as telomeres – in the CEO of their company, Elizabeth Parrish.

Implicated in the aging process, telomeres protect the DNA. BioViva claims that their experimental treatments that were given to Parrish over a year ago, used initially against loss of muscle mass and stem cell depletion, have had the result instead of increasing the lengths of the telomeres in her white blood cells. Others are highly skeptical.

Telomeres are found on the ends of each chromosome, which contain all the genetic information that codes for the organism, and protect the DNA from natural wear and tear. Think of them as the little bit of plastic on the end of shoelaces that prevent them from becoming unraveled. As a cell divides and the chromosomes are copied, a little bit gets shaved off each telomere meaning that as you age, they get shorter and shorter until they reach a critical length and the cell stops dividing or dies.

BioViva CEO Elizabeth Parrish claims that the gene therapy she received successfully lengthened her telomeres.

These caps and their shortening have been variously linked to aging and disease, and so the theory goes that if you can prevent, or somehow reverse this, it could also prevent the aging process. This is not as extraordinary as it sounds, as something to this effect has already been managed on human cells cultured in the laboratory. One team at Stanford University Medical Center, for example, introduced a modified type of RNA, which they engineered to extend the telomeres. They successfully managed to get the RNA to reverse the shortening of telomeres in skin cells, allowing them to divide more than 40 times more than untreated cells.

This method, however, is only designed to help extend the life of cultured human cells used in drug testing or disease modeling, and after a few days the protective effect wore off. This new announcement from BioViva claims to have made the leap from petri dish to human, saying that they have managed to lengthen the telomeres in Parrish's white blood cells. Unable to conduct the treatment in the U.S., Parrish flew to Colombia to get it done, adding to the murky circumstances surrounding the therapy, of which no other details seem to have been released.

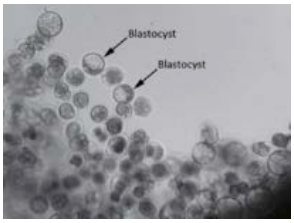
Without a published study or independent verification, a sample size of one – and that one being the CEO of the company in question and not in a clinical trial – it is impossible to say whether or not they have actually achieved this. It may simply be some form of PR campaign or, as others have put it, "a new low in medical quackery." Self-experimentation is not unheard of, with some who undertake it even going on to win a Nobel Prize, but that comes with hard data and evidence. Both are so far lacking here.

The researchers over at BioViva are saying that they will now continue to test Parrish for potentially years to come, though some have already hit out against the experiment, and even members of the company's own scientific advisory board have distanced themselves from Parrish and the experiment. It waits to be seen if any other information about the procedure is released by BioViva, and whether that will stand up to scrutiny.

Humans on the move – Chinese pave the way for having kids in space

New Chinese study shows mammals can be developed in spaceBy Cheng Yingqi (chinadaily.com.cn)

http://www.chinadaily.com.cn/china/2016-04/17/content_24611016.htm



The latest experiment results from China's SJ-10 recoverable satellite have been sent back with some groundbreaking news. For the first time in human history, it has been proven that the early stages of embryos in mammals can be developed completely in a space environment.

China launched the country's first microgravity satellite, the SJ-10, on April 6. The return capsule on the satellite will stay in orbit for several days before heading back to Earth. An orbital module will continue to conduct experiments for a few more days.

High-resolution photographs sent back by SJ-10 show that the mouse embryos carried by the return capsule completed the entire developing process within 96 hours from the launch, the first reported successful development of mammalian embryos in space.

"The human race may still have a long way to go before we can colonize the space. But before that, we have to figure out whether it is possible for us to survive and reproduce in the outer space environment like we do on Earth," said Duan Enkui, Professor of the Institute of Zoology affiliated to the Chinese Academy of Sciences, and principle researcher of the experiment.

"Now, we finally proved that the most crucial step in our reproduction – the early embryo development – is possible in the outer space," Enkui said.

The SJ-10 carried more than 6,000 mouse embryos in a self-sufficient, enclosed chamber, the same size of a microwave oven. Everything on the test load, from the cell culture system to the nutrient solution was refined with hundreds rounds of ground tests.

A camera took pictures of the embryos every four hours and sends the pictures back to Earth. It turns out some embryos developed into advanced blastocysts in four days and upon return scientists will immediately transport them to Beijing and perform further analyses on the developmental speed and changes in embryonic gene and protein expression.

Science publishing has a Zika problem
by Vincent Racaniello

http://www.virology.ws/2016/05/19/science-publishing-has-a-zika-problem/

Science publishing has a problem. I agree with Nobel Laureate Randy Schekman, who wrote that prestigious science journals like Cell, Nature, and Science – which he calls 'luxury journals' – are damaging science. The succession of articles on Zika virus nicely illustrates this problem.

The big three in science publishing – Science, Nature, and Cell – have published many papers on Zika virus since the beginning of 2016. Many of these have had a turnaround time of a week or two – the time between when the papers were submitted, and when they were published online. A rapid turnaround time is unusual, and not compatible with proper peer review of the work. Indeed, many of the papers have been clearly rushed into print, and lack proper controls and clear explanations of what has been done.

The recent publication in Cell Host & Microbe of a description of an infectious DNA clone of Zika virus is a perfect illustration of the problem with luxury journals. Infectious DNA clones of viral genomes are nothing new – the first were described the late 1970s and 1980s. They are important reagents, allowing manipulation of the viral genome to study replication and pathogenesis. But publishing a reagent has never been enough to get into a high profile journal.

As a postdoctoral fellow with David Baltimore in 1981, I was fortunate to publish the first report of an infectious DNA clone of an animal virus – poliovirus – in Science (At the time there were no luxury journals. Years later Nobel Laureate Paul Berg asked why we chose to publish in such a lowly journal). A few years later, I submitted a paper to the Journal of Virology describing the construction of an infectious DNA clone of a different serotype of poliovirus, which had the unique ability to infect mice. The paper was rejected because, I was told, it didn't contain any new results.

The first infectious DNA clone of a calicivirus – the family that includes noroviruses, agents of human gastroenteritis – was published in 1995 in Virology. The senior author told me the paper was rejected from the Journal of Virology because an infectious clone is 'just a tool'.

The Journal of Virology is a solid journal that publishes many important articles in the field. But no one would mistake it as a luxury journal.

Some infectious DNA clones of viruses have been published in prominent journals – for example, Ebolavirus and influenza virus in Science (2000 and 2001). Zika virus is a flavivirus, and the first

infectious DNA of a member of this virus family was for yellow fever virus, published 27 years ago in PNAS. Subsequently there have been many reports of infectious DNA clones of other flaviviruses, notably, West Nile virus, published in Virology in 2001. This virus, which entered the United States, gained quite a bit of attention in the press.

Technically, there is nothing novel about making an infectious DNA clone of Zika virus. It is an important reagent, just as infectious DNA clones are important for the study of all viruses. But the paper reports no experimental results using the Zika virus infectious DNA that advance the field. In my opinion, the infectious DNA clone of Zika virus should not have been published in a high profile journal.

Clearly the paper was published because Zika virus is hot and it will garner the journal a great deal of publicity, a consideration that should not determine whether an article should be published or not. It is the science that should drive publication – and the luxury journals have lost track of this fact.

Schekman points out that the reputations of luxury journals reputations as the "epitome of quality" is only "partly warranted": they don't always publish outstanding work, and they are not the only journals to publish great science. He feels that they "aggressively curate their brands, in ways more conducive to selling subscriptions than to stimulating the most important research". They are driven by impact factor, which Schekman and others, including myself, think is wrong. Highly cited papers are not necessarily correct; they might be "eye-catching, provocative or wrong". He says that editors accept papers that will 'make waves' and therefore influence, inappropriately, the direction of science. He favors open-access journals that are edited by scientists, and so do I.

In my view there are two main forces that have corrupted science publishing. The first is one that Schekman notes: that these journals are in the business of selling subscriptions. The Cell and Nature journals are owned by for-profit publishing companies. This situation is problematic because the drive for profit is not necessarily compatible with the need to publish high quality science. Editors know that controversial or prominent (e.g., Zika) papers will drive advertising revenue, but this should not even be a consideration when deciding what to publish. The publication of scientific data should not be a for profit enterprise. Unfortunately, Science magazine, which is published by the non-profit AAAS, seems to be driven by the same corrupting influences.

A second problem is that decisions at the luxury journals are typically not made by working scientists, but by full-time editors. A professional editor cannot possibly know the field as well as a working scientist, who spends his or her days in the trenches of science: designing experiments, interpreting data, guiding students and postdoctoral fellows, reviewing manuscripts, writing grants, going to meetings, and much more. The result is that the working scientist is fully immersed in science every day, all year, and is in the best position to know what work is significant, advances the field, and should be considered for publication.

These two factors control what kinds of papers are published. The luxury journals want high-impact papers that are of broad interest. But the problem is that it's not always clear exactly where a paper fits in. Many of us have had the experience of submitting a paper to Cell, Science, or Nature, only to be told 'it's not of sufficient interest'. But the real reason is that the paper won't sell advertising, or subscriptions; or perhaps the editor who made the decision simply doesn't sufficiently understand the field.

A paper on an infectious Zika virus DNA clone will help Cell Host & Microbe get more advertising. A year ago, the journal would not even have reviewed the paper.

It's no secret that publishing controls our scientific careers. Decisions about important things like hiring, promotion, tenure, and grant funding revolve around what you have published and where. I've been on many tenure or grant review committees, and it's common to count the number of Cell, Nature, and Science publications as a metric of quality. The same occurs when examining job candidates for professorial positions.

In other words, the luxury journals are controlling the careers of scientists. Journals motivated by profit, run by professional editors who are not scientists, are deciding who is hired, promoted, tenured, and who gets grant money.

Unfortunately it is a system that scientists have created and nurtured until it has become an absurd and untenable situation, and it has to change. The PLoS journals and eLife are helping to do that, but what is also needed is to diminish the importance of the luxury journals to the careers of scientists. That is a much harder goal to achieve, as all my colleagues who are sending their Zika virus papers to luxury journals, will admit.

The Neurophysiology of Vision laboratory (Visionlab-AQ)

Visionlab-AQ is directed by Prof. Silvia Bisti in collaboration with Dr. Rita Maccarone and Dr. Stefano Di Marco. Drs. Darin Zerti and Mattia Di Paolo, recent PhD graduates, and Dr. Serena Riccitelli, our former PhD student, also actively contribute to the different projects currently underway in our lab.

Visionlab-AQ integrates different research fields in order to broadly investigate multiple aspects of retinal physiology. We combine a high-level of expertise in *in vivo* and *in vitro* electrophysiology with immunohistochemical and molecular techniques in order to observe physiological problems from different points of view.

Physiopathological processes in the Retina must be observed at different scales, raging from the intracellular and network scales to the whole-retina. We achieve this by combining the techniques of *in-vitro* patch-clamping of light-responsive isolated retinas (synapse to network scale) with *in-vivo* electro-retinogram recordings (whole-retinal scale), Western blotting, RT-PCR (cellular scale) and immunohistochemistry (network scale).

Our research programs are designed to study the visual system, starting from pre and post-natal development. Original evidence of the importance of neurotransmitters in the morpho-functional retinal development (obtained in collaboration with Prof Chalupa, now vice president of Washington University, Washington D.C.) has been extended in collaboration with Dr. Dario Protti (University of Sydney) and confirms that environmental stress during neonatal life permanently reorganizes the receptive field of retinal ganglion cells and consequently visual perception. This interesting result has led to research focused on the mechanisms involved in retinal degeneration and the development of novel effective neuroprotective strategies.

Within this context, our main hypothesis is that there are two major reasons for visual dysfunction: 1) a loss of neurons and 2) inner retinal reorganization, both of which impinge upon visual perception.

As an "ARC center of excellence in visual science" (http://www.vision.edu.au) partner, Visionlab-AQ is also engaged an extensive research programs focus on the environmental control of retinal stability and its regulation by interacting genetic, environmental (light, oxygen) and tissue factors (regulation of blood flow, trophic factors), and is increasingly therapy-oriented. For this purpose we currently employ wild-type and transgenic rodent models of human Retinitis Pigmantosa, environmentally-induced retinal degeneration and the activation of protective mechanism(s). From these models, it is evident that loss of rod and cone vision is partially and substantially reversible by anti-oxidant dietary supplementation (saffron) and near-infrared radiation to repair mitochondria and drive oxidative phosphorylation. In parallel, we monitor the time course of retinal circuitry functional reorganization, following photoreceptor loss. The ability of the degenerating retina to self-repair and regain function provides the basis for therapy and the knowledge acquired from basic research has been successfully translated into the clinical setting with a clinical trial recently performed on AMD patients in collaboration with Prof Benedetto Falsini (Policlinico Gemelli, Università Cattolica di Roma).

Recently, we have also been awarded a Telethon grant for an experimental and clinical Study of Stargardt disease, entitled "*A Novel Therapeutic Strategy Targeting Photoreceptor Oxidative Damage in ABCR−related Retinal Degenerations"*, which will be coordinated by Prof B. Falsini.

Visdionlab-AQ is also a partner in the Telethon Project "*Development and application of opto-neural prosthetic devices as a therapeutic approach for Retinitis pigmentosa"* coordinated by Prof. Lanzani (Politecnico di Milano) and also partnered by Prof Benfenati (IIT and University of Genova). We have undersigned an agreement with the Italian Institute of Technology and the departments of "Neuroscience" and "Drug Discovery and Development", in collaboration with Dr. L. Berdondini and A. Maccione (IIT) to develop novel neuro-technologies to characterize functional changes at resolutions that have never previously been attained. For this purpose, the cellular/sub-cellular scale obtained by patch-clamping will be converged with the meso-scale obtained by simultaneous recordings of thousands of RGCs, utilizing novel emerging high-density multielectrode array technology developed by our collaborators. This novel approach will enable an unprecedented level of investigation into functional effects of early retinal Neurodegeneration, with direct implications for diagnosis, arising from multi-scale signal (ERGs and spikes) analysis, and for pharmacological research and development. We for-see that this

research and development. We for-see that this novel direction will contribute greatly to the development of novel retinal prosthetic devices.

Patents: 2 international patents

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- Di Marco, S., Nguyen, V. a, Bisti, S., & Protti, D. a (2009) Permanent functional reorganization of retinal circuits induced by early long-term visual deprivation. The Journal of neuroscience : the official journal of the Society for Neuroscience, 29, 13691–13701.
- Falsini B, Piccardi M, Minnella A, Savastano C, Capoluongo E, Fadda A, Balestrazzi E, Maccarone R, Bisti S. Influence of saffron supplementation on retinal flicker sensitivity in early age-related macular degeneration. Invest Ophthalmol Vis Sci. 2010 Dec; 51(12):6118-24. Epub Aug 4, 2010.
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- Ghezzi D, Antognazza M.R., Maccarone R., Bellani S., Lanzarini E., Martino N. Mete M., Pertile G., Bisti S., Lanzani G. and Benfenati F. A polymer optoelectronic interface restores light sensitivity in blind rat retinas. NATURE PHOTONICS;7: 400-406, 2013.
- Di Marco, S., Protti, D.A., & Solomon, S.G. (2013) Excitatory and inhibitory contributions to receptive fields of alpha-like retinal ganglion cells in mouse. Journal of neurophysiology, 110, 1426–1440.
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- Maccione, A., Gandolfo, M., Zordan, S., Amin, H., Di Marco, S., Nieus, T., Angotzi, G.N., & Berdondini, L. Microelectronics, bioinformatics and neurocomputation for massive neuronal recordings in brain circuits with large scale multielectrode array probes. Brain research bulletin, 2015.

Pathways to functional outcome in subjects with schizophrenia living in the community and their unaffected first-degree relatives.

Galderisi S, Rossi A, Rocca P, Bertolino A, Mucci A, Bucci P, Rucci P, Gibertoni D, Aguglia E, Amore M, Blasi G, Comparelli A, Di Giannantonio M, Goracci A, Marchesi C, Monteleone P, Montemagni C, Pinna F, Roncone R, Siracusano A, Stratta P, Torti MC, Vita A, Zeppegno P, Chieffi M, Maj M
Schizophr Res. 2016 May 18. PMID: 27209527

RATIONALE: Variables influencing real-life functioning have repeatedly been modeled in schizophrenia subjects but not systematically investigated in their unaffected first-degree relatives (SRs), in whom milder forms of deficits reported in schizophrenia have been observed, but confounders of clinical cohorts are not in play. Demonstrating that pathways to functional outcome are similar between patients and SRs would validate structural models developed in schizophrenia subjects. The present multicenter study aimed to explore whether variables associated with real-life functioning are similar in schizophrenia patients and their unaffected relatives. **METHODS:** The study sample included 921 schizophrenia patients, 379 SRs and 780 healthy controls. Structural Equation Models (SEMs) were used in patients and SRs to test associations of psychopathological dimensions, neurocognition, social cognition, resilience, perceived stigma and functional capacity with real-life functioning domains, impaired in both patients and SRs. **RESULTS:** Interpersonal Relationships and Work Skills were the only functional domains impaired in both patients and SRs. For both domains, functional impairment in patients was found to predict impairment in unaffected relatives, suggesting the involvement of similar illness-related vulnerability factors. In both groups variables significantly associated with Interpersonal Relationships included Social Cognition, Neurocognition, Avolition, Resilience, Disorganization, Perceived Stigma and Gender, and those significantly associated with Work Skills included Social Cognition, Neurocognition and Disorganization. **CONCLUSIONS:** Pathways to functional outcome for Interpersonal relationships and Work skills are similar between schizophrenia patients and their unaffected first-degree relatives. These findings validate, in the absence of confounders of clinical cohorts, structural models of determinants of functional outcome in people with schizophrenia.

Fentanyl Pectin Nasal Spray versus Oral Morphine in Doses Proportional to the Basal Opioid Regimen for the Management of Breakthrough Cancer Pain: A Comparative Study.

Mercadante S, Aielli F, Adile C, Costanzi A, Casuccio A.
J Pain Symptom Manage. 2016 May 18. PMID: 27208863

CONTEXT: Fentanyl products have shown superiority over oral opioids for the management of breakthrough cancer pain (BTcP). However, these studies did not use an appropriate patient selection and drugs have been compared using a different rationale. **OBJECTIVES:** The aim of this randomized, crossover, controlled study was to compare the efficacy and safety of fentanyl pectin nasal spray (FPNS) and oral morphine (OM), given in doses proportional to opioid daily doses. **METHODS:** Cancer patients with pain receiving ≥60 mg of OM equivalents/day and presenting with ≤3 episodes of BTcP/day, were included. Patients received, in a randomized, crossover manner, FPNS or OM at doses proportional to the daily opioid regimen in four consecutive episodes of BTcP. Pain intensity was measured before (T0), 15 (T15) and 30 minutes (T30) after study drugs. **RESULTS:** A total of 167 episodes were treated, 82 with FNPS and 85 with OM. A statistical difference in pain intensity between the two groups was observed at T15, but not at T30 (P=0.018 and P=0.204, respectively). In a greater number of episodes treated with FPNS, there was a pain decrease of ≥33% in comparison with OM after 15 and 30 minutes (76.5% vs. 32.8%, and 89% vs. 54.9%, respectively). Similar differences were found in the decrease in pain intensity of ≥50% after 15 and 30 minutes (52.3% vs. 11.4%, and 75% vs. 45.8%, respectively). The difference was highly significant at T15 (P< 0.0005). The mean (SD) pain difference at T15 of FPNS and OM were 3.24 (1.7) and 2.70 (1.2), respectively, while the mean (SD) SPIDs30 of FPNS and OM were 4.87 (1.7) and 4.54 (1.5), respectively. The difference was highly significant at T15 (P=0.019).

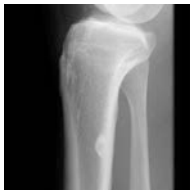
No severe adverse effects after study drug administration were observed. **CONCLUSION:** When used in doses proportional to the basal opioid regimen, FPNS showed a superior analgesic effect over OM for the management of BTcP. Only minor adverse effects were found with both medications.

Adult-onset Still's disease: an Italian multicentre retrospective observational study of manifestations and treatments in 245 patients.

Sfriso P, Priori R, Valesini G, Rossi S, Montecucco CM, D'Ascanio A, Carli L, Bombardieri S, La Selva G, Iannone F, Lapadula G, Alivernini S, Ferraccioli G, Colaci M, Ferri C, Iacono D, Valentini G, Costa L, Scarpa R, Lo Monaco A, Bagnari V, Govoni M, Piazza I, Adami S, Ciccia F, Triolo G, Alessandri E, Cutolo M, Cantarini L, Galeazzi M, Ruscitti P, Giacomelli R, Caso F, Galozzi P, Punzi L.
Clin Rheumatol. 2016 May 20. PMID: 27207567

Adult-onset Still's disease (AOSD) is a systemic inflammatory condition of unknown aetiology characterized by typical episodes of spiking fever, evanescent rash, arthralgia, leukocytosis and hyperferritinemia. Given the lack of data in Italian series, we promote a multicentric data collection to characterize the clinical phenotype of Italian patients with AOSD. Data from 245 subjects diagnosed with AOSD were collected by 15 centres between March and May 2013. The diagnosis was made following Yamaguchi's criteria. Data regarding clinical manifestations, laboratory features, disease course and treatments were reported and compared with those presented in other published series of different ethnicity. The most frequent features were the following: arthritis (93 %), pyrexia (92.6 %), leukocytosis (89 %), negative ANA (90.4 %) and neutrophilia (82 %). As compared to other North American, North European, Middle Eastern and Far Eastern cohorts, Italian data show differences in clinical and laboratory findings. Regarding the treatments, in 21.9 % of cases, corticosteroids and traditional DMARDs have not been able to control the disease while biologics have been shown to be effective in 48 to 58 patients. This retrospective work summarizes the largest Italian multicentre series of AOSD patients and presents clinical and laboratory features that appear to be influenced by the ethnicity of the affected subjects.

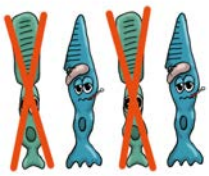
Treatment of focal benign lesions of the bone: MRgFUS and RFA.



Masciocchi C, Arrigoni F, La Marra A, Mariani S, Zugaro L, Barile A.
Br J Radiol. 2016 May 20:20150356. PMID: 27197743

The objective of this study was to evaluate the role of Magnetic Resonance guided Focused Ultrasound Surgery (MRgFUS) and Radiofrequency thermal Ablation (RFA) in the management of bone and soft tissue lesions. Musculoskeletal Interventional Radiology (IR) represents an interesting option for the treatment of benign bone and soft tissue lesions, to avoid invasiveness of surgery and related risks. The imaging techniques now available, besides representing an optimal guide, allow control of the temperature reached in the region of interest avoiding or minimizing damage to sensitive structures surrounding the lesion.

Conjunctivally Applied BDNF Protects Photoreceptors from Light-Induced Damage.
Cerri E, Origlia N, Falsini B, Barloscio D, Fabiani C, Sansò M, Ottino S, Giovannini L, Domenici L.



Transl Vis Sci Technol. 2015 Nov 2;4(6):1. eCollection 2015. PMID: 27190697

PURPOSE: To test whether the topical eye treatment with BDNF prevents the effects of continuous light exposure (LE) in the albino rat retina. **METHODS:** Two groups of albino rats were used. The first group of rats received an intraocular injection of BDNF (2 µL, 1 µg/µL) before LE, while the second group was treated

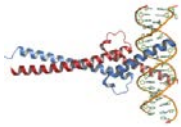
with one single drop of BDNF (10 µL, 12 µg/µL) dissolved in different types of solutions (physiological solution, the polysaccharide fraction of Tamarind gum, TSP, and sodium carboxy methyl cellulose), at the level of conjunctival fornix before LE. The level of BDNF in the retina and optic nerve was determined by enzyme-linked immunosorbent assay. We recorded the flash electroretinogram (fERG) in dark adapted rats 1 week after LE. At the end of the recording session, the retinas were removed and labeled so that the number of photoreceptors nuclear rows and thickness of the outer nuclear layer was analyzed. **RESULTS:** Intravitreal injection of BDNF before LE prevented fERG impairment. Different ophthalmic preparations were used for topical eye application; the TSP resulted the most suitable vehicle to increase BDNF level in the retina and optic nerve. Topical eye application with BDNF/TSP before LE partially preserved both fERG response and photoreceptors. **CONCLUSIONS:** Topical eye treatment with BDNF represents a suitable, noninvasive tool to increase the retinal content of BDNF up to a level capable of exerting neuroprotection toward photoreceptors injured by prolonged LE. **TRANSLATIONAL RELEVANCE:** A collyrium containing BDNF may serve as an effective, clinically translational treatment against retinal degeneration.

The Epidemiology of Atrial Fibrillation and Stroke.

Pistoia F, Sacco S, Tiseo C, Degan D, Ornello R, Carolei A.
Cardiol Clin. 2016 May;34(2):255-68. PMID: 27150174

The burden of stroke is increasing due to aging population and unhealthy lifestyle habits. The considerable rise in atrial fibrillation (AF) is due to greater diffusion of risk factors and screening programs. The link between AF and ischemic stroke is strong. The subtype most commonly associated with AF is cardioembolic stroke, which is particularly severe and shows the highest rates of mortality and permanent disability. A trend toward a higher prevalence of cardioembolic stroke in high-income countries is probably due to the greater diffusion of AF and the control of atherosclerotic of risk factors.

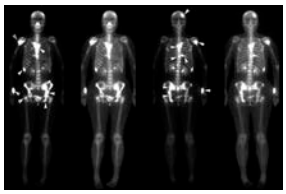
c-Myc Sustains Transformed Phenotype and Promotes Radioresistance of Embryonal Rhabdomyosarcoma Cell Lines.



Gravina GL, Festuccia C, Popov VM, Di Rocco A, Colapietro A, Sanità P, Monache SD, Musio D, De Felice F, Di Cesare E, Tombolini V, Marampon F.
Radiat Res. 2016 Apr;185(4):411-22. PMID: 27104757

We have previously reported that the MEK/ERK pathway sustains in vitro and in vivo transformed phenotype and radioresistance of embryonal rhabdomyosarcoma (ERMS) cell lines. Furthermore, we found that aberrant MEK/ERK signaling activation promotes c-Myc oncoprotein accumulation. In this study, the role of c-Myc in sustaining the ERMS transformed and radioresistant phenotype is characterized. RD and TE671 cell lines conditionally expressing MadMyc chimera protein, c-Myc-dominant negative and shRNA directed to c-Myc were used. Targeting c-Myc counteracted in vitro ERMS adherence and in suspension, growth motility and the expression of pro-angiogenic factors. c-Myc depletion decreased MMP-9, MMP-2, u-PA gelatinolytic activity, neural cell adhesion molecule sialylation status, HIF-1α, VEGF and increased TSP-1 protein expression levels. Rapid but not sustained targeting c-Myc radiosensitized ERMS cells by radiation-induced apoptosis, DNA damage and impairing the expression of DNA repair proteins RAD51 and DNA-PKcs, thereby silencing affected ERMS radioresistance. c-Myc sustains ERMS transformed phenotype and radioresistance by protecting cancer cells from radiation-induced apoptosis and DNA damage, while promoting radiation-induced DNA repair. This data suggest that c-Myc targeting can be tested as a promising treatment in cancer therapy.

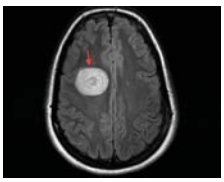
Bone targeted therapy for preventing skeletal-related events in metastatic breast cancer.



Irelli A, Cocciolone V, Cannita K, Zugaro L, Di Staso M, Lanfiuti Baldi P, Paradisi S, Sidoni T, Ricevuto E, Ficorella C.
Bone. 2016 Apr 23;87:169-175. PMID: 27091227

Cancer cells can alter physiological mechanisms within bone resulting in high bone turnover, and consequently in skeletal-related events (SREs), causing severe morbidity in affected patients. The goals of bone-targeted therapy, as bisphosphonates and denosumab, are the reduction of incidence and the delay in occurrence of the SREs, to improve quality of life and pain control. The toxicity profile is similar between bisphosphonates and denosumab, even if pyrexia, bone pain, arthralgia, renal failure and hypercalcemia are more common with bisphosphonates, while hypocalcemia and toothache are more frequently reported with denosumab. Osteonecrosis of the jaw (ONJ) occurred infrequently without statistically significant difference. The present review aims to provide an assessment on bone targeted therapies for preventing the occurrence of SREs in bone metastatic breast cancer patients, critically analyzing the evidence available so far on their effectiveness, in light of the different mechanisms of action. Thus, we try to provide tools for the most fitting treatment of bone metastatic breast cancer patients. We also provide an overview on the usefulness of bone turnover markers in clinical practice and new molecules currently under study for the treatment of bone metastatic disease.

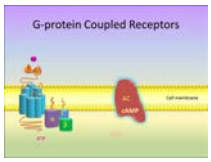
Occurrence and long-term outcome of tumefactive demyelinating lesions in multiple sclerosis.



Totaro R, Di Carmine C, Splendiani A, Torlone S, Patriarca L, Carrocci C, Sciamanna S, Marini C, Carolei A.
Neurol Sci. 2016 Apr 15. PMID: 27083895

Although tumefactive multiple sclerosis is a well recognized variant of multiple sclerosis, prognostic uncertainty still exists about long term prognosis. The aim of this study was to estimate the occurrence and long term outcome of tumefactive demyelinating lesions (TDLs) in a cohort of multiple sclerosis patients. We reviewed brain MRI of 443 patients referred to our MS clinic. All patients meeting the McDonald criteria for multiple sclerosis and showing at least one TDL were included. Kaplan-Meier estimates of disease-free survival in patient cohort were compared with control group without TDLs using a log-rank test. Seven cases with TDLs were identified (occurrence 1.58 %). Tumefactive demyelinating lesion recurrence was 16.6 %. Cumulative proportion of patients free from clinical relapse and from new T2 lesions was lower in the control group although not reaching statistical significance (30 vs 50 %; P = 0.666 and 21.7 vs 33.3 %; P = 0.761, respectively). Disability progression analysis showed a not significant trend towards lower probability of remaining progression free for TDL patients (50 vs 61 %; P = 0.295). Occurrence of tumefactive demyelinating lesions in our cohort was higher than those reported in other studies. Overall, TDLs were not predictive of poor outcome in terms of disability progression.

Variants of G protein-coupled receptors: a reappraisal of their role in receptor regulation.

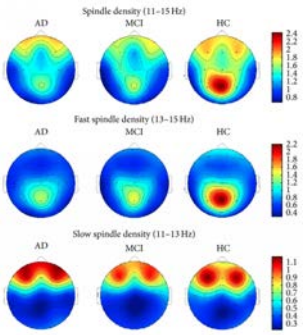


Maggio R, Fasciani I, Rossi M, Di Gregorio J, Pietrantoni I, Puca V, Flati V, Scarselli M.
Biochem Soc Trans. 2016 Apr 15;44(2):589-94. PMID: 27068974

Truncated or shorter forms of G protein-coupled receptors (GPCRs), originating by alternative splicing, have been considered physiologically irrelevant for a rather long time. Nevertheless, it is now recognized that alternative splicing variants of GPCRs greatly increase the total number of receptor isoforms and can regulate receptor trafficking and signalling. Furthermore, dimerization of these truncated variants with other receptors concurs to expand receptor diversity. Highly truncated variants of GPCRs, typically, are retained in the endoplasmic reticulum (ER) and by heteromerization prevent the wild-type receptor to reach the plasma membrane, exerting a dominant-negative effect on its function. This can be responsible for some pathological conditions but in some other cases, it can offer protection from a disease because the expression of the receptor, that is necessary for binding an infectious agent, is attenuated. Here, we propose a possible new mechanism of creation of truncated GPCR variants through an internal ribosome entry site (IRES), a nucleotide sequence that allows cap independent translation of proteins by recruiting the ribosome in proximity of an internal initiation codon. We suggest that an IRES,

situated in the third cytoplasmic loop, could be responsible for the translation of the last two transmembrane (TM) regions of the muscarinic M2receptor. IRES driven expression of this C-terminal part of the muscarinic M2receptor could represent a novel and additional mechanism of receptor regulation.

Parietal Fast Sleep Spindle Density Decrease in Alzheimer's Disease and Amnesic Mild Cognitive Impairment.



Gorgoni M, Lauri G, Truglia I, Cordone S, Sarasso S, Scarpelli S, Mangiaruga A, D'Atri A, Tempesta D, Ferrara M, Marra C, Rossini PM, De Gennaro L.
Neural Plast. 2016;2016:8376108. PMID: 27066274

Several studies have identified two types of sleep spindles: fast (13-15 Hz) centroparietal and slow (11-13 Hz) frontal spindles. Alterations in spindle activity have been observed in Alzheimer's disease (AD) and Mild Cognitive Impairment (MCI). Only few studies have separately assessed fast and slow spindles in these patients showing a reduction of fast spindle count, but the possible local specificity of this phenomenon and its relation to cognitive decline severity are not clear. Moreover, fast and slow spindle density have never been assessed in AD/MCI. We have assessed fast and slow spindles in 15 AD patients, 15 amnesic MCI patients, and 15 healthy elderly controls (HC). Participants underwent baseline polysomnographic recording (19 cortical derivations). Spindles during nonrapid eye movements sleep were automatically detected, and spindle densities of the three groups were compared in the derivations where fast and slow spindles exhibited their maximum expression (parietal and frontal, resp.). AD and MCI patients showed a significant parietal fast spindle density decrease, positively correlated with Minimental State Examination scores. Our results suggest that AD-related changes in spindle density are specific for frequency and location, are related to cognitive decline severity, and may have an early onset in the pathology development.

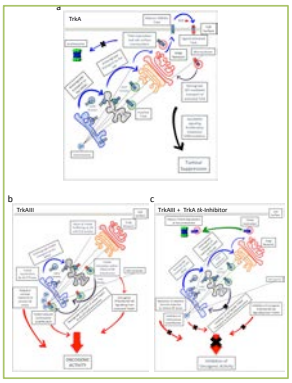
La sindrome metabolica in un campione italiano di pazienti psichiatrici: uno studio retrospettivo su soggetti trattati con antipsicotici.

Santini I, Stratta P, D'Onofrio S, De Lauretis I, Santarelli V, Pacitti F, Rossi A.
Riv Psichiatr. 2016 Jan-Feb;51(1):37-42. PMID: 27030348

RIASSUNTO. Introduzione. La sindrome metabolica (SM) è un tema di interesse centrale nell'ambito della salute mentale, visto l'aumentato rischio di comorbilità medica e di mortalità tra gli individui con patologia psichiatrica grave rispetto alla popolazione generale. Il presente studio trasversale è volto a stimare la prevalenza della SM in un campione di pazienti psichiatrici di nazionalità italiana, trattati con diversi tipi di antipsicotici. Metodi. I dati sono stati raccolti da cartelle cliniche di pazienti con psicosi affettive e non affettive, ricoverati consecutivamente presso il reparto psichiatrico dell'ospedale dell'Aquila, dal gennaio 2012 al luglio 2014. Il campione si riferisce a individui di entrambi i sessi e di età superiore ai 18 anni, in trattamento con uno o più antipsicotici. La diagnosi di SM è stata formulata in accordo ai criteri diagnostici del Treatment Panel (NCEP-ATP III). Risultati. Sono stati valutati 389 soggetti. Il 27,5% del campione risulta affetto da SM,prevalenza molto simile a quella riportata per la popolazione generale italiana che si attesta intorno al 26%. Allo stesso modo, i valori di BMI risultano essere molto simili tra queste due popolazioni, mentre, nel campione clinico, si registra un tasso di obesità più elevato. I tassi di prevalenza di SM nei sottocampioni di pazienti affetti da schizofrenia, disturbi bipolari e disturbi depressivi sono stati rispettivamente 30,6%, 36,4% e 36,8%. Fra i tre gruppi diagnostici non si evidenziano differenze significative nella prevalenza della SM, il diabete o la dislipidemia. Non emergono differenze significative nella prevalenza della SM né in relazione alla politerapia antipsicotica, né in relazione all'utilizzo di antipsicotici tipici o atipici. Nell'ambito del campione clinico, si registrano, tuttavia, tassi di

obesità più elevata per i soggetti di sesso femminile, con una distribuzione del tipo "Tutto o nulla" (cioè maggiori tassi di obesità e normopeso, minori tassi di sovrappeso) rispetto alla popolazione generale. Conclusioni. I risultati del nostro studio potrebbero essere spiegati con l'interazione di più fattori quali il trattamento farmacologico, i lifestyle malattia correlati, il sesso e altre variabili (per es., predisposizione genetica) che concorrono a determinare problematiche metaboliche di diversa natura.

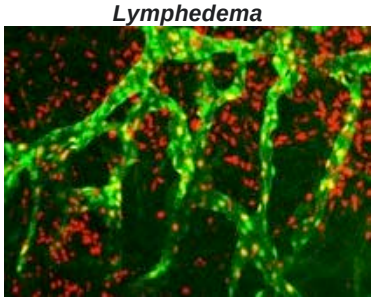
The enemy from within: mislocalization of a compromised receptor as a mechanism for TrkAIII oncogenic activity



Farina AR, Cappabianca L, Ruggeri R, Gneo L, Mackay AR
Cancer Cell & Microenvironment 2016; e1205; doi: 10.14800/com.1205

There is growing evidence that the mislocalisation of receptor tyrosine kinase oncogenes underpins downstream oncogenic signalling. Here, we highlight our recent work characterising the mechanism that underpins mislocalisation and subsequent oncogenic activity of the alternative TrkAIII splice variant of the tropomyosin related kinase A (TrkA) receptor, in human neuroblastoma cells. In primary neuroblastomas, expression of fully spliced TrkA associates with low-stage disease and better prognosis, whereas TrkAIII expression associates with advanced-stage disease and worse prognosis. In neuroblastoma models TrkA and TrkAIII exhibit opposite tumour suppressing and oncogenic activity, respectively. In an attempt to further understand the basis of this diametrically opposite behaviour, intracellular trafficking and activation TrkA and TrkAIII receptors was compared in SH-SY5Y neuroblastoma cells. We found that TrkAIII oncogenic activity originates from miss-localisation and spontaneous activation within the alternative membrane substrate context of the endoplasmic reticulum-Golgi intermediate (ERGIC)-COP-I vesicle compartment. This results from altered trafficking caused by interphase restricted spontaneous receptor activation, which impedes TrkAIII transport from the ERGIC to the Golgi network, associated with retrograde transport of activated TrkAIII from the ERGIC back to the endoplasmic reticulum (ER). Therefore, spontaneous TrkAIII activation within ERGIC/COPI membranes, facilitated by omission of the extracellular D4 spontaneous activation-prevention domain, sets-up self-perpetuating TrkAIII recycling between the ER and ERGIC. This mechanism ensures continuous accumulation of this compromised receptors above the spontaneous activation threshold of the ERGIC/COPI compartment, resulting in oncogenic signalling through IP3K from this altered substrate context. Furthermore, chronic ER stress caused by TrkAIII recycling back to the ER induces a protective ER-stress response, and also the recruitment of active TrkAIII to the centrosome, altering centrosome behaviour. These different tumour-promoting mechanisms all result from mislocalization and spontaneous activation of TrkAIII within the alternative substrate context of the ERGIC/COPI compartment and can be prevented by TrkA tyrosine kinase inhibitors.

New Target for Anti-Lymphangiogenesis Drugs New Hope for Organ Transplant Rejection, Cancer Metastasis, and Lymphedema



Chen, W-S.; Cao Z.; Sugaya S., et al., Pathological lymphangiogenesis is modulated by galectin-8-dependent crosstalk between podoplanin and integrin-associated VEGFR-3. Nature Communications. 2016; doi: 10.1038/NCOMMS11302.

New lymphatic vessels grow after injury to tissues, via lymphangiogenesis. A new mechanism has been shown to regulate this process, in corneal transplants and infectious eye disease. The inhibition of which successfully prevented corneal inflammation that adversely affects transpl-lantation, in a mouse animal model.

Lymphangiogenesis plays a significant role in organ transplant rejection, cancer metastasis, lymphatic obstruction (lymphedema), diabetes and hypertension and the new study focuses on the role of galectin-8, which promotes lymphangiogenesis by a novel, carbohydrate-dependent mechanism the inhibition of which reduces detrimental inflammatory lymph-angiogenesis, identifying galectin-8 as a potent lymphangiogenic factor and modulator of the severity of inflammatory diseases involved in organ transplant rejection, cancer metastasis, and lymphedema. In the future it is possible that galectin-8 inhibitors could be used in the treatment of chronic inflammatory diseases.

Abstract

Lymphangiogenesis plays a pivotal role in diverse pathological conditions. Here, we demonstrate that a carbohydrate-binding protein, galectin-8, promotes pathological lymphangiogenesis. Galectin-8 is markedly upregulated in inflamed human and mouse corneas, and galectin-8 inhibitors reduce inflammatory lymph-angiogenesis. In the mouse model of corneal allogeneic transplantation, galectin-8-induced lymphangiogenesis is associated with an increased rate of corneal graft rejection. Further, in the murine model of herpes simplex virus keratitis, corneal pathology and lymphangiogenesis are ameliorated in Lgals8(-/-) mice. Mechanistically, VEGF-C-induced lymphangiogenesis is significantly reduced in the Lgals8(-/-) and Pdpn(-/-) mice; likewise, galectin-8-induced lymphangiogenesis is reduced in Pdpn(-/-) mice. Interestingly, knockdown of VEGFR-3 does not affect galectin-8-mediated lymphatic endothelial cell (LEC) sprouting. Instead, inhibiting integrins α1β1 and α5β1 curtails both galectin-8- and VEGF-C-mediated LEC sprouting. Together, this study uncovers a unique molecular mechanism of lymph-angiogenesis in which galectin-8-dependent crosstalk among VEGF-C, podoplanin and integrin pathways plays a key role.

Bacteria rule in the new tree of life

A new view of the tree of life
Laura A. Hug LA, Baker BJ, Anantharaman K et al., Nature microbiology 2016; DOI:10.1038/NMICROBIOL.2016.48

The tree of life is one of the most important organizing principles in biology. Gene surveys suggest the existence of an enormous number of branches, but even an approximation of the full scale of the tree has remained elusive. Recent depictions of the tree of life have focused either on the nature of deep evolutionary relationships3–5 or on the known, well-classified diversity of life with an emphasis on eukaryotes6. These approaches overlook the dramatic change in our understanding of life's diversity resulting from genomic sampling of previously unexamined environments. New methods to generate genome sequences illuminate the identity of organisms and their metabolic capacities, placing them in community and ecosystem contexts. Here, we use new genomic data from over 1,000 uncultivated and little known organisms, together with published sequences, to infer a dramatically expanded version of the tree of life, with Bacteria, Archaea and Eukarya included. The depiction is both a global overview and a snapshot of the diversity within each major lineage. The results reveal the dominance of bacterial diversification and underline the importance of organisms lacking isolated representatives, with substantial evolution concentrated in a major radiation of such organisms. This tree highlights major lineages currently underrepresented in biogeochemical models and identifies radiations that are probably important for future evolutionary analyses.

Robotic Surgeons do it better!

Supervised autonomous robotic soft tissue surgery
Shademan A, Decker RS, Opfermann JD, Leonard S et al.,
www.ScienceTranslationalMedicine.org, 2016; Vol 8 Issue 337 337ra64

The current paradigm of robot-assisted surgeries (RASs) depends entirely on an individual surgeon's manual capability. Autonomous robotic surgery—removing the surgeon's hands—promises enhanced efficacy, safety, and improved access to optimized surgical techniques. Surgeries involving soft tissue have not been performed autonomously because of technological limitations, including lack of vision systems that can distinguish and track the target tissues in dynamic surgical environments and lack of intelligent algorithms that can execute complex surgical tasks. We demonstrate in vivo supervised autonomous soft tissue surgery in an open surgical setting, enabled by a plenoptic three-dimensional and near-infrared fluorescent (NIRF) imaging system and an autonomous suturing algorithm. Inspired by the best human surgical practices, a computer program generates a plan to complete complex surgical tasks on deformable soft tissue, such as suturing and intestinal anastomosis. We compared metrics of anastomosis—including the consistency of suturing informed by the average suture spacing, the pressure at which the anastomosis leaked, the number of mistakes that required removing the needle from the tissue, completion time, and lumen reduction in intestinal anastomoses-between our supervised autonomous system, manual laparoscopic surgery, and clinically used RAS approaches. Despite dynamic scene changes and tissue movement during surgery, we demonstrate that the outcome of supervised autonomous procedures is superior to surgery performed by expert surgeons and RAS techniques in ex vivo porcine tissues and in living pigs. These results demonstrate the potential for autonomous robots to improve the efficacy, consistency, functional outcome, and accessibility of surgical techniques.

Watch out, watch out there's an American Medic about!

Medical error—the third leading cause of death in the US (but is not included on death certificates or in rankings of cause of death).
Makary MA and Daniel M
BMJ 2016;353:i2139 doi: 10.1136/bmj.i2139

The annual list of the most common causes of death in the United States, compiled by the Centers for Disease Control and Prevention (CDC), informs public awareness and national research priorities each year. The list is created using death certificates filled out by physicians, funeral directors, medical examiners, and coroners. However, a major limitation of the death certificate is that it relies on assigning an International Classification of Disease (ICD) code to the cause of death. As a result, causes of death not associated with an ICD code, such as human and system factors, are not captured. The science of safety has matured to describe how communication breakdowns, diagnostic errors, poor judgment, and inadequate skill can directly result in patient harm and death. We analyzed the scientific literature on medical error to identify its contribution to US deaths in relation to causes listed by the CDC.

A literature review by James estimated preventable adverse events using a weighted analysis and described an incidence range of 210,000-400,000 deaths a year associated with medical errors among hospital patients. We calculated a mean rate of death from medical error of 251 454 a year using the studies reported since the 1999 IOM report and extrapolating to the total number of US hospital admissions in 2013. We believe this understates the true incidence of death due to medical error because the studies cited rely on errors extractable in documented health records and include only inpatient deaths.
Although the assumptions made in extrapolating study data to the broader US population may limit the accuracy of our figure, the absence of national data highlights the need for systematic measurement of the problem. Comparing our estimate to CDC rankings suggests that medical error is the third most common cause of death in the US.

Surprise, surprise! Same sex parenting has no adverse effects upon child health!

Same-Sex and Different-Sex Parent Households and Child Health Outcomes: Findings from the National Survey of Children's Health
Bos HMW, Knox JR, van Rijn-van Gelderen L, Gartrell NK
J Dev Behav Pediatr 37:179–187, 2016

ABSTRACT: Objective: Using the 2011–2012 National Survey of Children's Health data set, we compared spouse/partner relationships and parent-child relationships (family relationships), parenting stress, and children's general health, emotional difficulties, coping behavior, and learning behavior (child outcomes) in households of same-sex (female) versus different-sex continuously coupled parents with biological offspring. We assessed whether associations among family relationships, parenting stress, and child outcomes were different in the 2 household types. Methods: Parental and child characteristics were matched for 95 female same-sex parent and 95 different-sex parent households with children 6 to 17 years old. One parent per household was interviewed by telephone. Multivariate analyses of variance and multiple linear regressions were conducted. Results: No differences were observed between household types on family relationships or any child outcomes. Same-sex parent households scored higher on parenting stress (95% confidence interval 5 2.03–2.30) than different-sex parent households (95% confidence interval 5 1.76-2.03), p 5 .006. No significant interactions between household type and family relationships or household type and parenting stress were found for any child outcomes. Conclusion: Children with female same-sex parents and different-sex parents demonstrated no differences in outcomes, despite female same-sex parents reporting more parenting stress. Future studies may reveal the sources of this parenting stress.

Cancer-like mutations are prevalent in apparently healthy individuals

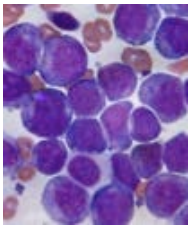
Ultra-deep sequencing detects ovarian cancer cells in peritoneal fluid and reveals somatic TP53 mutations in noncancerous tissues
Krimmela JD, Schmitta MW, Harrellc MI et al.,

Significance - The detection of rare tumor-specific somatic mutations in "liquid biopsies" is limited by the high error rate of DNA sequencing technologies. By sequencing peritoneal fluid from women with high-grade serous ovarian cancer, we demonstrate that duplex sequencing, currently the most accurate sequencing technology, is able to detect one cancer cell among tens of thousands of normal cells. This unprecedented sensitivity also revealed a striking prevalence of extremely low frequency *TP53* mutations in normal tissue. Women with and without cancer harbored *TP53* mutations of pathogenic consequences, both in peritoneal fluid and peripheral blood. These mutations likely represent a premalignant mutational background that accumulates in cancer and aging.

Abstract - Current sequencing methods are error-prone, which precludes the identification of low frequency mutations for early cancer detection. Duplex sequencing is a sequencing technology that decreases errors by scoring mutations present only in both strands of DNA. Our aim was to determine whether duplex sequencing could detect extremely rare cancer cells present in peritoneal fluid from women with high-grade serous ovarian carcinomas (HGSOCs). These aggressive cancers are typically diagnosed at a late stage and are characterized by *TP53* mutations and peritoneal dissemination. We used duplex sequencing to analyze *TP53* mutations in 17 peritoneal fluid samples from women with HGSOC and 20 from women without cancer. The tumor *TP53* mutation was detected in 94% (16/17) of peritoneal fluid samples from women with HGSOC (frequency as low as 1 mutant per 24,736 normal genomes). Additionally, we detected extremely low frequency *TP53* mutations (median mutant fraction 1/13,139) in peritoneal fluid from nearly all patients with and without cancer (35/37). These mutations were mostly deleterious, clustered in hotspots, increased with age, and were more abundant in women with cancer than in controls. The total burden of *TP53*

mutations in peritoneal fluid distinguished cancers from controls with 82% sensitivity (14/17) and 90% specificity (18/20). Age-associated, low frequency *TP53* mutations were also found in 100% of peripheral blood samples from 15 women with and without ovarian cancer (none with hematologic disorder). Our results demonstrate the ability of duplex sequencing to detect rare cancer cells and provide evidence of widespread, low frequency, age-associated somatic *TP53* mutation in noncancerous tissue.

Potential Therapeutic Breakthrough in FLT inhibitor-resistant AML



Palbociclib treatment of FLT3-ITD+ AML cells uncovers a kinase-dependent transcriptional regulation of FLT3 and PIM1 by CDK6
Uras IZ, Walter GJ, Scheicher R, et al., Blood, 2016; DOI: http://dx.doi.org/10.1182/blood-2015-11-683581

Key Points

CDK6 directly regulates transcription of *FLT3* and *PIM1* in a kinase-dependent manner.

CDK6 kinase inhibition impairs not only *FLT3*-dependent cell growth *in vitro* but also FLT3-driven leukemogenesis *in vivo*.

Abstract

Up to 30% of patients with acute myeloid leukemia (AML) have constitutively activating internal tandem duplications (ITDs) of the FLT3 receptor tyrosine kinase. Such mutations are associated with a poor prognosis and a high propensity to relapse after remission. FLT3 inhibitors are being developed as targeted therapy for *FLT3*-ITD+ AML; however, their use is complicated by rapid development of resistance, illustrating the need for additional therapeutic targets. We show that the FDA-approved CDK4/6 kinase inhibitor palbociclib induces apoptosis of FLT3-ITD leukemic cells. The effect is specific for *FLT3*-mutant cells and is ascribed to the transcriptional activity of CDK6: CDK6 but not its functional homolog CDK4 is found at the promoters of the *FLT3* and *PIM1* genes, another important leukemogenic driver. There CDK6 regulates transcription in a kinase-dependent manner. Of potential clinical relevance combined treatment with palbociclib and FLT3 inhibitors results in synergistic cytotoxicity. Simultaneously targeting two critical signaling nodes in leukemogenesis could represent a therapeutic breakthrough, leading to complete remission and overcoming resistance to FLT3 inhibitors.

Those mushrooms are magic!

Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study
Carhart-Harris RL, Bolstridge M, Rucker J et al., The Lancet Psychiatry 2016; DOI: http://dx.doi.org/10.1016/S2215-0366(16)30065-7

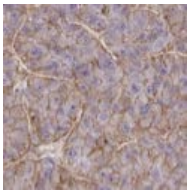
Background. Psilocybin is a serotonin receptor agonist that occurs naturally in some mushroom species. Recent studies have assessed the therapeutic potential of psilocybin for various conditions, including end-of-life anxiety, obsessive-compulsive disorder, and smoking and alcohol dependence, with promising preliminary results. Here, we aimed to investigate the feasibility, safety, and efficacy of psilocybin in patients with unipolar treatment-resistant depression.

Methods. In this open-label feasibility trial, 12 patients (six men, six women) with moderate-to-severe, unipolar, treatment-resistant major depression received two oral doses of psilocybin (10 mg and 25 mg, 7 days apart) in a supportive setting. There was no control group. Psychological support was provided before, during, and after each session. The primary outcome measure for feasibility was patient-reported intensity of psilocybin's effects. Patients were monitored for adverse reactions during the dosing sessions and subsequent clinic and remote follow-up. Depressive symptoms were assessed with standard assessments from 1 week to 3 months after treatment, with the 16-item Quick Inventory of Depressive Symptoms (QIDS) serving as the primary efficacy outcome. This trial is registered with ISRCTN, number ISRCTN14426797.

Findings. Psilocybin's acute psychedelic effects typically became detectable 30–60 min after dosing, peaked 2–3 h after dosing, and subsided to negligible levels at least 6 h after dosing. Mean self-rated intensity (on a 0–1 scale) was 0·51 (SD 0·36) for the low-dose session and 0·75 (SD 0·27) for the high-dose session. Psilocybin was well tolerated by all of the patients, and no serious or unexpected adverse events occurred. The adverse reactions we noted were transient anxiety during drug onset (all patients), transient confusion or thought disorder (nine patients), mild

and transient nausea (four patients), and transient headache (four patients). Relative to baseline, depressive symptoms were markedly reduced 1 week (mean QIDS difference −11·8, 95% CI −9·15 to −14·35, p=0·002, Hedges' g=3·1) and 3 months (−9·2, 95% CI −5·69 to −12·71, p=0·003, Hedges' g=2) after high-dose treatment. Marked and sustained improvements in anxiety and anhedonia were also noted.
Interpretation. This study provides preliminary support for the safety and efficacy of psilocybin for treatment-resistant depression and motivates further trials, with more rigorous designs, to better examine the therapeutic potential of this approach.

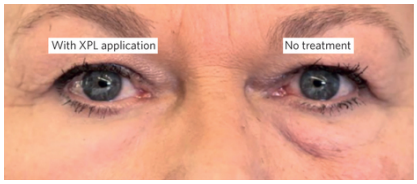
Breakthrough in the prostate cancer immunology



The DNA Structure-Specific Endonuclease MUS81 Mediates DNA Sensor STING-Dependent Host Rejection of Prostate Cancer Cells
Samantha S.W. Ho[1], Wendy Y.L. Zhang[1], Nikki Yi Jie Tan[1], et al.,
doi:10.1016/j.immuni.2016.04.010

Summary - Self-DNA is present in the cytosol of many cancer cells and can promote effective immune rejection of tumor cells, but the mechanisms leading to the presence of cytosolic DNA are unknown. Here, we report that the cleavage of genomic DNA by DNA structure-specific endonuclease MUS81 and PARP-dependent DNA repair pathways leads to the accumulation of cytosolic DNA in prostate cancer cells. The number of nuclear MUS81 foci and the amount of cytosolic dsDNA increased in tandem from hyperplasia to clinical stage II prostate cancers and decreased at stage III. Cytosolic DNA generated by MUS81 stimulated DNA sensor STING-dependent type I interferon (IFN) expression and promoted phagocytic and T cell responses, resulting in type I and II IFN-mediated rejection of prostate tumor cells via mechanisms that partly depended on macrophages. Our results demonstrate that the tumor suppressor MUS81 alerts the immune system to the presence of transformed host cells.

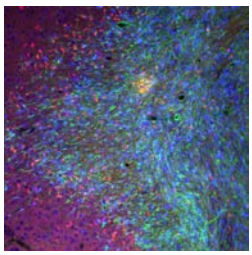
An elastic second skin. An anti-wrinkle cream that actually works!!!!!!!



Yu B, Kang S-Y, Akthakul A, Ramadurai N, Pilkenton M, et al., *Nature Materials* (2016)
doi: 10.1038/b nmat4635

Abstract - We report the synthesis and application of an elastic, wearable crosslinked polymer layer (XPL) that mimics the properties of normal, youthful skin. XPL is made of a tunable polysiloxane-based material that can be engineered with specific elasticity, contractility, adhesion, tensile strength and occlusivity. XPL can be topically applied, rapidly curing at the skin interface without the need for heat- or light-mediated activation. In a pilot human study, we examined the performance of a prototype XPL that has a tensile modulus matching normal skin responses at low strain (<40%), and that withstands elongations exceeding 250%, elastically recoiling with minimal strain-energy loss on repeated deformation. The application of XPL to the herniated lower eyelid fat pads of 12 subjects resulted in an average 2-grade decrease in herniation appearance in a 5-point severity scale. The XPL platform may offer advanced solutions to compromised skin barrier function, pharmaceutical delivery and wound dressings.

Breakthrough in Glioblastoma/Glioma Research



Olig2-Dependent Reciprocal Shift in PDGF and EGF Receptor Signaling Regulates Tumor Phenotype and Mitotic Growth in Malignant Glioma
Lu F, Chen Y, Zhao C, Wang H, He D et al., Cancer Cell 2016; 29(5): 669-683

Summary - Malignant gliomas exhibit extensive heterogeneity and poor prognosis. Here we identify mitotic Olig2-expressing cells as tumor-propagating cells in proneural gliomas, elimination of which blocks tumor initiation and progression.

Intriguingly, deletion of *Olig2* resulted in tumors that grow, albeit at a decelerated rate. Genome occupancy and expression profiling analyses reveal that Olig2 directly activates cell-proliferation machinery to promote tumorigenesis. *Olig2* deletion causes a tumor phenotypic shift from an oligodendrocyte precursor-correlated proneural toward an astroglia-associated gene expression pattern, manifest in downregulation of platelet-derived growth factor receptor-α and reciprocal upregulation of epidermal growth factor receptor (EGFR). *Olig2* deletion further sensitizes glioma cells to EGFR inhibitors and extends the lifespan of animals. Thus, Olig2-orchestrated receptor signaling drives mitotic growth and regulates glioma phenotypic plasticity. Targeting Olig2 may circumvent resistance to EGFR-targeted drugs.

New mutation links ALS/SLA and frontotemporal dementia

CCNF mutations in amyotrophic lateral sclerosis and frontotemporal dementia.
Willams KL, Topp S, Yang S, Smith B et al., Nature Communications 2016, 7:11253
DOI: 10.1038/ncomms11253

Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) are overlapping, fatal neurodegenerative disorders in which the molecular and pathogenic basis remains poorly understood. Ubiquitinated protein aggregates, of which TDP-43 is a major component, are a characteristic pathological feature of most ALS and FTD patients. Here we use genome-wide linkage analysis in a large ALS/FTD kindred to identify a novel disease locus on chromosome 16p13.3. Whole-exome sequencing identified a CCNF missense mutation at this locus. Interrogation of international cohorts identified additional novel CCNF variants in familial and sporadic ALS and FTD. Enrichment of rare protein-altering CCNF variants was evident in a large sporadic ALS replication cohort. CCNF encodes cyclin F, a component of an E3 ubiquitin–protein ligase complex (SCFCyclin F). Expression of mutant CCNF in neuronal cells caused abnormal ubiquitination and accumulation of ubiquitinated proteins, including TDP-43 and a SCFCyclin F substrate. This implicates common mechanisms, linked to protein homeostasis, underlying neuronal degeneration.

It's all in the Model

The Public Repository of Xenografts Enables Discovery and Randomized Phase II-like Trials in Mice.
Townsend EC, Murakami MA, Christodoulou A et al., Cancer Cell, 2016; 29 (4): 574 DOI: 10.1016/j.ccell.2016.03.008

More than 90% of drugs with preclinical activity fail in human trials, largely due to insufficient efficacy. We hypothesized that adequately powered trials of patient-derived xenografts (PDX) in mice could efficiently define therapeutic activity across heterogeneous tumors. To address this hypothesis, we established a large, publicly available repository of well-characterized leukemia and lymphoma PDXs that undergo orthotopic engraftment, called the Public Repository of Xenografts (PRoXe). PRoXe includes all de-identified information relevant to the primary specimens and the PDXs derived from them. Using this repository, we demonstrate that large studies of acute leukemia PDXs that mimic human randomized clinical trials can characterize drug efficacy and generate transcriptional, functional, and proteomic biomarkers in both treatment-naive and relapsed/refractory disease.

- **Postdoc position Single molecule imaging**

Postdoctoral position in my lab - correlating the spatial organisation of oncogene receptors as a function of the externally applied membrane potential on live cells. The project involves combining single-molecule fluorescence techniques with electrical (patch clamp) recordings.
http://www.jobs.ac.uk/job/ANG059/research-associate-biophysical-chemistry/
Please contact me directly: Dr. Steven F. Lee Royal Society University Research Fellow & Fellow of Sidney Sussex College University of Cambridge. Chemistry Department. Lensfield Road. Cambridge. CB2 1EW. sl591@cam.ac.uk
+44 1223 331509

- **Boden Research Conference (Sept 19-23, 2016)**

We are now inviting abstracts for the Boden Research Conference 2016: Animal, Vegetal, Mineral? Yallingup/Western Australia 19-23 September 2016.
The meeting will be an interdisciplinary open discourse on topics related to the formation mechanisms of complex structures in biological and synthetic systems, and their functions and properties. How far can (dead) physics, chemistry, material science and mathematics explain (living) biology? How can biology inform physics, chemistry, mathematics and material science? Emergent structure in physical and biological systems draws inspiration from a very broad section of the mathematical, physical and biological sciences. Topics from differential geometry to evolutionary biology, origami to drug delivery, all play critical roles in the field, and we encourage contributions from all backgrounds with a willingness to tackle the central questions of the conference.
See the website: www.animal-vegetal-mineral.org

- **Postdoc Position: Structural biology of proteins relevant for synaptic plasticity.**

Opening for a post-doctoral fellow (3 years) in my lab in Bergen, in a collaborative project with the Neuroscience research group. The project focuses on structural biology of proteins relevant for synaptic plasticity, and is part of a larger, recently funded multidisciplinary “top research” program at the department, focusing on this biological process using various approaches ranging from optogenetics to protein biophysics. I can be contacted for more details, but applications have to be submitted as described in the official advertisement:
https://www.jobbnorge.no/en/available-jobs/job/124068/full-time-temporary-position-as-postdoctoral-fellow-in-structural-neurobiology-at-the-department-of-biomedicine
I would be grateful, if you could bring this to the attention of potentially suitable candidates. Best regards, Petri Petri Kursula, PhD Professor of Biochemistry and Molecular Biology Department of Biomedicine University of Bergen, Norway
http://www.uib.no/en/persons/Petri.Kursula
E-mail: petri.kursula@uib.no

- **EBSA Course: Membrane Biophysics and lipid-protein interaction Montpellier – La Grande Motte, France (September 2016).**

Advanced course to provide young researchers (PhDs, postdocs) with a solid background in membrane biophysics and in the major methodological approaches. In addition, the course is also an excellent networking opportunity.
The course will contain several plenary and didactic lectures on membrane biophysics and lipid-protein interactions given by Professors specialist in their field. Major structural techniques (NMR, X-rays, Fluorescence, Electron Microscopy, CD, AFM, MD simulations) and concepts (thermodynamics, self organization, dynamics) will be developed in the context of different biological topics. Students will also actively participate in presenting shortly their ongoing work during case studies that will initiate students with research strategy, data acquisition and analysis. For more information visit the website: http://biophysics.wix.com/montpellier

- **PhD in Bio-(inorganic) chemistry on: Self Assembly and metal-binding of the Amyloid-beta Peptide.**

Envisaged starting date : 01/10/2016 Application deadline: 30 May 2016 Place: Institut de Chimie (UMR 7177), 4 rue B. Pascal, 67000 Strasbourg (France) Group : Biometals and Biological Chemistry Groupleader and supervisor: Peter Faller Project: There is a large body of evidence from In vivo, in cellulo and in vitro experiments that metal ions (mostly Cu, Zn and Fe) play an important role in the development of Alzheimer’s disease (AD). Cu and Zn ions are found in high concentration in the amyloid plaques, a hallmark of AD. These metal ions are bound to the peptide called amyloid-beta (Aβ), which is the major component of these plaques and are present in an aggregated form. Metal ions were reported to intervene in two key processes of Alzheimer’s disease: the aggregation of the peptide amyloid-β (Aβ) (mainly Cu and Zn) and the production of reactive oxygen species (ROS) (for Cu and Fe). Compounds that counteract the metal imbalance were reported to be a promising therapeutical approach. The objective of the project is to elucidate the role of metal ions in the aggregation of Aβ. We plan to generate Aβ peptides labeled by different fluorophores in order to probe metal-

binding, aggregation and interaction with different metalloproteins in the full-length Aβ under biologically relevant conditions. Techniques: chemical and biochemical methods; spectroscopy (NMR, fluorescence, FTIR, etc), microscopy (AFM, TEM), chromatography; electrophoreses; cell culture and fluorescence microscopy Key words: biometals; bioinorganic chemistry; copper, zinc; reactive oxygen species, self-assembly; amyloids; metal trafficking; fluorophores; spectroscopies. Recent reviews of the group: - Nasica-Labouze J, et al. Chem Rev. 2015, 115, 3518-63. - Faller P, et al. Acc Chem Res. 2014, 47,2252-9. Contact: Peter Faller, pfaller@unistra.fr
Application instructions:
+http://www.unistra.fr/index.php?id=22338
(see bottom for english version) Group Website: http://institut-chimie.unistra.fr/equipes-de-recherche/bcb-biometaux-et-chimie-biologique/

- **CECAM workshop in Toulouse – Mesoscopic modelling in Physics of Molecular and Cell**

Could you please bring to the attention of the EBSA affiliates the CECAM workshop "Mesoscopic Modeling in Physics of Molecular and Cell Biology" to be help from October 10th to October 13th 2016 in Toulouse, France?
More information can be found on the website: http://www.cecam.org/workshop-0-1269.html

- **Course: Advanced applications of flourescence. July 4-6 2016 CNR Institute of Food Science, Avelino Italy.**

Contact:
Dr. Olga Fierro (fluorescence.course@isa.cnr.it) for any more information.
Course Description
Fluorescence techniques are being used and applied increasingly in academics and industry. The Principles of Fluorescence Techniques course will outline the basic concepts of fluorescence techniques and the successful utilization of the currently available commercial instrumentation.
The course is designed for students who utilize fluorescence techniques and instrumentation and for researchers and industrial scientists who wish to deepen their knowledge of fluorescence applications. Key scientists in the field will deliver theoretical lectures. The lectures will be complemented by the direct utilization of steady-state and lifetime fluorescence instrumentation and confocal microscopy for FLIM and FRET applications provided by leading companies.
Participants are recommended to have at least a bachelor's degree in the life sciences, physical sciences or engineering before attending. Interactions between participants and lecturers will be fostered. Students will have ample opportunity to personally explain their research programs and ask questions about the applicability of specific fluorescence techniques to their course lecturers. Topics addressed in this course include: Basic Definitions and Principles of Fluorescence, Fluorescence Polarization,
Time-resolved Fluorescence, Instrumentation
Data Manipulation and Data Analysis, Fluorescence Probes, Confocal and Multiphoton Fluorescence Microscopy FFS, Fluorescence Fluctuation Spectroscopy, FLIM, Fluorescence Lifetime Imaging, Single Molecule Imaging
The number of participants to the course is limited: Lectures: Limited to a total of 70 participants (auditorium size). Practicals: Limited to a total of 30 participants (interactive, small-group sessions). Participation is granted on a first-registered, first-served basis. We encourage you to register as soon as possible at the online form:
http://www.fluorescence-foundation.org/registration.aspx?id=avellino2016
For any more information, visit the page: http://www.isa.cnr.it/web/?p=5170

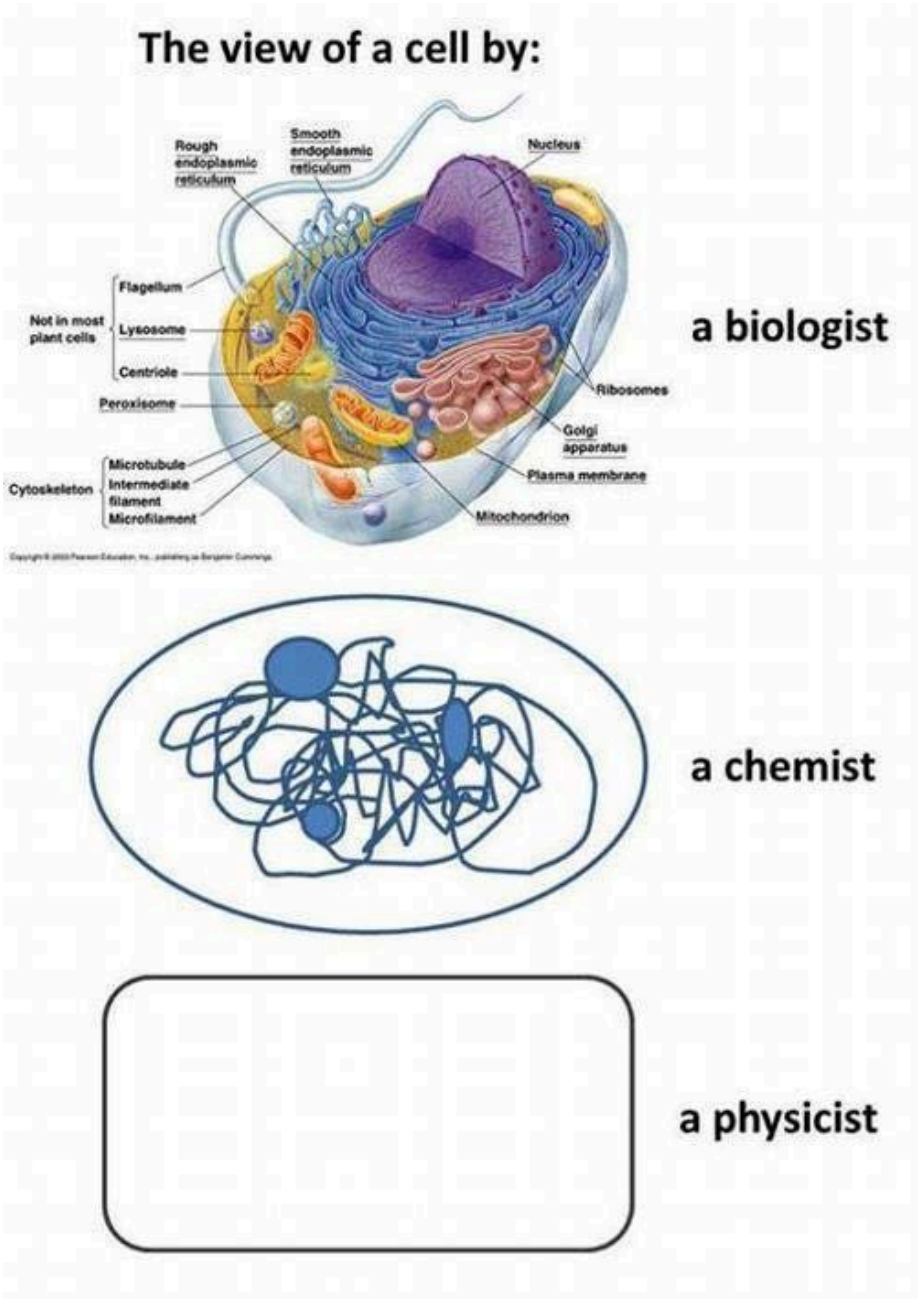
- **Fourth International Conference on Advances in Bio-Informatics and Environmental Engineering - ICABEE 2015.**

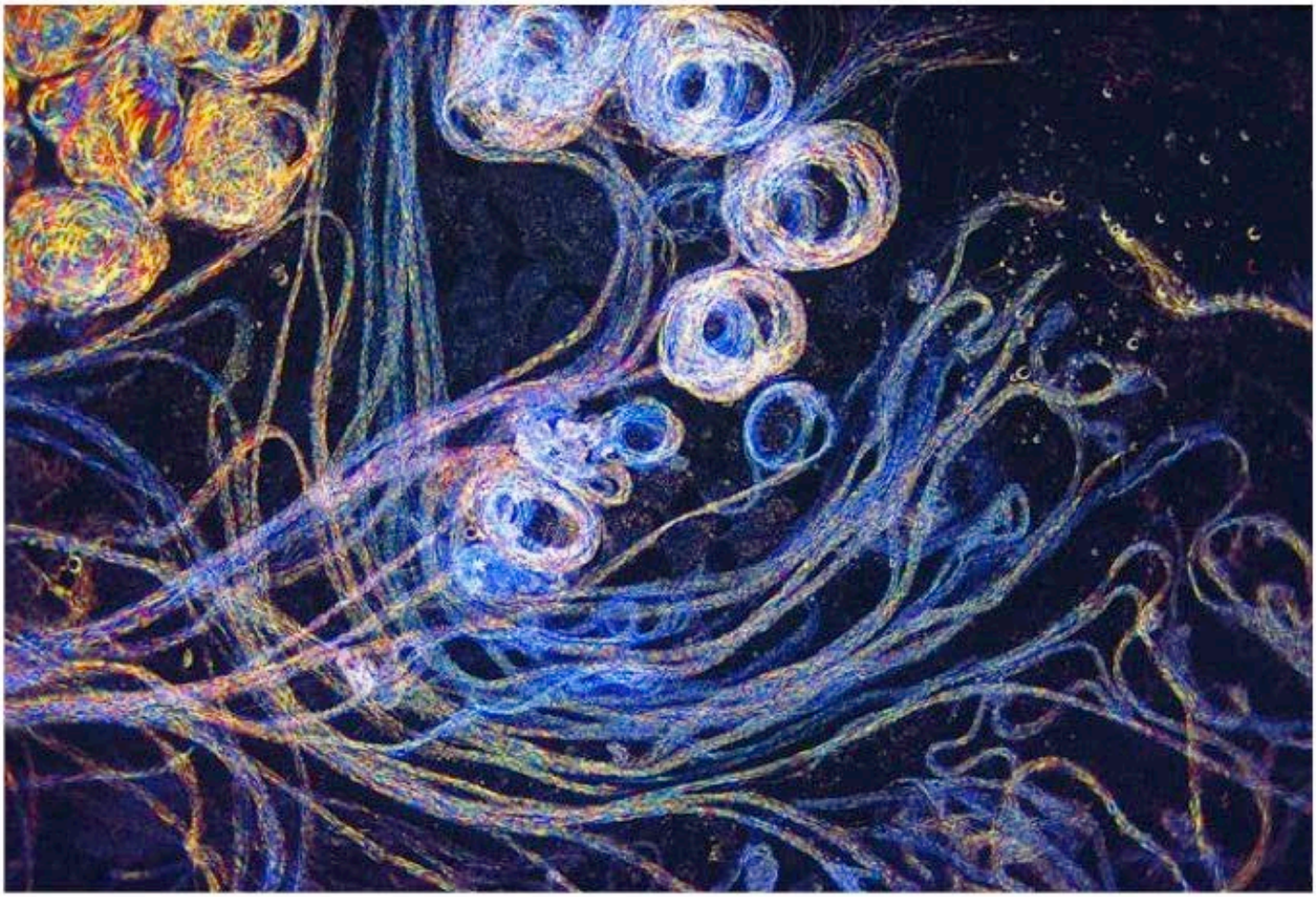
Organized by Institute of Research Engineers and Doctors at Rome, ITALY to bring together innovative academics and industrial experts to a common forum. **Official Website:**
www.icabee.theired.org
Email: icabee@theired.org
Conference Venue: HOTEL Novotel Roma La Rustica, Rome, ITALY Conference Date: 23 - 24 July 2016 Early Bird Round Paper Submission Important Dates: Abstract/ Full paper Submission: 27 May 2016 Paper Notification on or before 31 May 2016 Camera Ready Copy/ Paper Registration 17 june 2016 All the registered papers will proudly be published by IRED-CPS and stored in the SEEK digital Library (www.seekdl.org). Each Paper will be assigned DOI (Digital Object Identifier) from CROSSREF. The Proc. will be submitted to ISI Thomson for Review and Indexing. Proc. will also be published in International Journals. We Request you to forward this email to your colleagues/Researchers/students in order to promote the conference. The aim of the conference is to provide a platform to the researchers and practitioners from both academia as well as industry to meet and share cutting-edge development in the field. Please take the time to explore the website for more details, check on important dates, and keep yourself up to date on recent changes. Registered Papers (IRED Extended paper guidelines applicable) will be published in the various issues of International journals. Prospective authors are invited to submit full (original) research papers; which are NOT submitted or published or under

consideration anywhere in other conferences or journals; in electronic format via email. Thanks Much Stefania NEWS Division IRED

- **8 “Dream New” Student Fellowships (total value Eu 60,000)**

for adventurous students who want to spend an entire semester in 1 of 8 New Zealand Universities. For more information visit: http://www.european-funding-guide.eu/it/borsa-di-studio/dream-new
for more fellowship funding opertunities visit : www.european-funding-guide.eu/it


The view of a cell by:
Rough endoplasmic reticulum
Smooth endoplasmic reticulum
Nucleus
Flagellum
Not in most plant cells
Lysosome
Centriole
Peroxisome
Ribosomes
Golgi apparatus
Plasma membrane
Cytoskeleton
Microtubule
Intermediate filament
Microfilament
Mitochondrion
a biologist
a chemist
a physicist



Drosophila virilis (fruit fly) sperm (400x)

Credit: Earl Nishiguchi. Kauai Community College