II ANNUAL MEETING CINBIO

Abstracts book

25th & 26th of June 2018 – University of Vigo

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Conference Program

DAY 1 - 25th June, 2018

DIAGNOSIS

9:00 - 9:30	**Registration**
9:30 - 9:45	**Opening and Welcome: Prof. África González-Fernández - CINBIO Director**
Session 1	**Chairs: Prof. Ángel Rodríguez de Lera Dr. Ana Querejeta-Fdez**
9:45 - 10:45	**Opening plenary session: Prof. José L. Mascareñas** **CIQUS - Universidade de Santiago de Compostela. Spain** ***Metal-based tools in chemical biology and biomedicine***
10:45 - 11:15	**Invited speaker: Dr. Alexandr Missiul** **Sincotrón ALBA. Barcelona, Spain** ***ALBA synchrotron capabilities for biomedical studies***
11:15 - 11:30	**Dr. Manuel Pazos** **Instituto de Investigaciones Marinas (IIM-CSIC). Vigo, Spain** ***Metabolomics and lipidomics to improve diagnosis and nutritional therapy in obesity-related diseases***
11:30 - 12:00	**Coffee & Posters**
Session 2	**Chairs: Dr. José Souto Dr. Loretta De Chiara**
12:00 - 12:30	**Invited speaker: Dr. David Gómez-Cabrero** **NavarraBiomed - Universidad Pública de Navarra. Spain** ***Data integration methodologies in the era of multi-omics research***
12:30 - 13:00	**Invited speaker: Dr. Francisco Corzana** **Universidad de La Rioja. Spain** ***The use of unnatural MUC1 antigens enable efficient detection of antibodies in patients with cancer***
13:00 - 13:15	**Manuel Mendoza** **Universidade de Vigo. Spain** ***Hunting new potential TB-biomarkers by RNA-Seq***
13:15 - 13:30	**Paula Casal-Beiroa** **Instituto de Investigación Biomédica de A Coruña (INIBIC). Spain** ***Optical biomarkers for the early diagnosis of osteoarthritis***
13:30 - 15:00	**Lunch & Networking**
Session 3	**Chairs: Dr. Sara Núñez-Sánchez Dr. Sonia Prado**
15:00 - 15:30	**Invited speaker: Dr. Mar Rodríguez-Girondo** **Leiden University Medical Center. The Netherlands** ***Integration of omic datasets in biomedical prediction models: statistical challenges***
15:30 - 16:00	**Invited speaker: Dr. Alex McMillan** **University of Bristol. United Kingdom** ***Overcoming classical imaging limitations with quantum light***
16:00 - 16:15	**Sarah De Marchi Lourenço** **Universidade de Vigo. Spain** ***Metal nanoparticles@MOF nanocomposites as SERS tags for biodetection***
16:15 - 16:45	**Invited speaker: Dr. Lorena Diéguez** **International Iberian Nanotechnology Laboratory. Braga, Portugal** ***Liquid Biopsy: what can the KETs do for precision medicine?***
16:45 - 17:00	**Thais Pereira-Veiga** **Oncomet. IDIS, Health Research Institute of Santiago - CIBERONC. Spain** ***CTCs-derived xenograft development in a triple negative breast cancer case***
17:00 - 18:30	**Coffee & Posters**

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DAY 2 - 26th June, 2018

THERAPY

Session 1	Chairs: Dr. Diego Fernández — Dr. Daniel Glez-Peña
9:30 - 10:30	**Plenary session: Prof. Arturas Volianskis** **Queen Mary University of London. United Kingdom** ***Pharmacological targeting of NMDA receptors and different forms of synaptic plasticity***
10:30 - 10:45	**Dr. Ana Isabel Fernández-Mariño** **National Institute of Neurological Disorders and Stroke, NIH. United States of America** ***Understanding potassium channels architecture and gating***
10:45 - 11:00	**Elena Piñeiro-Yáñez** **Spanish National Cancer Research Centre (CNIO). Madrid, Spain** ***PanDrugs: novel method to prioritize anticancer drug treatments according to individual genomic data***
11:00 - 11:30	**Invited speaker: Dr. Laura Muinelo** **Oncomet. IDIS, Health Research Institute of Santiago - CIBERONC. Spain** ***Application of liquid biopsy in oncology: opening new horizons to fight cancer***
11:30 - 12:00	Coffee & Posters
Session 2	**Chairs: Dr. Elina Garet — Dr. Yolanda Diz**
12:00 - 12:30	**Invited speaker: Dr. Carlos Palo-Nieto** **Uppsala Universitet. Sweden** ***Synthesis of complex carbohydrates and potential angiotensin II AT2R ligands***
12:30 - 12:45	**Rocío Castro-Viñuelas** **Universidade da Coruña. Spain** ***Generation of human induced pluripotent stem cell lines from patients with hand osteoathritis***
12:45 - 13:00	**Dr. Sergio Gómez-Graña** **Instituto de Investigación Hospital 12 de Octubre. Madrid, Spain** ***Selective melanoma treatment using a targeted chemo-photo thermal therapy***
13:00 - 13:15	**Alba Vázquez-Arias** **Universidade de Vigo. Spain** ***Nanolamps for light-induced modulation of cell function***
13:15 - 13:45	Prizes and closing remarks

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INVITED ORAL COMMUNICATION

The use of unnatural MUC1 antigens enable efficient detection of antibodies in patients with cancer

F. Corzana

Department of Chemistry, University of La Rioja, ES.

Abstract:

MUC1 is a glycoprotein overexpressed in most types of cancer.[1] This overexpression is associated with elevated concentrations of antibodies against MUC1 in the blood of patients.[2] In this talk, a structure-based design of a new generation tumor-associated glycopeptides with improved affinity against two anti-MUC1 antibodies is described.[3] These unique antigens feature a fluorinated proline residue, such as a (*4S*)-4-fluoro-L-proline or 4,4-difluoroproline, at the most immunogenic domain (see Figure). Binding assays using bio-layer interferometry reveal 3-fold to 10-fold affinity improvement with respect to the natural glycopeptides. According to X-ray crystallography and MD simulations, the fluorinated residues stabilize the antigen-antibody complex by enhancing key CH/π interactions. Interestingly, a notable improvement in detection of cancer-associated anti-MUC1 antibodies from serum of patients with prostate cancer is achieved with the non-natural antigens, which proves that these derivatives can be considered better diagnostic tools than the natural antigen for this type of cancer.

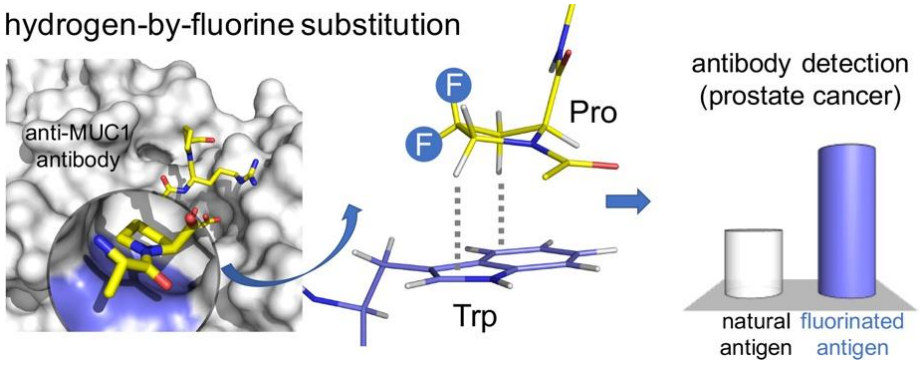

Figure 1

[1] N. Martínez-Sáez, J. M. Peregrina, F. Corzana, *Chem. Soc. Rev.* **2017**, *46*, 7154-7175.
[2] Z.-M. Tang, Z.-G. Ling, C.-M.Wang, Y.-B. Wu, J.-L. Kong, *PLoS One* **2017**, *12*, e0182117.
[3] V. J. Somovilla, I. A. Bermejo, I. S. Albuquerque, N. Martínez-Sáez, J. Castro-López, F. García-Martín, I. Compañón, H. Hinou, S.-I. Nishimura, J. Jiménez-Barbero, J. L. Asensio, A. Avenoza, J. H. Busto, R. Hurtado-Guerrero, J. M. Peregrina, G. J. L. Bernardes, F. Corzana, *J. Am. Chem. Soc.* **2017**, *139*, 18255–18261.

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INVITED ORAL COMMUNICATION

Data integration methodologies in the era of multi-omics research

D. Gómez-Cabrero

Translational Bioinformatics Unit, Navarrabiomed, Complejo Hospitalario de Navarra (CHN), Public University of Navarra (UPNA), ES

Abstract:

Research in recent decades have uncovered that transcriptomic regulation of the cell occurs at multiple layers, genetic and epigenetic regulation among others. Furthermore, non-coding genes - including miRNAs and lncRNAs - have been shown to play an important role in several diseases such as cancer.

Hence, to understand biological systems and diseases the challenge is two-fold. First to collect and manage data from all those regulatory layers over the same type of cells and/or conditions; successful projects covering such goal are TCGA, ENCODE, FANTOM5 or IHEC projects. Secondly, and equally important, is the development of methodologies able to INTEGRATE all those regulatory layers.

In my seminar I will first review the concept of data integration, with clear and simple examples. Next, I will describe the outcomes of two integrative projects:

1) The search for immune disregulation in Multiple Sclerosis and

2) STATegra: a “eight-omic” benchmarking dataset obtained under a controlled experimental setting.

Finally I will provide a brief overview on existing challenges in data-integration.

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INVITED ORAL COMMUNICATION

Metal-based tools in Chemical Biology and Biomedicine

J.L. Mascareñas

University of Santiago, CIQUS, ES.

Abstract:

Transition metal complexes have found widespread utility in a variety of scientific fields ranging from catalysis to photophysics and supramolecular chemistry. The different coordination and redox characteristics of metals, together with the possibility of tuning their properties by changing the nature of the ligands, provides innumerable possibilities for generating new reactivities, and for implementing physicochemical responses.

Building upon these characteristics, recent work in our work group aims at unveiling new metal-promoted catalytic reactions, and developing metal-dependent strategies to be used in Biosupramolecular Chemistry and Chemical Biology. Our work in catalysis has been mostly focused on discovering new annulation reactions,[1] while in the supramolecular field we have been mainly centered in the area of DNA recognition.[2]

Finally, in an effort to combine our knowledge in metal catalysis with our work in Chemical Biology, we have recently demonstrated the viability of achieving metal-promoted processes in biological media, inside living cells, and even in specific cellular organelles such as mitochondria.[3]

1. F. López, J. L. Mascareñas, Chem. Soc. Rev. 2014, 43, 2904; M. Gulías, J. L. Mascareñas, Angew. Chem. Int. Ed. 2016, 55, 11000.

2. J. Rodríguez, S. Learte, J. Mosquera, G. Celaya, D. Rodríguez-Larrea, M. E. Vázquez, J. L. Mascareñas, Chem. Sci. 2018, 0.1039/C7SC05441F; M. I Sánchez, J. Mosquera, M. E. Vázquez, J. L. Mascareñas, Angew. Chem. Int. Ed. 2014, 53, 9917; J. Mosquera, A. Jiménez-Balsa, V. I. Dodero, M. E. Vázquez, J. L. Mascareñas, Nature Commun. 2013, 4, 1874; S. Learte, N. Curado, J. Rodríguez, M. E. Vázquez, J. L. Mascareñas, J. Am. Chem. Soc. 2017, 139, 16188.

3. M. I. Sánchez, C. Penas, M. E. Vázquez, J. L. Mascareñas, Chem. Sci. 2014, 5, 1901; M. Tomás-Gamasa, M. Martínez-Calvo, J. R. Couceiro, J. L. Mascareñas, Nature Commun. 2016, 7, 12538.

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INVITED ORAL COMMUNICATION

Overcoming classical imaging limitations with quantum light

A.R. McMillan[1*], J. Sabines-Chesterking[1], J. Mueller[1], E. Allen[1], P.A. Moreau[2], S. Joshi[1], P. Mosley[3], J.G. Rarity[1], J.C.F. Matthews[1]

1. University of Bristol, UK. 2. University of Glasgow, UK, 3. University of Bath, UK.

*Presenting author.

Abstract:

Imaging and sensing using light continues to be an invaluable tool across scientific disciplines. In particular, optical measurements of properties such as absorption, refractive index and spectral response has driven new understanding in the life sciences through high fidelity images of microscopic biological structures.

The precision with which sample parameters can be estimated is bounded by the stability of the light source used to probe them, and this directly affects the quality of optical imaging. Particularly in the limit of weak illumination, it becomes apparent that any accurate physical description of a light source must account for the particle-like nature of the photons which make up the light, and their statistical distribution in time. Even the most stable classical light source – an ideal laser – is ultimately limited by the "shot noise" that results from these intrinsic properties.

Recent years have seen rapid progress in the development of new sources of light, based on the principles of quantum mechanics, which can overcome traditional limits in imaging, enabling super-sensitive phase and absorption measurements, super-resolution beyond the diffraction limit, and ghost imaging of samples, where the probe and detection wavelengths can differ significantly.

I will describe the recent progress in generating quantum states of light through the nonlinear optical interactions possible in carefully engineered crystals and optical fibres. In particular, by generating photons in correlated pairs, we are able to overcome the classical shot noise limit and realise an absorption imaging microscopy system with an absolute quantum advantage in precision. I will also discuss the generation of brighter non-classical states of light, including intensity correlated twin beams and optically squeezed laser pulses, which can operate close to the damage threshold of light-sensitive samples, whilst obtaining more information from each illuminating probe photon than an ideal classical light source.

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INVITED ORAL COMMUNICATION

ALBA synchrotron capabilities for biomedical studies

A.B. Missiul

ALBA Synchrotron Light Source, ES.

Abstract:

ALBA is a 3rd generation Synchrotron Light facility located in Cerdanyola del Vallès, Barcelona, being the newest synchrotron light source in the Mediterranean area. ALBA currently has eight operational beamlines, comprising soft and hard X-rays, which are devoted mainly to biosciences, condensed matter and materials science. Additionally, three beamlines are under construction. The life science section currently includes four beamlines: BL01-MIRAS; BL09-MISTRAL; BL11-NCD-SWEET; BL13-XALOC.

MIRAS beamline is devoted to FTIR spectroscopy and microscopy. Transmission, reflection, attenuated total reflection and grazing incidence geometries are available at the beamline. The temperature controlled sample stage allows infrared analysis of samples from -196 up to 600°C. The sample can be placed within a gas tight chamber for atmospheric control.

The full-field transmission X-ray microscopy beamline MISTRAL is devoted to cryo nano-tomography in the water window for biological applications. In addition, spectroscopic imaging at several interesting X-ray absorption edges such as, for example, Ca, Ni, O, Fe can be performed, as well as magnetic imaging.

NCD-SWEET beamline allows to perform the small angle X-ray scattering experiments which provide structural and dynamic information of large molecular assemblies like polymers, colloids, proteins and fibres. A wide range of fields (medicine, biology, chemistry, physics, archaeological, environmental and conservation sciences and materials) can be covered by this technique.

XALOC aims to provide the present and future structural biology groups with a flexible and reliable tool to help in finding solutions for structures of macromolecules and complexes. The beamline copes with a broad variety of crystal sizes and unit cell parameters, and allows both wavelength dependent and independent experiments.

The talk will be devoted to the experimental opportunities provided by ALBA for the users from the scientific community. Several representative examples will be presented. The application procedure and experiment preparation will be described.

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INVITED ORAL COMMUNICATION

Application of liquid biopsy in oncology: opening new horizons to fight cancer

L. Muinelo-Romay

Oncomet, IDIS, Health Research Institute of Santiago – CIBERONC, ES.

Abstract:

During cancer progression, different subclonal tumour populations change over time and become dominant due to the selective therapy pressure. Traditionally, the molecular characterization of solid tumours is based on surgical or biopsy tissue samples. In some cancers these biopsies are really difficult to obtain and sometimes only represent part of the tumour, causing the loss of relevant information to design a personalized therapy. To improve the tumour characterization and monitoring body fluids have emerged as key elements to reach a precision oncology.

Early in the formation and growth of a primary tumour cells are released into the bloodstream. Thanks to an important technological development, nowadays these circulating tumour cells (CTCs) can be enriched and characterized using different strategies. CTCs research initiated the field known as “liquid biopsy”. It meant a great revolution in oncology because using a liquid sample, usually blood, that can be obtained easily, dynamically, and less invasively than tissue biopsy, oncologists can determine prognosis, recurrence, and improve the treatment selection. Nowadays, other tumoural components found in blood such as ctDNA, microRNA, and extracellular vesicles are also being analysed to obtain a better picture of the tumour. For a research point of view the option to characterize and perform functional studies using circulating tumour elements constitutes an incredible tool to go insight the mechanisms behind tumour dissemination and the development of resistances to the standard and new target therapies. However, although the “liquid biopsy” field is growing exponentially, some important questions must be answered during the following years to reach its general application to manage cancer patients.

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INVITED ORAL COMMUNICATION

Synthesis of complex carbohydrates and potential angiotensin II AT2R ligands

C. Palo-Nieto

University of Sweden, SE.

Abstract:

The field of glycobiology has exploded in the last few decades, identifying oligosaccharides and glycoconjugates as key components in a wide range of biological processes. These developments have prompted renewed interest, in their synthetic preparation with a predominant focus on the development of new stereoselective glycosylation approaches.[a] The chemical synthesis of complex carbohydrates generally involves the coupling of a fully protected glycosyl donor bearing a leaving group at its anomeric centre, with a suitably protected glycosyl acceptor (R-OH). In many instances, these reactions lead to a mixture of two stereoisomers. To this day, the stereoselective synthesis of glycosides remains one of the biggest challenges in carbohydrates chemistry. [b] Herein, and corresponding with the work carried out at Bristol University, is reported the development of different catalytic methods for the synthesis of glycosides under mild conditions. Some practical approaches has been developed for the glycosylation of D-glycals with excellent yields and α-stereocontrol using different catalysts. In addition, herein is presented the work that it is being carried out in the angiotensin II field in the Hallberg-Larhed group at the Department of Medicinal Chemistry, Uppsala University. There are a large number of structurally diverse angiotensin II AT1 receptor (AT1R) antagonists in clinic, for example, the well-known drug losartan. There are, however, neither any AT2 receptor (AT2R) agonists, nor AT2R antagonists on the market. In healthy adults, expression of AT2R is normally low but is noteworthy that AT2R are upregulated during certain pathological conditions, such as myocardial infarction, vascular injury, brain ischemia and renal failure. Selective AT2R ligands, proposed to act as agonists, have been known for a long time and have been used extensively as research tools, but those agonists are all peptides. [c] Short peptides exhibit in general a very low bioavailability and in consequence, limited as drugs. Consequently, metabolically stable, drug-like AT2R agonists with fair oral bioavailability are desired both as research tools and possibly as potential therapeutics. The first disclosed, potent, selective and small-molecules agonist to the AT2R was synthetized in our laboratory. [d] Notably, a minor structural alteration of C-21 converts this selective AT2R agonist to a selective AT2R antagonist (C-38). Currently, in our group we are working in the synthesis of new molecules with potential AT2R activity.

[a] Galan M C; Benito-Alifonso D; Watt. G M. "Carbohydrate Chemistry in Drug Discovery". Org Biomol Chem 2011, 9 (10), 3598. [b] I) Palo-Nieto C; Sau A; Williams R; Galan MC. "Cooperative Brønsted Acid-Type Organocatalysis for the Stereoselective Synthesis of Deoxyglycosides". J Org Chem 2017, 82, 407. II) C Palo-Nieto, A Sau, MC Galan. "Gold(I)-Catalyzed Direct Stereoselective Synthesis of Deoxyglycosides from Glycals". Journal of the American Chemical Society, 2017, 139, 14041. III) A Sau, R Williams, C Palo-Nieto, A Franconetti, S Medina, MC Galan. "Palladium-Catalyzed Direct Stereoselective Synthesis of Deoxyglycosides from Glycals". Angewandte Chemie 2017, 56, 1. [c] Georgsson J, Rosenström U, Wallinder C, Beaudry H, Plouffe B, Lindeberg G, et al. Short pseudopeptides containing turn scaffolds with high AT2 receptor affinity. Bioorg Med Chem 2006;14:5963–72. [d] I) Larhed M, Hallberg M, Hallberg A. Med Chem Reviews 2016; 51:69-82. II) Larhed M, Isaksson R, Hallberg A. The protective arm of the renin angiotensin system (RAS), London:Elsevier; 2015 131-140.

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INVITED ORAL COMMUNICATION

Liquid Biopsy: what can the KETs do for Precision Medicine?

S. Ribeiro-Samy[1], S. Abalde-Cela[1], L. Wu[1], M.I Oliveira[1], T. Pereira-Veiga[2], L. Muinelo-Romay[2], S. Carvalho[1], J. Gaspar[1], P.P. Freitas[1], R. López-López[2], C. Costa[2], L. Diéguez[1*]

1. International Iberian Nanotechnology Laboratory, PT. 2. IDIS-CHUS, ES.

*Presenting author.

Abstract:

Early dissemination of tumour cells is difficult to detect by traditional imaging and pathological methods. Cancer cells can be disseminated from the primary tumour through the lymphatic or circulatory systems; therefore isolating and analysing cancer cells from the peripheral blood of cancer patients offers a great alternative to tumour biopsy for low invasive diagnosis of metastasis. The P4 medicine concept (Predictive, Preventive, Personalized and Participatory) is fully realised in the context of Liquid Biopsy, since patient's blood is used as a biomarker for the prognosis and diagnosis of the disease status. Therefore, Liquid Biopsy provides the ideal scheme to personalize the treatment in precision medicine.

While the potential of liquid biopsy is clear, current techniques for the isolation, analysis and characterization of cancer cells are not efficient. Key Enabling Technologies, including microfluidics and nanotechnology, offer the desired miniaturization, automation, high-throughput, multiplexing ability, sensitivity and intrinsic reproducibility to develop efficient diagnostic technologies able to tackle the urgently required challenges to make P4 liquid biopsy a reality.

P4 medicine will permit to identify predictive and preventive biomarkers and genomic mapping, adapting treatments to each patient, and having the patients engaged for a successful outcome.

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INVITED ORAL COMMUNICATION

Integration of omic datasets in biomedical prediction models: statistical challenges

M. Rodríguez-Girondo

Department of Medical Statistics and Bioinformatics, Leiden University, Medical Centre, NL

Abstract:

In the last decades, biomolecular research developments led to an increasing number of omics measurements. These omic measurements have been widely used to improve prediction of numerous phenotypes and diseases using single omic models. The next step is to combine various types of omics data to further improve prediction models. However, the combination of heterogeneous datasets, in terms of scale, noise structure, and normalization, is challenging and there is not yet any state-of-the art approach. In this talk, I will give an overview of several approaches based on (group) regularized regression to combine several omics sources in one prediction model while taking into account the possible interaction between omic sources. I will illustrate the methods through the analysis of transcriptomics and metabolomics as predictors of obesity using data from the Dietary, Lifestyle, and Genetic determinants of Obesity and Metabolic syndrome (DILGOM) study, a population-based cohort, from Finland and prediction of treatment response in terms of transcriptomics and copy number variants using a breast cancer cell lines pharmacogenomics dataset.

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INVITED ORAL COMMUNICATION

Pharmacological targeting of NMDA receptors and different forms of synaptic plasticity

A.Volianskis

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Abstract:

N-methyl-d-aspartate receptors (NMDARs) are centrally involved in normal brain function, supporting synaptic transmission and learning and memory, and their dysfunction is implicated in many pathophysiological processes. NMDARs are composed of tetraheteromeric assemblies containing specific combinations of GluN1, GluN2 and GluN3 subunits. GluN2 subunits, of which there are four different subtypes (termed A through D), bind glutamate whereas GluN1 and GluN3 subunits are glycine binding. NMDARs are triple-gated, requiring co-activation by glutamate and glycine together with the voltage dependent relief of the Mg2+ block, which makes them particularly suited to regulate synaptic plasticity. When situated post-synaptically, NMDARs can sense the incidence of pre-synaptic neurotransmitter release that has to be synchronized with significant depolarizing post-synaptic activation in order to result in channel opening and Ca2+ influx into the intracellular compartment. Thus, NMDARs act as coincidence detectors of pre- and post-synaptic activity, endowing synapses with "Hebbian like" plasticity or function as autoreceptors controlling release of glutamate at presynaptic sites. The strength of the compartmentalized Ca2+ signal is thought to underlie induction of different forms of synaptic plasticity such as short-term potentiation (STP), long-term potentiation (LTP) and long-term depression (LTD), which are likely to mediate different physiological functions in cognition.

During my talk I will review some of the evidence supporting the roles of NMDARs and synaptic plasticity in learning and memory. I will also discuss involvement of NMDAR-subunits in STP, LTP and LTD and will provide evidence that different types of synaptic plasticity can be targeted pharmacologically using subunit-preferring NMDAR-ligands. I will discuss GluN2D subunits in particular, whilst presenting unpublished observations regarding selective pharmacological regulation of STP, which shed some insight about the role of STP in cognition.

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ORAL COMMUNICATION

Optical biomarkers for the early diagnosis of osteoarthritis

P. Casal-Beiroa[1,2*], E.F. Burguera[1,2,3], T. Hermida[1,2,3], N. Goyanes[1,2], N. Oreiro[1], P. González[4], F.J. Blanco[1,2], J. Magalhaes[1,2,3]

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*Presenting author.

Abstract:

Osteoarthritis (OA) is a rheumatic disease characterized by articular cartilage degradation. On its early stages, OA is asymptomatic and its current gold-standard diagnosis (X-Rays), focused on bone, limits the diagnosis to its moderate or advanced stages. Raman spectroscopy (RS) has been recently described as a non-invasive tool to detect molecular changes in biological tissues, producing a unique fingerprint. The aim of this work was to evaluate RS potential for OA early diagnosis.

Human hip cartilage (n=14), from healthy (H) and OA donors, with Kellgren-Lawrence (K-L) radiological grades from 0 to IV, were obtained after informed consent and frozen at -80ºC until analysis, using a Raman Bruker RFS100 Spectrometer equipped with a Nd:YaG laser. Main peaks were assigned according to literature, following area measurement. One-way ANOVA tests were performed to detect statistically significant differences, considering $p<0.05$. We further analyzed correlations between peaks variation and K-L grade. RS cartilage spectra revealed the following assignments: 1245-1270cm-1 amide III doublet (random-coil and α-helix collagen), 1063cm-1 (sulfated glycosaminoglycans, GAGs), 1377cm-1 (proteoglycans, PG), 1450cm-1 (lipids and proteins) and 1668cm-1 (proteins). For higher K-L grades, a peak appeared at 960cm-1 (apatite phosphate), related to tissue mineralization. The main quantitative molecular changes are hereby described: an increase in 1245/1270 ratio (defective/functional collagen) could indicate collagen arrangement loss, although there was low correlation vs K-L ($R2=0.3764$); GAGs and PG peaks showed a significant decrease with OA severity ($p<0.01$), supported by high correlation coefficients ($R2=0.7361$ and $R2=0.7999$, respectively), related to GAGs' degradation. An indirect lipid index (IL), calculated as A1450/A1668, showed an increase in lipids in OA tissues. Differences found between H and OA tissue are representative of the molecular changes during OA progression.

Our results suggest a set of parameters as optical biomarker panel for OA early diagnosis: defective/functional collagen (1245-1270cm-1), GAGs (1063cm-1), PG (1377cm-1) and IL (1450/1668).

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ORAL COMMUNICATION

Generation of human induced pluripotent stem cell lines from patients with hand osteoathritis

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*Presenting author.

Abstract:

Background: Induced pluripotent stem cells (iPSCs) are considered a powerful tool for studying diseases such as hand osteoarthritis (OA), since they represent an unlimited cell source with chondrogenic differentiation potential.

Aim: To generate an iPSC-line from human fibroblasts obtained from patients with radiographic hand OA, and characterize the cell line obtained.

Methods: Cells from patients with OA hand and a healthy donor were isolated from skin biopsies. These cells were histologically characterized and positivity for fibroblast markers was quantified. These cells were also karyotyped in order to confirm that chromosomal abnormalities did not exist before reprogramming, which was conducted by introducing Oct4, Sox2, Klf4 and c-Myc transcriptional factors with Sendai virus. Cell lines obtained were morphological, phonotypical and functionally characterized.

Results: Isolated fibroblasts showed normal karyotype 46,XX. Three weeks after reprogramming, embryonic stem cell-like colonies emerged in culture. These cells showed positivity for alkaline phosphatase activity and pluripotency markers, such as Tra1-81 and Nanog. Molecular analyses showed high relative expression levels of the pluripotency-related genes OCT4, SOX2, NANOG and CRIPTO in the iPSCs. These cells were also able to give rise to cells from the three germ layers. Regarding mesodermal differentiation, spontaneously beating cardiomyocytes were seen in culture.

Conclusions: The reprogramming process using Sendai virus and transcriptional factors Oct4, Sox2, Klf4 and c-Myc enabled us to generate iPSCs from two hand OA patients and one healthy donor.

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ORAL COMMUNICATION

Metal nanoparticles@MOF nanocomposites as SERS tags for biodetection

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*Presenting author.

Abstract:

The use of metal organic frameworks (MOFs) for biodetection is gaining increasing attention due to their large internal surface area, tunable crystal porosity and unique chemical properties. In this context, nanocomposites of plasmonic metal nanoparticles and MOFs are powerful alternatives for bioimaging due to the combination of MOFs with the SERS (Surface Enhanced Raman Scattering) properties that characterize plasmonic nanostructures. In this study we aimed to fabricate novel MOF-based imaging nanoprobes, formed by a plasmonic core (Au@Ag core-shell nanorod) and a zeolitic imidazolate framework ZIF-8 shell (Zn[2-methylimizadole]2) encoded with Raman active molecules. The surface of ZIF-8 nanocrystals was used for the direct bioconjugation of poly-histidine-tagged proteins, as targeting entities, through the interaction of unsaturated Zn2+ and imidazole moiety of histidines. This strategy led to a robust and oriented immobilization of different types of poly-histidine-tagged proteins (e.g. protein G, green fluorescent protein, and nanobodies) on the ZIF-8 surface. The imaging capabilities of the plasmonic@MOF nanocomposites was demonstrated through their functionalization with a poly-histidine-tagged nanobody against the epidermal growth factor receptor (EGFR), which allowed us to discriminate A431 (EGFR+) from 3T3 (EGFR−) cells by means of SERS spectroscopy.

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ORAL COMMUNICATION

Understanding potassium channels architecture and gating

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Abstract:

Voltage-gated potassium channels are central players in neural excitability and cardiac function. The publication of the crystal structures of the Kv1.2 and Kv1.2/2.1 paddle chimera in 2005 established a “domain-swapped architecture” within the voltage-gated activated ion channels. In the crystal structures, a rigid helical S4-S5 linker positions the voltage-sensing S4 helix of one subunit near the S5 helix of the neighboring subunit. In the tetrameric channel, the S4-S5 linker helices are positioned parallel to the membrane, wrapping the pore domain so that movements of the S4 helix can electromechanically couple to open and close the pore. Similar domain-swapped architecture architectures are also seen in Nav and Cav channels. The presence of a structured helical S4-S5 linker was challenged when experiments in the “Ether-a-go-go” EAG and in the “human EAG-Related-Gene” hERG, showed that it was possible to couple the voltage sensor to the pore when the voltage-sensing and pore domains of the channels were expressed as separate proteins without an intact S4-S5 linkers. Interestingly, the recently published cryoEM structures of the EAG channel family (EAG, CNG, HCN1 and hERG) revealed that this family has a “non-domain swapped” architecture, without rigid S4-S5 linker helices where the S4 helix is positioned close to the S5 of the same subunit. In order to understand the relationship between the voltage sensor and the pore domain, we chose Shaker as a model ion channel and we used the GIA (generalized interaction energy-analysis) method to determine the pairwise interaction energies between residues at the voltage-sensor pore coupling interface. This analysis allowed us to create an approximate map of the interaction networks that are responsible for transducing the voltage-signal from the voltage-sensor to the channel pore. These results are discussed in the context of electromechanical coupling and the role of non-charged residues in voltage-sensing and channel gating.

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ORAL COMMUNICATION

Selective Melanoma Treatment using a Targeted Chemo-Photo Thermal Therapy

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Abstract:

In the last years, melanoma is becoming an important severe public health problem worldwide, not only because of the increased number of cases every year, but also for its poor prognosis in late stages. Consequently, diagnosis in early stages of the cancer with an efficient treatment are crucial for a good life expectancy.

In this context, we have developed a therapeutic approach based on a melanoma-targeted chemo-photothermal nanotransporter of cytotoxic compounds. Our proposed strategy for melanoma treatment us based on core@shell gold nanorods@mesoporous silica covered with a thermosensitive polymeric shell capable of release (in response to near infrared, NIR, illumination) the transported cytotoxic compounds (Figure 1). The selectivity of the nanocarrier is provided by the peptide NAPamide which is anchored onto the polymer shell, being enhanced the internalization of the drug-loaded nanocarrier inside the melanoma cells. By this design, it is possible to achieve a higher therapeutic efficacy while minimizing the administered drug dose due to the specificity and the synergetic effect of the chemo-photothermal therapy (PTT).

We have demonstrated that the NAPamide peptide is an excellent targeting molecule for melanoma cells, as it could discriminate melanoma cells from healthy (human fibroblast foreskin cells). The viability of cancer cells treated with DOX-loaded nanocarriers was significantly reduced at low nanoparticle concentration and short NIR laser irradiation time. Accordingly, DOX-loaded nanoparticles have exhibited higher cytotoxicity as compared with the not loaded nanoparticles, due to the synergistic effect between chemo and PTT. Our results demonstrate the viability of such nanocarriers to be a powerful instrument for drug delivery systems, in response to thermal/NIR laser irradiation, for melanoma cancer cells, on account of the discrimination between cancerous and healthy cells present in tumors.

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ORAL COMMUNICATION

Hunting new potential TB-biomarkers by RNA-Seq

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1. University of Vigo, ES.

*Presenting author.

Abstract:

Mycobacterium tuberculosis is an old enemy of humans, nowadays it kills more than one million of people worldwide every year. These bacilli are able to dodge the immunitary surveillance and switch down the normal antigen presentation by macrophages and dendritic cells. The mechanism to do this remains unclear but, it is known that *M. tuberculosis* establishes a crosstalk with macrophages and dendritic cells, and drops as well the phagosome maturation. During this crosstalking, the bacteria can modify the gene expression profile. The immunopathology of tuberculosis infection is very complex and, for this reason, there is not yet any biomarker that allows an early and reliable diagnosis of tuberculosis infection. RNA-Seq may be a powerful technique to find new tuberculosis-biomarkers so, we analysed the differential gene expression of a cohort of 34 individuals (6 active tuberculosis patients, 16 latent tuberculosis infected contacts and 12 healthy controls). Our results were: four genes differentially expressed between healthy controls and active tuberculosis patients (CLC, GOLGB1, MON2, and CSNK1E). However, only one gene was differentially expressed in latent tuberculosis contacts respect to healthy controls (PAXBP1). None of these genes have been described in tuberculosis before, so these five genes could be promising candidates for the diagnosis of active and latent tuberculosis. Although further studies are required to confirm these results, they may open a new path to elucidate the mechanisms involved in the anti-Mtb immune response. A possible mechanism to explain all these differential expressions might be the regulation mediated by miRNA or any other ncRNA.

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ORAL COMMUNICATION

Metabolomics and Lipidomics to Improve Diagnosis and Nutritional Therapy in Obesity-related Diseases

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*Presenting author.

Abstract:

Obesity and concomitant diet-related metabolic diseases such as hepatic steatosis, hyperlipidemia, insulin resistance and type-2 diabetes, pose one of the major threats to public health and economic development in the 21st century. The modern incorporation of that has been termed The Western diet, essentially enriched in saturated lipids and simple sugars, is well-known to trigger a cascade of metabolic changes that finally lead to the above diet-induced metabolic disorders, although the molecular mechanisms are mainly unknown, hampering early diagnosis and the development of effective nutritional and pharmacological treatments. In this context, our investigation puts into relevance a key role of metabolomics and lipidomics, two OMICS technologies recently developed for the global analysis of low molecular weight compounds (metabolites and lipids), to provide relevant mechanistic data of the diet-induced metabolic diseases and improve early diagnosis and the design of optimized nutritional therapies. The present study integrates mouse models of diet-induced obesity and hyperglycemia with several mass spectrometry-based metabolomic and lipidomic platforms aiming to identify changes on energy, carbohydrate, amino acid and lipid metabolism with the potential to early detect obesity-related diseases and/or to better evaluate the therapeutic effectiveness of nutritional treatments. The results indicate that metabolomic and lipidomic data clearly discriminate by diet, but more importantly, also by disease phenotype, suggesting the synthesis and accumulation of lipid species in the liver, and changes in the amino acid metabolism and eicosanoid production as main contributors to the development of obesity and hyperglycemia. These findings also illustrate the great potential of metabolomics and lipidomics to comprehensively understand the molecular complexity in the crosstalk between genes, diet and obese phenotypes that is inherent in obesity and other diet-induced metabolic diseases, and fundamental to improve early diagnosis and get safe and cost-effective nutritional (and pharmacological) therapies.

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ORAL COMMUNICATION

CTCs-derived xenograft development in a Triple Negative breast cancer case

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*Presenting author.

Abstract:

Breast cancer is an heterogeneous disease that encompasses multiple subgroups with different molecular signatures, prognoses and responses to therapies. Despite the progress made in diagnosis and treatment in breast cancer in recent years, metastatic disease continues to be a clinical challenge to this day. Among the different subgroups, triple-negative breast cancer (TNBC) is characterized by high rates of cancer recurrence and metastasis and no available molecular targets.

Circulating tumor cells (CTC) are cells that have shed from the primary tumor into the vasculature or lymphatic nodes from a primary tumor and constitute the seeds for the tumors metastases. CTC derived xenograft (CDX) technology has demonstrated to be a promising tool to obtain a better understanding of cancer biology. In this study a CDX from a TNBC patient, which reproduces the main characteristics of the original tumor, was developed for the first time.

Using RNA sequencing to examine CDXs and patient´s tissue samples, we found WNT signalling as the main mechanism related with this tumor biology and lead us to identify CTC markers and therapeutic targets in TNBC patients. Furthermore, high of expression of one of these markers was associated with poorer survival rates in a wide cohort of TNBC patients. This study demonstrates that CTC from TNBC are tumorigenic and CDX is a useful model that provides relevant information about the molecular actors participating in this tumor formation and evolution.

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ORAL COMMUNICATION

PanDrugs: a novel method to prioritize anticancer drug treatments according to individual genomic data

E. Piñeiro-Yáñez[1*], M. Reboiro-Jato[2,3], G. Gómez-López[1], J. Perales-Patón[1], K. Troulé[1], J.M. Rodríguez[4], H. Tejero[1], T. Shimamura[6], P.P. López-Casas[1], J. Carretero[5], A. Valencia[1], M. Hidalgo[1,7], D. Glez-Peña[2,3], F. Al-Shahrour[1]

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*Presenting author.

Abstract:

Background: Large-sequencing cancer genomes projects have shown that tumours have thousands of molecular alterations and their frequency is highly heterogeneous. In such scenario, physicians and oncologists are routinely facing lists of cancer genomic alterations where only a minority of them are relevant biomarkers to drive clinical decision-making. By this reason, medical community agrees on the urgent need of methodologies to establish the relevance of tumour alterations, assisting in genomic profile interpretation and, more importantly, to prioritize those that could be clinically actionable for cancer therapy.

Results: We present PanDrugs (Piñeiro-Yáñez et al, 2018 Genome Medicine), a new computational methodology to guide the selection of personalized treatments in cancer patients using the variant lists provided by genome-wide sequencing analyses. PanDrugs offers the largest database of drug-target associations available from well-known targeted therapies to preclinical drugs. Scoring data-driven gene cancer relevance and drug feasibility PanDrugs interprets genomic alterations and provides a prioritized evidence-based list of anticancer therapies. Our tool represents the first drug prescription strategy applying a rational based on pathway context, multi-gene markers impact and information provided by functional experiments. Our approach has been systematically applied to TCGA patients and successfully validated in a cancer case study with a xenograft mouse model demonstrating its utility.

Conclusions: PanDrugs is a feasible method to identify potentially druggable molecular alterations and prioritize drugs to facilitate the interpretation of genomic landscape and the clinical decision making in cancer patients. Our approach expands the search of druggable genomic alterations from the concept of cancer driver genes to the druggable pathway context extending anticancer therapeutic options beyond already known cancer genes. The methodology is public and easily integratable with custom pipelines through its programmatic API or its docker image. PanDrugs webtool is freely accessible at http://www.pandrugs.org.

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ORAL COMMUNICATION

Nanolamps for light-induced modulation of cell function

A.Vázquez-Arias[1*], S. Nuñez-Sánchez[1], M.J. Cordero-Ferradás[1], G. Bodelón[1], J. Pérez-Juste[1], I. Pastoriza-Santos[1]

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*Presenting author.

Abstract:

Light-triggered activation of photochemical processes has emerged as a potential alternative therapy where light offers high spatiotemporal precision control of live cell functioning. For that, we use our knowledge in the optimization of dopant distributions for rare-earth (RE) doped amplifiers to design light actuators at nanoscale, i.e. up-converting nanoparticles (UC-NPs)-based nanostructures (i.e.Nanolamps), as light sources for optical control of cellular activity at the nanoscale.

Here we explore the potential application of Nanolamps as bio-activators for reversible oligomerization of modified Arabidopsis thaliana photoreceptor cryptochrome 2 (CRY2olig) optogenetic module, that is genetically fused to mCherry fluorescent protein (CRY2-mCherry) which act as reporter to visualize and record the process by epi-fluorescence microscopy.

In this study, we have demonstrated that this optogenetic module induces rapid, robust and reversible protein oligomerization in response to blue light once transfected into HeLa cells. The cells were successfully grown upon glass dishes functionalized with the UC-NPs. Future work will aim to exploit this UP-NPs based optogenetic tool that will expand the growing arsenal of optogenetic strategies. Moreover, a better understanding about protein-protein interactions and protein function disruption would be of high value toward control cellular processes.

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POSTER COMMUNICATION

P1- GOING INSIDE THE PHENOTYPIC PLASTICITY OF TRIPLE NEGATIVE BREAST CANCER CIRCULATING TUMOR CELLS

M. Abreu[1,2*], P. Cabezas[3], A. Abalo[1,2], N. Martínez[1], V. Varela[1], P. García[4], L. Sánchez[3], R. López López[1,2,5], L. Muinelo-Romay[1,2,5]

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*Presenting author.

Abstract:

Background: Despite advances in prevention, diagnosis and treatment of breast cancer, triple negative subtype tumors or TNBC (ER-/PR-/ErB2-), present poor prognosis, characterized by high incidence of metastasis and resistance to conventional chemotherapy treatments. Classically, to improve the understanding of this tumor biology studies have been focused on the characterization of the primary tumor. However, there is a key step in tumor progression, the presence of circulating tumor cells (CTC) in blood, which has not been sufficiently studied. The present study aims to characterize the population of CTC present in TNBC patients, focusing on genes highly implicated in the EMT process and the stem-like phenotype, in order to identify new CTC markers and therapeutic targets.

Materials and Methods: CTCs were immunoisolated from peripheral blood in 32 TNBC patients (stage III and IV) and 30 healthy controls using magnetic beads coated with EpCAM antibodies (CELLection™ Epithelial Enrich Dynabeads™, Invitrogen). After the enrichment steps, the expression of a panel of cellular plasticity related genes was analyzed by RT-qPCR. In order to analyze the role of TIMP1, the marker that presented the higer prognostic value, we create a TIMP1 knock-down MDA-MB 231 cell line and we tested it in vitro and in vivo in a zebra fish model.

Results: CTCs characterization indicated an important plasticity phenotype defined by the expression different mesenchymal (VIM and SNAIL1) and stem (CD49F, ALDH2, CD44 and BCL11A) markers reinforced the idea of an important role of cell plasticity for the dissemination process in TNBC. In addition, after Kaplan-Meier analysis, we observed that some of these markers (TIMP1, CD49F, CD44, ALDH2) presented prognostic value, being their high expression associated with lower survival rates. Regarding TIMP1 assays, we observed a lower grow rate in TIMP1 knock-down cells both in vitro and in vivo.

Conclusion: In conclusion, our study provides evidence that isolation and characterization of CTC in TNBC patients could improve the knowledge of the main mechanisms that regulate this tumor aggressiveness and provide us with valuable prognostic markers. Also we observed that TIMP1 is involved in MDA-MB 231 TNBC cell line growth.

Keywords: TNBC, CTC, EMT, Stem, RT-qPCR, TIMP1.

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POSTER COMMUNICATION

P2 - Formin 2 links neuropsychiatric phenotypes at young age to an increased risk for dementia

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*Presenting author.

Abstract:

Introduction: Age-associated memory decline is due to variable combinations of genetic and environmental risk factors. How these risk factors interact to drive disease onset is currently unknown. Epidemiological data indicates that individuals suffering at a young age from neuropsychiatric diseases (eg. PTSD, depression) have an increased risk to develop dementia at old age, which is mechanistically poorly understood.

Objectives: Our main objective is studying the link between PTSD at young age to an increased risk for dementia.

Methods: Here we begin to elucidate the mechanisms by which post-traumatic stress disorder (PTSD) at a young age contributes to an increased risk to develop dementia at old age. We employed various mouse models for age-associated memory impairment and asked if cognitive decline is preceded by deficits in fear extinction, a well-established paradigm to assay PTSD-like phenotypes in rodents. We also analyzed human samples from PTSD and Alzheimer´s disease patients. We performed behavioral analysis and diverse molecular biology techniques.

Results: In the mouse models, we identify the Formin 2 (Fmn2) gene and show that FMN2 is a synaptic protein. Fmn2 levels are deregulated in PTSD and Alzheimer´s disease patients. Young mice lacking the Fmn2 gene exhibit PTSD-like phenotypes and corresponding impairments of synaptic function. However, Fmn2 mutant mice develop accelerated age-associated memory decline that is linked to aberrant transcriptome plasticity reflecting loss of cellular homeostasis affecting synaptic actin dynamics. This effect is further accelerated in the presence of additional Alzheimer´s disease risk factors but it is ameliorated by administration of the FDA approved HDAC inhibitor Vorinostat (SAHA).

Conclusion: In conclusion, our data present a new approach to explore the connection between AD risk factors across life span and provide mechanistic insight to the processes by which neuropsychiatric diseases at a young age affect the risk for developing dementia.

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POSTER COMMUNICATION

P3 - Comparison of bacterial heat transfer under exposure to solutions with Cobalt and Titanium. Potential implications in orthopaedic surgery

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*Presenting author.

Abstract:

Introduction: Most joint prosthesis that are currently used in orthopedic surgery are made with alloys of Titanium and Cobalt, with the formation of periprosthetic bacterial biofilm being one of the major complications. Alongside the increasing joint replacement performance, bacterial infections have become a great concern due to its significant impact to patients´ health and national health budget. The purpose of this study was to evaluate the differences on bacteria growth when they are exposed to solutions that contain these metals at different concentrations.

Methods: Dissolutions of titanium tetrachloride and cobalt acetate were prepared with concentrations from 0 to 10 mM, and saturated. A suspension of 106 CFU/ml of Pseudomona aeruginosa, and a culture medium of a liquid soya-casein-digested liquid were used. The measurements were carried out in a Calvet microcalorimeter at constant temperature of 309.65 K for 48 hours, and thermograms were obtained.

Results: The phases of the bacterial growth showed an initial ascending phase with two main leaps, then a descending curve showing an exponential shape, which is prolonged over time. Using 3 mM of titanium tetrachloride and cobalt acetate, the highest voltage peaks were 101 µV and 119µV respectively. In addition, at concentrations of 6 mM: 81µV and 97µV; and with 10 mM: 74µV and 86µV respectively. Both saturated concentration resulted in complete signal suppression.

Conclusions: Both metallic dissolutions showed a suppressive effect of the voltage signal as the concentrations increased. However, the solutions containing titanium showed a stronger bactericide effect than the solutions with cobalt. This study supports a wider use of titanium alloys rather than cobalt alloys for the orthopaedic prosthesis. However in-vivo studies are needed for clarification. In addition, this study highlights the potential use of microcalorimetry in monitoring bacteria growth, and therefore as a possible diagnostic tool for infections of joint replacements.

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POSTER COMMUNICATION

P4 - IC-Tagging: a general platform for production of protein microspheres as immunogens. Different expression systems, particle size and successful expression of difficult proteins

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*Presenting author.

Abstract:

Introduction: IC-Tagging is a patented methodology with many potential applications (Brandariz Nuñez et al, 2010a, Brandariz Nuñez et al, 2010b, Brandariz Nuñez et al, 2011). We have shown that epitope-loaded microspheres (MS) are potent immunogens in absence of any added adjuvant (Alejandro Marin et al 2014, Barreiro Piñeiro et al, 2016). We wanted to extend the capabilities of our method by loading problematic proteins to the MS. We also wanted to test its performance in prokaryotic expression systems that would.

Materials and methods: Recombinant plasmids and baculoviruses were generated using standard techniques. DF1 or Sf9 cells were plated onto glass-bottom dishes and observed on a Nikon Ti-E microscope. Alternatively, cells were seeded on glass coverslips and used for transfection with lipofectamine as indicated by the provider or infection with recombinant baculoviruses. Expressed proteins were localized by immunofluorescence using specific primary antibodies and detected with the corresponding commercial fluorophore-conjugated secondary antibodies. Images were obtained with an Olympus DP- 71 digital camera mounted on an OlympusBX51 fluorescence microscope.

Results: When adding a N-terminal signal sequence to muNS-Mi, MS are formed inside the endoplasmic reticulum (ER). IC-tagged mRFP co-localizes with such MS, while untagged mRFP does not. The ectodomain of glycoprotein Gn from RFVF gets loaded into ER MS, and its glycosylation pattern is not changed whether the protein is loaded or not into MS. muNS-Mi expressed in bacteria form spherical inclusions of 0,4 µm inside the cells, that are easily purified. IC-tagged proteins co-expressed with muNS-Mi in bacteria are loaded onto the MS and can be easily co-purified with them. Several difficult to express proteins were purified using the bacterial IC-Tagging system.

Conclusion: We can produce microspheres inside the ER and loaded IC-tagged protein inside them. We can express toxic and difficult protein using our IC-tagging system in bacteria.

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POSTER COMMUNICATION

P5 - Highly frequent mutations in a Spanish Alström cohort

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*Presenting author.

Abstract:

Alström syndrome (ALMS) is a rare disease whose symptoms include defects of cardiac function, progressive loss of vision, early onset diabetes mellitus type 2, obesity, deafness, growth retardation and renal failure. It is caused by mutations in the ALMS1 gene which encodes the ALMS1 protein, a structural component of centrosome involved in intracellular transport among many other roles.

We analyzed the sequence of ALMS1 in a cohort of 11 unrelated ALMS families. Several mutations were identified in exons 7, 8, 16 and 17.

Most of the mutations were found in exon 8. Two mutations had a high incidence in the cohort: p.(Tyr1714 *) (exon 8; rs772136379) with 36% and p.(Ser3872Tyrfs * 19) (exon 17), with 27%. We described one homozygote for p.(Tyr1714 *) mutation and one for p.(Ser3872Tyrfs * 19), all the other families with this mutations were compound heterozygotes. Segregation analysis showed that the p.(Tyr1714 *) mutation is linked to the SNP rs45608038 which presents a low frequency (≈2%) in European populations.

ALMS patients usually account for private mutations. For the first time we can see mutations with a large incidence in an ALMS cohort.

Additional analyzes are underway to decipher whether these families maintain a genealogical relationship, although families have been recruited from different national geographic areas and none of them reported to have kinship relations with the other ones. If the common heritage of mutation p.(Tyr1714 *) were demonstrated, we could be talking about a founder allele for Spanish patients.

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POSTER COMMUNICATION

P6 - Dibenzylidene Sorbitol gels: Structural studies.

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Abstract:

Dibenzylidene sorbitol (DBS) is a molecule used in both the cosmetic and pharmaceutic industry due to its well-known water-gelating ability, but it is also capable of forming gels with many organic solvents at concentrations as low as 0.1 wt%. The gelation process is due to H-Bonding between the free OH groups in the sorbitol, followed by subsequent π-π stacking between the phenyl rings which favours the formation of helical fibrils.

Depending on the solvent used and on the DBS concentration the gel transparency varies, from a pretty transparent gel to a murky, whitish gel at higher DBS concentrations. Hydrogen bonding by the solvent as assessed through Hansen Solubility Parameters (∂h) seems to play a role. Gels in acetone and isopropyl alcohol (high ∂h) are transparent, while those in ethyl acetate and toluene (low ∂h) are opaque.

With the goal of describing the packing arrangement of DBS in different hydrogen bonding solvents, we examined DBS gels in acetone, isopropyl alcohol, toluene and ethyl acetate at different concentrations by electronic microscopies (SEM, TEM) and X-ray scatterings, specifically small-angle X-ray scattering (SAXS) and wide-angle X-ray scattering (WAXS).

Electron microscopy images revealed the formation of a fibrous network. Our X-ray studies showed that the phase in acetone is the same at different temperatures and that, at concentrations above the critical gelator concentration (cgc), microcrystalline phases emerged above the gelation temperature (Tg). We will discuss the dependence of profiles with temperature, concentration and solvent and also the model that describes best the packing arrangement of DBS within the fibers.

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POSTER COMMUNICATION

P7 - Au@Ag SERRS tags coupled to a lateral flow immunoassay for the sensitive detection of Pneumolysin

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*Presenting author.

Abstract:

Pneumonia is an inflammatory condition of the alveolar spaces of the lungs caused mainly by Streptococcus pneumoniae, a pathogenic bacterium which affects two thirds of both adults and children. Establishing a definitive diagnosis of pneumonia is difficult using conventional diagnostic tests. Nowadays, the most advantageous option is the development of a point-of-care (POC) test, based on antigen detection. These assays are portable, with short analysis time, and they can be used by untrained personnel in any location. Lateral Flow immunoassay (LFIA) is a very successful POC test in which an immunoassay takes place at a membrane. Typically, the sensitivity and quantification capabilities are constrained to the measurement of the optical density at the test zone (colorimetric test), which has some limitations in terms of detection and quantification.

In this work we have developed a lateral flow immunoassay for the ultrasensitive detection of pneumolysin, an important biomarker of pneumonia, employing plasmonic Surface-Enhanced Resonance Raman Scattering (SERRS) tag as labelled probe. The combination of Au@Ag core-shell nanoparticles as plasmonic platform and Rhodamine B Isothiocyanate as Raman reporter has allowed us to fabricate a SERRS tag with high efficiency and reliability. Moreover we carried out the bioconjugation of the plamonic nanoparticles with anti-pneumolysin antibody (PLY-7) with the aim of the detection of pneumolysin in a lateral flow immunoassay by SERRS. Finally, we demonstrated that Au@Ag NPs allowed the detection and quantification through both, SERRS-based LFIA and optical density readings. The comparison of the sensitivity of the SERRS-based LFIA with the value achieved based on the optical density reading showed a better performance of the SERRS assay.

The coupling of a SERRS-based sensor within a lateral flow immunoassay strip will boost its sensitivity and quantitative capabilities, showing a great potential for the qualitative and quantitative detection of analytes in biomedical, food and environmental analysis.

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POSTER COMMUNICATION

P8 - Early detection of Alzheimer's disease by identifying soluble fragments of LRP2 receptors

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Abstract:

Alzheimer's disease (AD) is the most common cause of dementia in the world. A prompt detection of this disorder is critical since it would allow dealing with potentially reversible dementias. For this reason, developing predictive blood tests to assist neurologists in establishing rapid and differential diagnoses will make possible a more systematic allocation of the effective treatment.

In this work, we have focused on the early detection of AD through the identification of a soluble fragment (220 kDa) from the low-density lipoprotein receptor-related protein 2 (LRP2) as a potential biomarker. The LRP2 transmembrane receptor is susceptible to be cleaved by matrix metalloproteinases (MMPs) releasing the ectodomain region into blood and/or cerebrospinal fluid where these soluble fragments can be quantified. Experimental evidence of changes in the concentration of different fragments of LRP2 in AD has been previously reported by our group.

In order to determine the presence of this 220-kDa fragment, a detection method based on surface-enhanced Raman spectroscopy (SERS) has been developed. Gold nanostars (AuNSs) have been deposited onto silica nanospheres in order to ensure their colloidal stability. In this case, AuNSs act as plasmonic antennas to enhance the Raman cross-section of the SERS reporter (4-aminobenzene-1-thiol) to which a specific antibody of LRP2 is covalently attached. Through this approach, the concentration of soluble fragments can be estimated by monitoring the Raman shift of the reporter's main peak.

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POSTER COMMUNICATION

P9 - Thermal spas in Asturias in the 19th. Perspectives for the 21st Century

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*Presenting author.

Abstract:

The year 2017 was the INTERNATIONAL YEAR OF SUSTAINABLE TOURISM FOR DEVELOPMENT, a fact that is used to highlight the importance of the health and leisure offer.

In this sense, the Mineral spring spa facilities combine this dual objective, therefore mineral spring waters, “both naturally and artificially emerging waters that by their characteristics and qualities are declared of public utility” and thermal springs, “those whose temperature of upwelling is higher than four degrees Celsius as annual average of the place where they upwell”, they become a water resource with outstanding economic potential, as well as therapeutic.

The Spanish State, with a population in which the elderly represent almost twenty percent and with an increasing life expectancy, through the Institute for Seniors and Social Services (IMSERSO), offers Programs of Thermalism, which together with other Private initiatives strive for the recovery and use of water for curative or industrial purposes.

The Government of the Principality of Asturias taking into account what has been mentioned above, and the possible contribution to the economic development of the Autonomous Community, promoted the realization of an inventory and characterization of thermal and mineral-medicinal waters in the region, for which it had the collaboration of the Geological and Mining Institute of Spain (IGME). From these studies and considering the active health spas in Asturias in the 19th century, we intend to select which ones can be currently a source of wealth, focusing on their particular chemical characteristics and their possible therapeutic use.

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POSTER COMMUNICATION

P10 - Biocompatible sphingolipid nanoemulsions for PET imaging

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*Presenting author.

Abstract:

Metastasis accounts for nearly 90% deaths related to cancer. Their early diagnosis can consequently lead to an increase in patient survival. Positron Emission Tomography (PET) imaging is one of the most used whole-body diagnosis techniques in cancer. On view of this, we aimed to develop biocompatible nanoemulsions (NEs) that can specifically reach disseminated cancer cells and act as PET probes.

Oil in water (O/W) NEs composed by sphingomyelin (Lipoid GmbH) and oleic acid, were prepared by ethanol injection and characterized using a Nanosizer 2000® (Malvern Instruments). NEs had a small colloidal size (130 nm) a polydispersity index correspondent of a monodisperse population (0.2), and a negative surface charge (-50 mV). For PET purposes, two chelating agents were associated to the NEs, PE-DTPA (Avanti Polar Lipids) and a synthesized derivative of NOTA (NOTA-SA), without appreciating relevant changes in their physicochemical properties. Afterwards, 68Ga was associated to the NEs by incubation, and purification was achieved by ultrafiltration. The radiolabeling was performed efficiently, obtaining high percentages of gallium association, 89% for NE-DTPA and 86% for NE-NOTA-SA. However, NE-NOTA-SA showed a better stability in mice serum. Both types of NEs were injected intravenously in healthy mice, and PET/CT images were acquired using a Gemini TF-64 scanner (Philips Healthcare) at 2h post-administration. Biodistribution studies were done by the collection of mice organs and the quantification of their radioactivity (Wizard 1470 gammacounter) at the end of the experiment. Results showed accumulation of the two formulations mainly in liver. Significant differences were observed with respect to the presence of radioactivity in blood, liver, kidneys and spleen.

In conclusion, we have developed biocompatible nanoemulsions that can be efficiently radiolabelled and have potential for the development of novel tools for PET diagnosis. Next experiments will be aimed to explore their potential in a mice model of metastatic disease.

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POSTER COMMUNICATION

P11 - Assessment of single-cell whole-genome amplification strategies

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Abstract:

Single-cell whole-genome amplification (scWGA) is a recent and powerful technology which helps us to decipher tumor heterogeneity, to understand the role of rare cells in tumor progression and to elucidate the appearance of therapy resistance. Unluckily, these techniques suffer from multiple technical errors such as uneven amplification, loss of genomic regions (ADO; allelic dropout), chimera formation or amplification errors which affect to the interpretation of the results. In this work, we benchmarked six scWGA kits based on different methodologies; PCR, Multiple Displacement Amplification (MDA) and a combination of both PCR+MDA. These kits were tested on a healthy diploid cell line (HDF; Human Dermal Fibroblasts) where all the cells are genetically identical. We sequenced 24 single-cells at shallow depth (0.25-1.64X) and an unamplified bulk as control at 30X in an Illumina HiSeq 4000 machine. We mapped the obtained reads to the hg19 reference using BWA and calculated the expected coverage breadth at different sequencing depths (1X, 5X, 10X and 20X) with Preseq. In addition, we estimated chimera formation, ADO and false positive rates and the heterogeneity of the amplification bias. We observed that cells amplified with the same kit clustered together, suggesting that the amplification is not a random process. Our results propose that different kits are best at different aspects. For example, GenomiPhi provided the highest expected coverage breadth at 10X (56.47 % 5.57, SD) but it also showed the highest chimera rate (>15%). On the other hand, Ampli1 showed the lowest ADO rate (37.69 % 3.99, SD) while REPLIg displayed the lowest false positive rate for single nucleotide variants (7.28 % 5.31, SD). These results therefore provide a useful guide for selecting scWGA protocols depending on the particular question of interest.

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POSTER COMMUNICATION

P12 - Liraglutide prevented the deposition of Collagen in the animal model of Bleomycin-induced lung fibrosis

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*Presenting author.

Abstract:

Idiopathic pulmonary fibrosis (IPF) is an excessive accumulation of fibrous filaments in the extracellular matrix (ECM), in response to an inflammatory reaction that disrupts normal lung architecture and physiology. Collagen is the most abundant fibrous protein in the ECM. The GLP-1 receptor is highly expressed on lung tissue, where his activation plays an essential role in the synthesis and secretion of surfactant proteins.

The objective of this study was to elucidate the effect of Liraglutide treatment on collagen synthesis and deposition in the lungs of an animal model of IPF.

IPF was induced in male rats by a single intra tracheal instillation of bleomycin (BLM, 2.5 mg/kg) on day 0. Animals were treated with Liraglutide using two different protocols. 1-Preventive treatment: LIR treatment was given from day-1 to day 6 and animals were sacrificed in day 21. 2-Therapeutic intervention: animals were treated from day 10 to day 20 after BLM; and animals were sacrificed on day 21. Lung lobes were isolated and frozen for mRNA expression analysis by Real time PCR, and for hydroxyproline quantification. We obtained Broncho alveolar lavage liquid for analysis of soluble collagen.

The mRNA expression of Collagen type 1 and the enzymes Arginase-1 and prolyl hydroxylase, which are essential for collagen fibre synthesis, were increased in day 21 in BLM instilled animals. Tissue levels of hydroxyproline were very increased. LIR treatment normalized the mRNA expression levels of the two enzymes. In addition, LIR administration decreased day 21 type I collagen mRNA expression and total collagen deposition on lung tissue, as well the soluble collagen in alveolar lavage fluid.

In conclusion, incretins play an important role in the regulation of the synthesis and activity of key enzymes in the formation of collagen fibres and deposition. Since, incretins may be useful molecules in the treatment and prevention of the pulmonary tissue fibrotic processes.

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POSTER COMMUNICATION

P13 - Thermal behaviour of a mixture with mineral water from Laias Spa for thermotherapy

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*Presenting author.

Abstract:

Keywords: peloid, mineral water, thermotherapy

Peloid is a maturated mud with healing and/or cosmetic properties, composed of a complex mixture of a solid substrate, mineral water or sea water, and organic compounds from a biological metabolic activity. The maturation can take place in the natural environment or not. When the peloid is prepared at the local and time of use, blending clays, or algae with mineral water or sea water without maturation they are called extemporaneous peloids. Thermotherapy is one of the therapeutic applications of peloids, that is, the use of heat for therapeutic purposes. This kind of therapy can be applied in the form of packs, mud baths or poultices, and for various diseases. The thermal behaviour of peloids is important for predicting their possible use in thermotherapy. In this work the physical properties of the mud such as density, specific heat, thermal conductivity, and diffusivity were measured. The sample is prepared with bentonite and mineral water from Laias Spa. The density data were measured by pycnometry. The specific heat was determined using a CALVET microcalorimeter. The thermal conductivity was determined using a Decagon KD2 Pro thermal properties analyser. The thermal diffusivity (D) was calculated in order to predict the thermal behaviour of the peloids using the expression: $D = \rho\, cp/\, \lambda$. Where λ is the thermal conductivity, cp is the specific heat and ρ is the density.

This study contributes new knowledge about the thermal behaviour of peloids for their therapeutic use.

Acknowledgments: The authors are grateful to María Perfecta Salgado González for her collaboration with the experimental measurements. We are also thankful for the financial support provided by the projects ED431C 2016-034 “Axudas a Grupos de Referencia Competitiva” funded by Xunta de Galicia and ED431G/02 “Centro de Investigacións Biomédicas” (CINBIO) co-financed with FEDER funds.

POSTER COMMUNICATION

P14 - Generation of the Cancer Pathway Prototype - a platform for predictive cancer pathway modeling

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Abstract:

Purpose: One of the greatest challenges in cancer research is to utilize the vast and dynamic influx of "omics" data. Current approaches exploring these data are confined to statistical and pattern recognition techniques or modeling of single signalling pathways - rather than considering/modelling the complex cross-talk among pathways that determines cancer initiation, progression and drug response. New solutions to optimally exploit this wealth of data for basic research, improved treatment and stratification of patients, as well as more efficient targeted drug development are required.

Methods: CanPathPro addresses the challenge of predictive modelling of biological data by developing and refining bioinformatics and experimental tools for the creation and experimental validation of systems biology modelling predictions. Components comprise highly defined mouse and organotypic experimental systems, next generation sequencing, quantitative proteomics and a systems biology computational model for data integration, visualisation and predictive modelling.

Results: CanPathPro will build and validate a new biotechnological application: a combined experimental- & systems biology validation platform, which will be utilised in generating and testing cancer signalling hypotheses in biomedical research. The CanPathPro project is currently at the beginning of its third year, and a number of milestones have already been reached. This presentation will focus on the advances made in computational methodology, including model simulation, parameter estimation, uncertainty and identifiability analysis. Furthermore, it will highlight the relevance of these methodologies in the context of biomedical research.

Impact: CanPathPro is set to have broad and significant impact on diverse areas, from cancer research and personalised medicine to drug discovery and development, ultimately improving outcomes for cancer patients.

Funding: CanPathPro has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 686282.

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POSTER COMMUNICATION

P15 - Cytotoxic activity of bioactive fractions obtained from Sargassum muticum with green technologies

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Abstract:

Sargassum muticum (Sm) is a brown seaweed from Japan. On the America coasts and western coasts of Europe, including Galician (Incera et al., 2011), Sm is an invasive alga, causing negative impact on ecology, fishing and recreate activities. Marine brown seaweeds contain alginate, laminaran, fucoidan and other minor compounds. Sulfated polysaccharides known as fucoidan, present different activities (Wijesinghe et al., 2012), such as antioxidant, antiviral, antitumoral, anticoagulant or anti-inflammatory, among others. These biological properties depend on the algal species and other factors such as harvesting conditions, life cycle and the extraction and purification conditions.

S. muticum was collected in Mourisca Beach (Pontevedra, Spain) in August 2016, was washed with tap water and stored at -18°C until use. Two technologies were proposed for the depolymerisation of fucoidan. Ultrasound-assisted extraction4 with liquid:solid ratio of 20:1, 40 Hz, at room temperature, during 5-30 minutes (Flórez-Fernández et al., 2017), and subcritical water extraction (autohydrolysis) with compressed hot water (Balboa et al., 2013) using a liquid:solid ratio of 30:1 and non isothermal operation during heating up to 150 °C, after autohydrolysis extraction, ultrasound-assisted extraction was performed for 5-30 min. In both extractions technologies, the alginate was precipitated (autohydrolysis extraction adding 1% $CaCl_2$; ultrasound-assisted extraction after overnight at 4 °C). Liquid alginate free and solid phases were separated by centrifugation. Liquid phase, containing both crude fucoidan and the solubilised phlorotannins, was analysed. Mono and oligosaccharides were determined by HPLC, sulfate, total phenolics and antioxidant activity were measured by spectrophotometric methods. Selected fractions were studied in human cell lines (A549, HCT-116, PSN1, T98G) by MTT assay. The obtained outcomes indicated that both environmental friendly extraction techniques could be adequate to obtain bioactive compounds from this invasive seaweed with potential attractive features for food, cosmetic or pharmaceutical industries, with the subsequent revalorisation of this seaweed biomass.

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POSTER COMMUNICATION

P16 - Liquid biopsy in colorectal cancer: deciphering novel non-invasive methylation biomarkers for colorectal cancer screening in serum circulating cell-free DNA

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Abstract:

Colorectal cancer (CRC) diagnosis at early stages associates with good prognosis and reduced mortality rates, while detection and removal of premalignant advanced adenomas (AA) result in the reduction of CRC incidence. Invasive approaches for CRC screening, such as colonoscopy, have low participation rates and high cost. On the other hand, non-invasive procedures like faecal immunological test have the advantage of increased acceptance, though sensitivity for proximal colorectal tumours and AA is moderate to low. Thus, there is a clear demand for novel non-invasive tests for the early detection of CRC and AA, to be used in population-wide screening programs. DNA methylation detected in liquid biopsies, such as serum circulating cell-free DNA (cfDNA), is a promising source of non-invasive biomarkers, because it has been demonstrated that cfDNA reflects the aberrant methylation events occurring in neoplastic and tumour cells. In a previous work we reported that, when using cfDNA, a sample pooling strategy offers a new affordable approach for methylation biomarker discovery. In this study, applying the sample pooling strategy, we aim to identify novel non-invasive methylation biomarkers for the early detection and screening of colorectal advanced neoplasia (AN: CRC or AA). We extracted cfDNA from serum samples from 130 individuals with no colorectal neoplasia (NN) and from 150 AN cases. Pooled samples were prepared for each pathological group using equal amounts of cfDNA from 10 individuals, sex-, age- and recruitment hospital-matched. DNA Methylation levels of 866,836 CpG positions across the genome were measured with the MethylationEPIC array. Bioinformatics preprocessing and statistical analyses were conducted with specific R/Bioconductor packages. The epigenome-wide analysis of serum cfDNA revealed 376 differentially methylated positions (DMPs) at 10% FDR, between NN and AN cases. Unsupervised clustering analyses showed that differential methylation patterns could distinguish AN samples from NN controls. We applied the Statistically Equivalent Signature algorithm for feature selection and we identified 3,256 combinations of 118 DMPs with statistically equivalent predictive value for “no neoplasia vs advanced neoplasia” classification. We used cross-validation to select a subset of 30 CpG sites as the most robust and predictive candidate set for biomarker validation in an independent cohort.

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POSTER COMMUNICATION

P17 - Microfluidic induced supercrystals for on-chip ultrasensitive SERS detection

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Abstract:

Microfluidic platforms allows generating a highly-ordered assembly of uniform gold/ nanoparticles inside their microchannels through the pervaporation of the solvent. Furthermore, the microfluidic approach enables the fabrication of uniform assemblies of any dimension or morphology. The resulting plasmonic devices could be used for the detection of analytes, even without affinity for gold nanoparticles.

Surface-enhanced Raman spectroscopy, SERS, is an advanced analytical technique that can be used for the ultrasensible detection of analytes since it offers orders of magnitude increases in Raman signals. It occurs at the surface of a plasmon surface mainly due to the presence of strong electromagnetic fields generated after the plasmon excitation. Moreover, this effect could be more intense in the case of hierarchical nanoparticles assemblies due to an antenna effect as demonstrated by recent simulations.

While the plasmonic substrates made by drop-casting show poor uniformity that limits their potential plasmonic applications, the microfluidic approach gives rise to platforms with highly uniform and intense SERS activity (being both key parameter to achieve quantitative analysis and low detection limits (LOD). Herein we will show the fabrication and characterization of plasmonic platforms fabricated using Au octahedra synthesized through a wet chemical method. Besides, the sensing capabilities of the platforms will be analyzed by investigating the SERS efficiency using different Raman active analytes. For instance, experiment performed with Crystal Violet showed a great LOD, lower than 100fM, which is several orders of magnitude lower than those found in the literature.

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POSTER COMMUNICATION

P18 - Metallosupramolecular systems for drugs liberation

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Abstract:

Dynamic polymers(*1) based on metallosupramolecular chemistry can be built with monomeric components connected through either labile noncovalent interactions or reversible covalent bonds. Specifically, the "MBioF's"(*2) are synthesized with structures similar to the ones found in our organism using flexible ligands which can lead to the formation of interesting architectures without loss of control in the self-assembly process. So it is possible to prepare metallic complexes which could accommodate biological active molecules reversibly.

In our research group(*3) we have used the biocompatible and essential Zn(II) cation coordinated to the linker ligand SCS(*4) (bis(pyridine-4-ylthio)methane) for loading ibuprofen (ibu) as biological active molecule. So we have prepared the 1D polymers (_∞^1)[$Zn(ibu)_2$(SCS)] (1) and (_∞^1)[ZnCl(ibu)(SCS)] (2). Furthermore, it was tested the liberation of ibuprofen employing different media like ionic interchange with NaCl(ac) and PBS, or modifying the pH conditions. Also the cytotoxicity and the relationship between the size and the synthetic method to obtain these compounds were investigated.

We have expanded our research using the essential and biocompatible Cu(II) cation coordinated to the new linker N,N'-donor dithioether ligand 1,3-bis(1-methyl-1H-imidazole-2-ylthio)propane (BMITP) obtaining the ibuprofen loaded 1D coordination polymer (_∞^1)[$Cu_2(ibu)_4$(BMITP)] (3). We are currently doing studies of liberation that show interesting results.

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POSTER COMMUNICATION

P19 - Splicing mechanism evaluation of NGS detected variants using hybrid minigenes

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Abstract:

Pulmonary Arterial Hypertension (PAH) is a rare and progressive disease characterized by vascular remodeling and the increase of vascular resistance that leads to right heart failure and, ultimately, death. PAH genetic basis has been slowly uncovered during the last decades. After screening with a sequencing panel for PAH related genes, several mutations were detected in the ATP-Binding Cassette transporter subfamily C member 8 (ABCC8) (Exon 3 c.G298A p.E100K, Exon 11 c.C1643T p.T548M, Exon 22 c.2694+1G>A, Exon 26 c.3288_3289del pL1096fs, Exon 27 c.G3384A p.D1132N), a gene widely related to congenital hyperinsulinism. DNA fragments, wild type and mutated sequence, were cloned into the pSPL3 vector. After PCR and Sanger sequencing to confirm the fragment insertion into the plasmid, pSPL3 was transfected into the COS-7 cell line by triplicate. 48 hours' post-transfection, RNA was isolated and cDNA was generated using RT-PCR. Lastly, a high fidelity polymerase was used to perform a PCR using primers surrounding vector's exon trap, the product was analyzed via electrophoresis and the bands of interest were sequenced. In silico analysis predicted a moderate ANNOVAR effect in 3/5 mutations, high in 1/5 and no effect in the last one. Our preliminar experimental results showed an altered splicing pattern in 1/5 mutations tested. Sequencing is in progress to confirm the differential pattern. In conclusion, minigene assay is a simple and effective method to check for splicing alterations and pathogenicity of the variants detected. Nonetheless, analysis of patient´s RNA will be definitive to confirm our results.

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POSTER COMMUNICATION

P20 - Inferring the nature of missing heritability in human diseases

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Abstract:

Genome Wide Association Studies (GWAS) have become the standardized method to detect genomic SNPs linked to loci responsible for most quantitative traits. It is expected that a better knowledge of the genetic basis of human diseases and their heritability will improve our understanding of their biology, playing an important role in their prevention and treatment.

However, candidate causal variants found so far usually explain only a small fraction of the heritability estimated by family data, while the rest remains 'missing'. The most common assumption is that missing heritability is due to common variants of very small effect that pass undetected in most GWAS due to a lack of statistical power. In consequence, the main strategy for new gene discovery goes into the direction of increasing population sample sizes.

Here we performed a meta-analysis using data from the NHGRI-EBI GWAS Catalog in order to explore the distribution of gene effects for a set of complex traits, including human diseases, and to quantify their contribution to heritability. Given that the GWAS Catalog keeps track of a history of gene discovery for these traits, we also investigated the factors related to new gene discovery, and made inferences on the expected distribution of gene effect sizes, the missing number of genes, and the role of common additive variants to heritability. Our results suggest that, while GWAS are still useful to find missing variants, part of the missing heritability can only be explained by the contribution of non-additive effects.

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POSTER COMMUNICATION

P21 - A toolbox for facilitating the manipulation of FASTA sequences

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Abstract:

Introduction: One of the most important types of data used in biological research is DNA or protein sequence data. They are usually stored in FASTA files, which can store one or more sequences. Public databases such as GenBank, NCBI or Ensembl provide huge collections of genomes, genome annotations, and so on, in FASTA format. Nevertheless, downloaded files usually must be preprocessed before subsequent analysis depending on each researcher needs. Despite the simplicity of these preprocessing operations (e.g. remove sequences without a minimum number of bases), processing of large batches of FASTA files is a complex task that usually requires advanced bioinformatics skills and the combination of different tools (including the bash command line) to achieve the desired result. In order to allow researchers to easily perform these operations we are developing the SEDA software application (http://www.sing-group.org/seda/).

Results: SEDA (SEquence DAtaset builder) is a Java desktop multiplatform application specifically created to perform processing of FASTA sequence files. Currently, SEDA allows researchers to filter sequences based on different criteria (including text patterns), translate nucleic acid sequences into amino acid sequences, execute Blast analyses, remove duplicated sequences, and sort, merge, split or reformat files, among others. Moreover, its plugin-based architecture makes it useful for programmers of bioinformatics software that want to make use of the SEDA core operations or extend it by creating new plugins.

Conclusions: SEDA is completely free, distributed under license GPLv3, and provide a friendly graphical user interface designed to allow researchers saving time in processing FASTA files.

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POSTER COMMUNICATION

P22 - Analysis of endothelin-1 (EDN-1) promoter region

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Abstract:

Endothelin-1 (ET-1) is a peptide secreted by the endothelium of blood vessels that promotes vasoconstriction. A deregulation in the synthesis of endothelin-1, increasing its secretion, is a triggering factor for Pulmonary Arterial Hypertension (PAH). We carried out the characterization of the promoter region of endothelin-1gene (EDN-1), in order to determine possible variations that may be associated with this disease and therefore target possible treatments.

The genetic analysis was carried out in 13 patients with Idiopathic PAH (IPAH), analysing a fragment of 2 kb promoter region. First, an in silico analysis was performed to evaluate binding transcription factors and CpG islands. Sequencing data was aligned to the reference Ensembl EDN-1 sequence. Luciferase assay was done to evaluate in vitro the SNP influence in gene expression.

A deletion in the promoter region was found (rs397751713). The distribution of the genotype frequencies in our IPAH patients were: A/A: 0.15; A/-: 0.31; -/-: 0.54.This variation is located in a KLF4 binding sequence, a transcription factor related to PAH development. A CpG island was also detected that comprise the aforementioned variation. Future methylation pattern studies will be performed.

In conclusion, this SNP in the promoter region of END1 could be related with gene expression levels. Even more, the epigenetic regulation could be also related to the methylation state of this region. All these data have to be taken carefully as these are preliminary data from 13 patients. Deciphering the regulation of EDN1 expression could shed light in the molecular basis of this disease.

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POSTER COMMUNICATION

P23 - Guanylyl Cyclase C-targeted nanoemulsions for metastasic colorectal cancer treatment

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Abstract:

Introduction: Colorectal cancer (CRC) is the fourth leading cause of cancer deaths in the world. The nanotechnology has led to significant advances in the cancer field. The Guanylyl Clyclase C (GCC) receptor has been proposed as a biomarker of interest for targeted imaging of CRC metastases. The possibility of exploiting this receptor for the targeted delivery of nanomedicines has not been reported so far.

Objectives: We propose the development of nanoemulsions specifically targeted to the GCC receptor upon functionalization with the peptide Uroguanilin (UroG).

Methods: A UroG derivative was covalently linked to C18-PEG12-COOH, to improve peptide integration in the nanoemulsions, and was characterized by HPLC, NMR, and MALDI-TOF. Nanoemulsions functionalized with C18-PEG12-UroG were developed and characterized with respect to their physicochemical properties. The incorporation of C18-PEG12-UroG into the nanoemulsions was determined by RMN. In vitro experiments were carried out in colon cancer cell lines (SW480 and SW620). In vivo assays were performed in a SW620 xenograft model.

Results: We have efficiently conjugated UroG to C18-PEG12, as confirmed by HPLC (75.45% conjugation yield), MALDI-TOF (2560 Da, which corresponds to the formation of the 1:1 conjugate) and NMR determining the diffusion coefficients (a lower diffusion coefficient value was determined for the conjugate due to its higher molecular weight). Surface-decorated nanoemulsions had a small size, narrow distribution, and neutral zeta potential. NMR confirmed the association of C18-PEG12-UroG to the nanoemulsions. In vitro assays confirmed that UroG-decorated nanoemulsions can efficiently interact with CRC cells and deliver their payload. In vivo assays showed an improved therapeutic effect for the decorated nanoemulsions and confirmed the potential of this approach for development of nanosystems targeted to metastatic CRC.

Conclusion: We have efficiently modified a peptide against GCC and we have decorated the nanoemulsions with this peptide for targeting CRC.

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POSTER COMMUNICATION

P24 - Mutational analysis of EDN1 gene as a key gene in Pulmonary Arterial Hypertension

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Abstract:

Endothelin (ET) is the peptide with the strongest vasoconstrictor effect of all the substances known to the human body. High blood levels of ET have been related with the deveplopment of cardiovascular conditions like Pulmonary Arterial Hypertension (PAH). PAH has been described as a multifactorial condition that results from the combination of enviromental, physiologic and genetic factors. It would be necessary a combination of key genes with a preexistant condition or enviromental exposure to develop the disease.

The main objective of this study is to determine the role of endothelin-1 gene (EDN1) in the deveplopment of PAH. To accomplish this, all EDN1 coding fragments of 24 patients with PAH were sequenced and the resulting sequences were compared with the Ensembl EDN1 (ENSG00000078401) reference sequence. We observed that this gene's sequence is greatly preserved in most of the patients with the exeption of the rs5370 polymorphism. This polymorphism has been detected in 8 of the studied patients and is described in the literature as a posible arterial hypertension risk marker.

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POSTER COMMUNICATION

P25 - Delivery of sphingomyelin nanoemulsions to colorectal cancer cells for miRNA replacement therapies and diagnosis

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Abstract:

Introduction: The engineering of nanotechnology has the potential for incorporating various kinds of molecules, including anticancer drugs, genes, and contrast agents, and target these agents to tumors. This work aims to develop novel biodegradable nanocarriers, of utility to detect colorectal cancer cells, and to interfere the process of tumour growth by selectively delivering oncosuppressor microRNAs.

Meterials and Methods: Biocompatible sphingomyelin nanoemulsions, easy to prepare by ethanol injection, were selected for the development of nanocarriers for gene therapy. Nanoemulsions were characterized by Dynamic Light Scattering, Laser Doppler Anemometry, and Transmission Electronic Microscopy. Association of miRNA was attempted upon inclusion of the cationic lipid stearylamine in the composition, and determined by agarose gel electrophoresis. Radiolabelling was achieved by establishment of a controlled chemical reaction with a fluorine derivative, [18F]-4-fluorobenzamido-N-ethylamino-maleimide ([18F]FBEM). Characterizations of [18F]FBEM-labelled nanoemulsions were confirmed by UPLC using gamma and UV detectors with their references.

Results and discussion: miRNA-loaded nanoemulsions (miR NE) formed monodispersed populations with size of approximately 170-190 nm and a negative zeta potential (-15mV). Experiments carried out under the confocal microscope showed a colocalization of Cy5-miRNA and NBD-Sphingomyelin labelled nanoemulsions in colorectal cancer cells (HT29). Radiolabelling was successfully achieved 35+5.7% of [18F]FBEM on the nanoemulsions. Biodistribution studies from positron emission tomography after 2 hours of injection exhibited two ways of clearance (liver and renal excretion).

Conclusions: We have developed lipidic nanoemulsions with potential for cancer diagnosis and therapy. Nanoemulsions had efficiently incorporated miRNA (miR NE). NE showed a good interaction with human colorectal cancer cells and successfully delivered the associated miRNA intracellularly. First biodistribution studies in healthy mice and PET images allowed us to conclude that we can track the radiolabelled nanoemulsions after intravenous injection to mice. Thus, these nanoemulsions have high potential for the development of nanotheranostics.

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POSTER COMMUNICATION

P26 - Analysis of the genomic position of human traits using GWAS data

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Abstract:

A more extensive knowledge about the genetic basis of diseases and the relationship between them leads to a better understanding of their pathological mechanisms, which may result in an improvement of their treatments. This study analyses the position of human SNPs associated to several complex traits, including diseases, using data from the NHGRI-EBI GWAS Catalog. After selecting the most meaningful information, we studied the genomic position of 59 traits. First, we assessed for each trait which chromosomes have an unexpectedly high or low number of risk genes. Second, we assessed which traits do not have their genetic basis randomly distributed in the genome, and which pairs of traits have their risk genes in matching positions. Both analyses were made considering full chromosomes and 2 Mb regions of the genome. We verified that chromosome 6 allocates more risk genes than expected for many diseases, because this chromosome carries the HLA region, whose alterations easily lead to disease, in particular, to immunological disorders. Chromosome X carries fewer risk disease genes than expected, as this chromosome is subjected to a stronger selective pressure than autosomal chromosomes. Risk genes associated to 95 % of the studied traits are not randomly distributed across the genome. We found a strong association between the positions of risk genes for immunological, dermatological, gastrointestinal and respiratory diseases, due to their connection to the immune system. In addition, we detected unexpected correlations among risk genes positions for other traits, including lung cancer and schizophrenia, or urate levels and vertical cup-disc ratio. These associations suggest common molecular mechanisms for those pairs of traits.

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POSTER COMMUNICATION

P27 - Comparison of cfDNA Isolation Yield from Human Plasma

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*Presenting author.

Abstract:

Liquid biopsy has recently become an important, non-invasive technique for screening and monitoring cancer patients1. One of the most studied components in this case is the cell-free circulating tumor DNA (ctDNA), which represents a fraction of the total patient cell free circulating DNA (cfDNA)2. The study of ctDNA in liquid biopsies from blood or other body fluid has some advantages over classic solid biopsy studies. It is less invasive, presents less risk for the patient, might offer a more accurate portray of the spatiotemporal tumoral heterogeneity and opens the possibility of tracking tumor dynamics in real time3. However, there is a lack of standardization and optimization of the isolation and processing methods for cfDNA, the first step for the subsequent study of ctDNA, which causes limitations in downstream applications.

Here, we evaluated three different methods to isolate cfDNA from human plasma based on magnetic beads4, vaccum5 and columns6. The DNA fragment sizes obtained after cfDNA isolation were between 148-173 bp (mean 161.3 bp), 114-159 bp (mean 125.4 bp) and 158-171 bp (mean 165.7 bp) with beads, vacuum and column isolation, respectively, independently of the initial plasma volume. These sizes correspond well with the expected apoptotic nucleosomal fragmentation sizes.

In conclusion, the method of choice will depend on whether total yield or fragment size is more important for the downstream application.

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POSTER COMMUNICATION

P28 - Development of an intracellular nanoreactor with catalytic and biodegradation resistance properties

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Abstract:

Cancer, nowadays, represents a major cause of death worldwide. As a result, in the last years, many research efforts have been made to improve the reliability of its diagnosis and therapy, representing Nanotechnology one of the greatest contributors. However, there are still issues on the Nanomedicines actuation, namely related with their selectivity and biodegradation.

To overcome these obstacles, a nanoreactor composed by mesoporous silica nanoparticles marked with a fluorescent tracer, rhodamine, and functionalized with dendritic platinum nanoparticles (Pt NPs) and oxidized multiwalled carbon nanotubes (ox-MWCNTs) is being developed. The ox-MWCNTs are meant to perform the lysosomal escape of the nanomedicine to the cytoplasm and the Pt NPs pretend to actuate as a catalyst to an intracellular reaction of formation of magnetic nanomaterial of nickel, endowing this nanosystem with a potential theranostic application. In the next phase of the work, the particles will be submitted to assays under different biological conditions.

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POSTER COMMUNICATION

P29 - Systems biology advanced methods to elucidate key regulators in cell signaling

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Abstract:

Understanding the molecular basis of diseases and mechanisms of drug action is important for the design of effective treatments. For this purpose, Systems Biology approaches combine experimentation with mathematical modeling and computational methods to elucidate molecular mechanisms in cell signaling and gene regulation.

In this context, we develop methods that allow detecting key regulators in cell decision-making processes. Cells process information from their environment through transduction and genetic circuits, modulating cellular behaviour/phenotypes in response. A "cell decision" occurs when a choice is made from competing options and persists at a certain degree as conditions change. Cell differentiation, apoptosis, or epigenetic switches associated to disease are a few examples involving cell decision-making processes. Other example of particular interest for biomedical applications in which cell decision-making can play an important role is differential signaling.

I will illustrate our methods through a recently published result where we found a mechanistic explanation for type 1 interferon differential signaling, i.e. how type 1 interferons elicit different activities ranging from antiviral to antitumor/apoptotic coding through the same receptor and signaling pathway, and also show how these methods are being applied in cancer signaling pathways for identification of potential biomarker and therapeutic targets.

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POSTER COMMUNICATION

P30 - Towards the Identification of Tumor Samples with High Rates of Somatic Retrotransposition by Agilent SureSelect System.

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*Presenting author.

Abstract:

Approximately the half of a human genome is composed of retrotransposons: sequences with the capacity to move from one to other site, integrating themselves in a new location. Among them, long interspersed nuclear element (LINE)-1 (L1) retrotransposons are widespread repetitive elements in the human genome, representing 17% of the entire DNA content. Due to this mobilization, they can change the normal genome structure in the places where they integrate, leading to cells to develop mechanisms for their inactivation. However, when a cell becomes tumoral, these inactive elements sometimes become active, leading to hundreds of mutations and showing specially high retrotransposition rates in determined cancer types. The resulted mutations can be really relevant for tumor evolution, causing important changes in the tumor genome that help some tumor clones to grow and expand. We have identified a small subset of L1 elements, 124 L1 loci, still active in the average human genome, acting as source elements. Of them, a small number are really active copies, termed hot-L1s, showing high rates specially in certain tumors as lung cancer, head and neck tumors, and esofagous adenocarcinoma. Here, using a new technology from Agilent, known as SureSelect, we have designed specific probes against these identified source elements with the aim of developing a new genetic test that will allow to detect tumors with high retrotransposition rates at diagnosis. This promising tool would allow oncologic patient to have a more personalized treatment according the results of the test and monitor the evolution of the retrotransposition rate along the therapy.

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POSTER COMMUNICATION

P31 - Generation and characterization of human bone marrow-mesenchymal stromal cell lines

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Abstract:

Between promising cell sources for Regenerative Medicine, human bone marrow-mesenchymal stromal cells (hBM-MSCs) stand out because of its ability to repair bone and cartilage. Nevertheless, a lot of research is still needed and limited by the fact that primary hBM-MSCs in vitro expansion eventually leads them to senescence. To overcome this problem, immortalized hBM-MSC lines may be developed.

The objective of this research was to generate and characterize two hBM-MSC lines, starting from primary hBM-MSCs derived from an osteoarthritis patient and a healthy donor. Primary hBM-MSCs were transduced with Simian Virus 40 large T antigen (SV40LT) and human telomerase reverse transcriptase (hTERT) employing retroviruses produced by Phoenix cells. Changes in proliferation ability of hBM-MSCs after immortalization were analysed. Maintenance of hBM-MSCs characteristics in immortalized hBM-MSCs was also tested, including mesenchymal superficial markers expression and multidifferentiation potential.

Immortalized hBM-MSCs (ihBM-MSCs) avoid senescence and maintain their proliferation rate over long-term in vitro culture, unlike primary hBM-MSCs. Expression of SV40LT and hTERT was detected in the nucleus of ihBM-MSCs. CD29, CD44, CD73 and CD90 expression and lack of CD34 and CD45 were conserved in ihBM-MSCs, while CD105 expression was reduced with subculturing. ihBM-MSCs keep their multipotency, although differentiation potential seems to be altered after transduction.

In conclusion, two hBM-MSC lines have been developed: one “osteoarthritic” and one “healthy”. Immortalized hBM-MSCs obtained unlimited proliferation capacity while maintaining most primary BM-MSCs features, although some alterations have been detected. hBM-MSC lines generated could be useful for bone and cartilage Medicine Regenerative research and may be employed as an in vitro osteoarthritis disease model.

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POSTER COMMUNICATION

P32 - Discovery and prevalidation of salivary miRNAs in patients with colorectal cancer

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Abstract:

Circulating microRNAs (miRNAs) have emerged as potential diagnostic and prognostic biomarkers for colorectal cancer (CRC), however, very few studies have investigated its deregulation in saliva until now. The present study was conducted to identify salivary miRNAs that could be used for CRC diagnosis in order to provide oncologists with new non-invasive strategies to detect the disease earlier.

The study consisted of two phases: a discovery phase and a validation phase. Patients included in both phases were recruited at Complexo Hospitalario Universitario de Santiago de Compostela. After total RNA isolation (miRNeasy extraction Micro Kit), 754 miRNAs were analyzed using TaqMan Array Low-Density Human MicroRNA Arrays (TLDA; Thermo Fisher Scientific) in 14 CRC patients and 10 healthy controls (HC). For the validation phase, miRNAs that were significantly upregulated in discovery phase were analyzed in the saliva of 30 CRC patients and 15 HC using qRT-PCR. A receiver operating characteristic (ROC) curve was drawn to evaluate the diagnostic accuracy of validated miRNAs.

After the screening phase, 22 miRNAs were found to be significantly dysregulated in CRC patients compared with HC. We selected a panel of 10 miRNAs out of 22 for a further validation using a larger cohort of patients and controls. A total of 7 miRNAs were significantly upregulated in CRC patients respect to HC, reaching areas under ROC curve (AUC) ranged from 0.68-0.72. In addition, the ROC curve that combines the 7 miRNAs showed a better discriminatory power with AUC-up to 0.83. We identified a panel of 7 salivary miRNAs that represents a promising non-invasive tool to diagnose CRC.

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POSTER COMMUNICATION

P33 - Closed-hollow Au SERRS-tags for bioimaging

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Abstract:

Noble metal nanoparticles (NPs) present unique optical properties that arise from localized surface plasmon resonances (LSPRs). The LSPRs are strongly dependent of NPs size, morphology and composition. Our group has developed strategy to fabricate Ag/Au nanorattles combining galvanic replacement coupled with seeded growth method [1]. It opens new avenues towards the shape control of multimetallic hollows nanostructures beyond the morphology of sacrificial templates.

Surface-enhanced Raman scattering (SERS) is an ultrasensitive technique which relies on the enhancement of the Raman scattering signals of a certain molecule when is close/attach to a plasmonic nanostructure. This technique also allows the indirect identification of target molecules through the use of SERS tags, Raman encoded NPs, which comprises a specific organic Raman reporter attached to plasmonic NPs which are often surrounded by a protected shell.

Herein we report the fabrication and characterization of closed-hollow encoded gold NPs for detection and imaging of cellular proteins. The plasmonic nanostructures were fabricated by a novel synthetic route involving the transformation of Ag nanoparticles into closed hollow Ag@Au nanospheres in the presence of the Raman-active dye. Remarkably, this approach allowed us to codify the nanoparticles with numerous Raman reporters independently of their affinity towards the metallic surface. The SERS encoded NPS have been also characterized by advanced microscopies revealing the formation of complete shell and that the structure of sacrificial templates remained during the reaction. Moreover SERS tags exhibited a good SERS activity.

Finally, we investigated the use of the SERS tags for bioimaging. For doing that, SERS tags were bioconjugated with antibodies specific of certain cell membranes. Final, their targeting and imaging capabilities were demonstrated in cultured cells by Raman microscopy.

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POSTER COMMUNICATION

P34 - Calretinin in the enteric nervous system: clinical and research applications

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Abstract:

The enteric nervous system is organized into two ganglion plexuses in the wall of the digestive tract and participates in the regulation of its motility, glandular secretion and blood flow. The neurochemical phenotype of the plexus components is diverse and similar to that found in other subdivisions of the nervous system.

Here, we have carried out immunohistochemical techniques to describe the distribution of calretinin in different segments of the digestive tract of mice and humans. The aims of the study were to assess the utility of calretinin as a marker for diagnostic evaluation and to explore differences and similarities in the expression of calretinin between mice and humans.

A strong calretinin immunoreactivity was seen in ganglia of both myenteric and submucosal plexus in the stomach, appendix and human colon. Labelling was noticeable in interganglionic strands of fibers among myenteric neurons as well as in isolated nerve fibers supplying the submucosa and the lamina propria of the appendix and human colon.

Anatomic organization of the ganglia in mice differs from that found in humans. Enteric neurons of the intestine were calretinin positive, but labelled fibers were far less numerous.

Our results support the efficacy of calretinin as marker of enteric neurons in mice and humans, and accordingly its application in the diagnosis of pathologies of the digestive tract associated with processes of agangliosis, including Hirschsprung's disease and total colon agangliosis. Moreover, these results validate the use of mice in experimental research dealing with enteric nervous system disorders.

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POSTER COMMUNICATION

P35 - Methylation of IGFBP-3 in liquid biopsy predicts chemotherapy response in non-small cell lung cancer

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*Presenting author.

Abstract:

Background: Methylation status of IGFBP-3 promoter in tumor tissues was associated with response to chemotherapy. Considering the limitations to obtain tumor tissue of patients, the possibility of analyzing the methylation of this gene in liquid biopsy is of great value.

Objectives: To assess the clinical value of analyzing IGFBP-3 methylation in liquid biopsy (plasma) to predict response to chemotherapy in advanced non-small cell lung cancer (NSCLC).

Methods: A total of 17 patients were recruited at Complejo Hospitalario Universitario de Santiago de Compostela. The methylation of IGFBP-3 was analyzed in plasma samples collected prior to chemotherapy treatment. The response to therapy was evaluated by computed tomography (CT). After plasma DNA conversion by bisulfite, methylation was analyzed by quantitative methylation-specific PCR (qMSP). This work was performed under the EPIGEN project, collaboration between IDIS, IDIPAZ and igen biotech for validation of the EPIGEN-kit.

Results: Plasma methylation levels of IGFBP-3 (% methylation) before starting chemotherapy were significantly higher (p=0.0111) in patients with disease progression after the treatment (N=8; mean±SD: 37.00%±23.81%) than those with disease stabilization (N=9; mean±SD: 13.83%±9.77%). Receiver operating characteristic (ROC) curve analysis showed that methylation of IGFBP-3 in plasma before chemotherapy has a high diagnostic accuracy to identify the patients whose disease will progress after treatment (AUC= 0.86; 95%CI: 0.68-1.00; p= 0.0124). With a methylation cut-off for IGFBP-3 of 21.89% the highest combination of sensitivity and specificity to identify the progression of patients was 87.5% and 77.8%, respectively. With this cut-off, we obtained a positive predictive value (PPV) of 77.8% and a negative predictive value (NPV) of 87.5% to predict the response to chemotherapy.

Conclusions: The methylation status of IGFBP-3 in liquid biopsy before treatment allows to predict the response to therapy in advanced NSCLC, indicating that IGFBP-3 methylation in liquid biopsy could be a biomarker for precision oncology in lung cancer.

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POSTER COMMUNICATION

P36 - Cell viability assay in corneal endothelium

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*Presenting author.

Abstract:

Introduction: Endothelium is the inner layer of the cornea, which must be viable for transplanting. The limited availability of corneas makes necessary the developing of preservation techniques that allow a long storage without losing endothelial viability.

Objectives: Optimization of a cell viability assay in preserved corneas.

Methods: One half of an endothelium from a cornea that was storage in hypothermic conditions and an endothelium of a cryopreserved cornea were stained with LIVE/DEAD imaging kit and Hoechst. The other half of endothelium was the negative control. Corneal endothelia were imaged using a fluorescence microscope.

Results: Four sort of cells were visualized on both endothelia: viable cells with high esterase activity, intermediate cells with low esterase activity, non-viable cells without esterase activity, and cells only stained by Hoechst.

Conclusions: Triple stain is effective to detect different sort of cells in endothelium of preserved corneas, included viable cells, depending on their esterase enzymatic activity and on cell and nuclear membrane damage.

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POSTER COMMUNICATION

P37 - Tissue microarrays: Use of metacrylate molds to enhance performance and decrease technique costs

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Abstract:

The tissue microarray (TMA) technology allows to cluster different organ samples into a single block of paraffin to obtain sections in which to apply the same histological treatment. The technique has special relevance in basic research and pathological diagnosis based on immunohistochemical evaluation. In these studies, the application of the same antibody to multiple samples entails a considerable saving of time and money. The manufacture of a TMA requires the production of “recipient” paraffin molds with holes in which tissue cylinders extracted from "donor" paraffin blocks are inserted.

The methodology to obtain TMA is diverse and ranges from the use of specialized, expensive TMA builder instruments to the development of cheaper homemade devices. Here, we show the design of a piece of methacrylate used as a cast for the production of silicone molds to obtain easily “recipient” paraffin blocks. A comparison with methods in which donor tissue cylinders were included in liquid paraffin was performed.

The piece of methacrylate includes two elements united in an indivisible set. The external element is configured as an open box with a rectangular base and without a lid. The inner one, centered on the bottom of the outer box, consists of a solid rectangular prism with 15 cylindrical perforations aligned in rows and columns equidistant from each other. The size of the external and internal elements are based respectively on the measurements of the histology cassettes and in the inner dimensions of the molds used in the production of paraffin blocks.

The pouring of a mix of silicone elastomer and a catalyst compound into the methacrylate cast polymerizes in a silicone mold which is easily separated from the methacrylate and which is flexible and tear resistant. Silicone molds are ready to be used to prepare paraffin recipient blocks with high efficiency and speed.

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POSTER COMMUNICATION

P38 - The role of Dock6 gene in non-canonical signaling pathways of the TGF-β family

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Abstract:

Dock 6 belongs to the Dock family of guanine-nucleotide-exchange factors (GEF), which are responsible for activating Rho GTPases through the exchange of guanosine diphosphates (GDP) by guanosine triphosphates (GTP). Particularly, Dock 6 protein activates Rac1 and Cdc42 which, just like all Rho GTPases, are involved in the appropriate organization of actin cytoskeleton and, thus, in the correct formation of the primary cilium. In turn, ciliary pocket plays a key role in the regulation of TGF-β signalling pathway, which is related to ciliopathies. Therefore, in this study, we knocked-down (KD) the Dock6 to check it in non-canonical signaling pathways of the TGF-β family. Firstly, a reverse transfection with siRNA was performed in order to obtain the knock down. After reaching an average reduction in the gene expression of 85,6%, we measured the expression levels of two proteins implicated in non-canonical pathways through immunoblot, the non-phosphorylated form of PI3K and the phosphorylated form of ERK 1/2 (pERK 1/2). Cells were stimulated with the specific ligand (TGF-β1) at different times (0, 10, 30 and 90 minutes). Finally, with respect to the level of pERK 1/2 at 10 and 30 minutes, there was a statically significant difference between mock cells and silenced cells, existing a reduction in the activation of the protein in the KD cells, which suggests the possible implication of the gene Dock6 in TGF-β signalling. On the contrary, the PI3K protein levels were not significantly different between mock and KD cells.

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POSTER COMMUNICATION

P39 - Gemini steroids

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Abstract:

Nuclear receptors (NRs) are ligand-regulated transcription factors that regulate metabolism, development and immunity. The NR superfamily is one of the major classes of drug targets for human diseases. Retinoic acid receptor-related orphan receptor (ROR) α, β and γ belong to the NR superfamily, and these receptors are still considered as 'orphan' receptors because the identification of their endogenous ligands has been controversial.

Recent studies have demonstrated that these receptors are regulated by synthetic ligands, thus emerge as important drug targets for the treatment of multiple sclerosis, rheumatoid arthritis, psoriasis, etc. One of the families of compounds that have been shown to act on RORα and RORγ are steroids, specifically the hydroxiderivatives of cholesterol.

Using the methodology developed in our research group to obtain Gemini analogs of vitamin D, we have prepared the synthesis of different cholesterol analogues with modifications in the side chain with potential activity on this type of receptors.

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POSTER COMMUNICATION

P40 - Supercritical CO_2 foaming: from the basics towards the processing of optimized scaffolds for bone regeneration

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Abstract:

Osteodegenerative diseases and accidental bone fractures represent a global healthcare concern due to their strong prevalence and growing incidence. Innovative synthetic bone grafts are being developed aiming at improving the recovery of the injury not only by providing mechanical support but also by promoting the tissue formation on the bone defect. Supercritical CO2 foaming is an emerging green technology able to process bone grafts under mild operating conditions and in the absence of solvents. Nevertheless, there is a paucity of information on this technology to establish the effect of the main processing variables on the scaffold end properties. In this work, processing temperature (37-41ºC) and soaking period time (1-5h) were evaluated regarding their effect on the porous structure and mechanical properties of the resulting scaffolds of poly(ε-caprolactone) (PCL). A new in situ method was developed to visually follow up the different steps of the process and to optimize the overall processing times. Mechanical properties of the PCL scaffolds were evaluated with a texturometer and the morphological characterization was performed by scanning electron microscopy, X-ray microtomography and mercury intrusion porosimetry. Results showed that the proposed analytical method for the in situ follow-up of the foaming process allowed a better understanding of the sequential physical phenomena taking place. Furthermore, temperature and soaking time had an outstanding influence in the porosity and the pore size distribution of the obtained scaffolds, whilst their mechanical properties were suitable for bone graft applications.

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POSTER COMMUNICATION

P41 - Increased therapeutic efficacy of dexamethasone palmitate in rheumatoid arthritis using polymeric nanoparticles

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Abstract:

Glucocorticoids (GC) are potent anti-inflammatory and immunosupresant drugs that are useful in the treatment of many inflammatory and autoimmune diseases. However, their unfavorable pharmacokinetics (PK), the high doses needed to reach a therapeutic effect, and the associated side effects have limited their prescription. Hence, the therapeutic use of GC could benefit from a targeted delivery into the inflamed tissues by using polymeric nanoparticles (NPs). This strategy could improve their PK by means of the enhanced permeation and retention effect (EPR), reducing at the same time the side effects.

In the present work, the prodrug dexamethasone palmitate (DXP), a suitable GC for the treatment of rheumatoid arthritis (RA), was encapsulated into PLGA-PEG nanoparticles (NPs). The size and Z potential of the NPs was characterized by DLS. The PK of this formulation was studied in vivo, in healthy mice, and compared with the commercial injectable form of dexamethasone sodium phosphate (DXM). The therapeutic efficacy of the formulation was tested in collagen-induced RA (CIA) mice. The clinical score, a measure of the severity of the disease, and the paw volume were measured before, along and after the treatment.

The PLGA-PEG NPs, unloaded and DXP-loaded, showed a diameter of about 150 nm and a negative Z potential. Both formulations were stable up to 30 days. The drug loading followed a linear behavior and the encapsulation efficiency was about 75%. The release of DXP and the DXM concentration in plasma were high for almost 18 hours, much longer than the commercial DXM, with low plasma levels after two hours. Moreover, the DXP-loaded NPs induced a significant decrease in the clinical score and paw volume of CIA mice compared with the same dose of commercial DXM or non-treated animals.

In summary, DXP was efficiently encapsulated into PLGA-PEG NPs. The PK of the DXP-PLGA-PEG formulation was much favorable than the commercial dexamethasone and this was correlated with an improved therapeutic efficacy in the treatment of RA. The results have demonstrated that encapsulation of GC is a good approach for the treatment of inflammatory diseases.

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POSTER COMMUNICATION

P42 - GLP-1 increases the availability of substrates and prioritizes the use of lipids in muscle metabolism.

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Abstract:

The skeletal muscle expresses the Glucagon-like Peptide 1 (GLP-1) receptor, although its effects in this tissue are not well known. Muscles are a major sink of energy substrates. The aim of our study was to examine the mid-term effect of Liraglutide (LIRA), a GLP-1 receptor agonist, in the expression of molecular indicators of the metabolic activity of the muscle, which includes enzymes, transporters, and intracellular signals.

Twenty young Spague-Dawley male rats (350-400 g) were treated for seven days with LIRA (100µg/Kg/12 hours / i.p) or vehicle. Body weight and food intake were monitored daily. After the sacrifice, samples of muscle and serum was stored at - 80 ° C. We studied the expression by rtPCR of mRNA for GLUT-4, CD-36, GAPT-1, GAPT-4, Fosfofructo-kinase-1 (FFK-1), CPT-1, UCP-2, PPAR-gamma and mTOR. In addition, we studied serum proteomics by the profile adipokine Array Kit (RD systems, bio-Techne) for rat.

Treatment with LIRA, reduces total food intake (kCal) and body weight gain just in the first 24 hr but not afterwards. LIRA treatment increases the mRNA expression of the translocase CD36 (+ 74%) that facilitates the entry to the cell of fatty acids, and the expression of the glucose transporter GLUT4 (+ 317%). LIRA also increases the expression of PPARγ (+800%) involved in the biogenesis of mitochondria and UCP2 (+ 298%) that promote the oxidation of fatty acids to the detriment of pyruvate from glycolysis. LIRA does not modify the phosphofructokinase 1 nor of CPT-1 expression. In addition, it reduces the expression of glycerol-3-phosphate acyltransferase-1 (GAPT 1, -80%), limiting the formation of mitochondria ketone bodies, and mTOR (- 70%), determinant in the synthesis of new fibres. The administration of LIRA also reduce total fat mass (g/100g bw) and the serum circulating levels of total triglycerides.

In conclusion, LIRA promotes the entry of fatty acids and glucose in muscle, facilitates the production of energy from fatty acids and the biogenesis of mitochondria, all together improving the efficiency of the muscular energy machinery.

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POSTER COMMUNICATION

P43 - The druggable immune system: drug repositioning in immune transcriptome.

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Abstract:

PURPOSE: Immune cells can control the fate of tumor, either promoting its growth or diminishing it (1). The goal of this work is finding drugs that can promote a better immune-environment to improve responses to antitumoral treatments. For instance, avoiding the effect of immunosuppressive T-helper, MDSC or T-reg cells by reverting its signature towards conventional T-reg, reverting the immunosuppressive M2 macrophages signature towards a more favorable macrophage state such M1.

METHOD: We have employed an in-house version of Connectivity Map (2) to predict single drug treatments and revert expression signatures integrating data from L1000, CCLE, GDSC2.0 and CTRP projects, and comprising more than 5,000 compounds and ~4 million drug-drug interactions. We have applied this approach to study 156 selected immunologic gene expression signatures associated to T-reg, T-helper, MDSC and macrophages obtained from MSigDB (3) and scientific literature. The analysis has been performed both for human and mouse signatures.

RESULTS: Using our methodology we have obtained at least one significant signature-drug prediction for 44% of the immune signatures. In total, we obtained 5,472 immune gene expression signature-drug interactions corresponding to 1,081 drugs (FDR < 0.05). To validate our approach, we have manually reviewed some of our predictions checking scientific literature. For instance as previously reported, we predict that PI3K inhibitors (i.e.wortmannin), suppress Treg activity.

CONCLUSIONS: We have built a catalogue of prioritized drug predictions for some highly relevant immune cells involved in tumor's fate that can either promote or rever a give immune signature. Our approach can be extended to predict drug treatments in other curated immunological studies. The final goal is the creation of a database containing predictions of immune signature-drugs interaction that potentially may revert immune cellular states.

1 10.1016/j.cell.2010.01.025
2 10.1126/science.1132939
3 10.1016/j.cels.2015.12.004

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POSTER COMMUNICATION

P44 - Use of IPPs for biological tissues imaging

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Abstract:

In the last decade, several works have shown the interest of using polarimetric images in the characterization and visualization of structures in biological tissues, for example, in the detection of several types of cancers. Several studies reveal that the most sensitive polarization channels to image biological tissues are related with retardance and depolarization properties. Retardance is completely defined by several parameters (global retardance, R, linear retardance, LR, neutral and extraordinary axes orientation, etc.). By contrast, in the depolarization case, the most used channels are the well-known degree of polarimetric purity, PΔ, and the depolarization power, Δ, which give an overall measure of the depolarization introduced by a sample (i.e., as far as it is from an ideal depolarizer). Other indicators of great interest are the so-called Indices of Polarimetric Purity (IPPs), proposed by J.J. Gil. et al., being three mathematical indicators that allow a greater synthetization of the polarimetric content associated to a depolarizing sample. The IPPs are 3 easy-to-calculate mathematical criteria that can be obtained from the Mueller matrix of the sample, this being the polarimetric transfer matrix that relates the polarizations at the entrance and at the exit of the sample. In this context, we used the IPPs for the first time to improve the image quality of different biological samples. The experimental results obtained when imaging several ex-vivo tissues demonstrate the potential of these indicators for their use in biomedical applications. Finally, we propose a pseudo-coloured combination of the parameters to synthetize the depolarizing information and enhance the contrast in one image.

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POSTER COMMUNICATION

P45 - Production of paper-based SERS substrates by Inkjet Printing Method

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Abstract:

Owing to its advantages such as rapidity, portable and high sensitivity, Surface Enhanced Raman Spectroscopy (SERS) is an analytical technique widely employed in studies of the detection of environmental pollutants, biological molecules, and food contaminants. Inkjet printing technique is a highlighted method in the production of SERS substrates and consists of the deposition of nanoparticle ink on a substrate by an inkjet printer. This deposition method presents the advantages of low-cost and simplicity by employing a common office printer to print a nanoparticle ink directly on paper. In addition, the method permits the production of SERS substrates with great homogeneity and reproducibility since the size of the drops generated by the printer is in the order of picoliters. The aim of the work is optimizing the gold nanoparticle ink and develop a hydrophobic paper that allows increasing the detection limit of the inkjet printed SERS substrate. Hydrophobic surface decreases the penetration of the colloidal suspension while preventing its spread on paper, promoting the concentration of nanoparticles on a small area of the surface. This effect increases the number of hot spots and leads to the increase of efficiency and, therefore, decreasing the detection limit. On a modified chromatography paper with a hydrophobic surface, inks with different composition and concentration have been tested, as well as different numbers of prints to achieve an optimum concentration of nanoparticles on the substrate. The described parameters were evaluated by the SERS signal of a probe molecule and the preliminary results indicate a high reproducibility and homogeneity SERS substrate that allows obtaining high detection limits.

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