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SILICON CHIPS FOR LOCAL AND SELECTIVE IMMOBILIZATION IN DIAGNOSIS

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The presence of many single-stranded antibodies that bind to DNA often result from autoimmune reactions or viral infections. Method for label-free diagnosis of inflammatory processes comprises incubating solid phase immobilized DNA-probes with single stranded nucleic acid analytes for forming a hybridizing complex. Chemical treatment of glass slides by GOPS/poly-L-lysine is typically used to immobilize DNA-probes. Nevertheless, it has been estimated that nearly half of all cases of autoimmune diseases remain undiagnosed because of the challenges posed by diagnosis including immobilization of DNA-probes. Therefore, there is still a strong demand for the development of smart chips with high accuracy, selectivity, lower detection limits and robustness during autoclaving for sterilization, incubation, and cryogenic applications for shock freezing. We have fabricated a silicon chip with a charge pattern in order to realize defined microscopic to nanoscopic patterns of surface-near electrostatic forces (SNEF). Finally, these charge patterned silicon wafers are protected by a thin 2-3 nm thick insulting oxide layer. Using combined atomic and Kelvin probe force microscopy measurements (KPFM) we could prove that positively and negatively charged species are preferentially adsorbed at n-type and p-type conducting regions of the of locally implanted silicon chips with different SNEF patterns. The selective attachment of biological species on flat silicon chips will also play a critical role towards advancements in the field of diagnosis of inflammatory process. Herein we present a promising concept for selective biomolecule assembly onto the bulk-functionalized PolCarr® chip. The binding of the electrically polarizable biological species is onto PolCarr® is purely driven by SNEF. The design of PolCarr® can be adjusted to the individual target application, e.g. local immobilization of DNA probes. We believe the unique features of the PolCarr® chips make it a promising solution to meet increasing health standards and awareness of autoimmune diseases.

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FCγRIIIA IS A DISTINCT ACTIVATING COSIGNAL IN CD4+ T CELLS THAT SYNERGIZE WITH TLR9

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We have been exploring the mechanistic insight of the stimulatory effects of FcγRIIIa cosignaling in human $CD4^+$ T-cells. $CD4^+$ T cells also express FcγRIIa and these cells accumulate HIV provirus. We have previously shown that FcγRIIIa cosignal participate in relocating endosomal NA-TLRs to the cell surface, where they can recognize modified self-nucleic acid. Joint signaling from FcγRIIIa and TLR9 (CpG ODN 2006) enhances IL-17A, IL-21 production. Now, we show that FcγRIIIa cosignaling generate a new subset that show Syk phosphorylation and express TFH markers i.e. Bcl6, CXCR5, ICOS and PD1. In HIV infection, blood TFH cells do not express Bcl6+, contrary to this finding we observed Bcl6 in blood pSyk+ T cells *in vivo* in systemic lupus erythematosus (SLE) and in *in vitro*. Bcl6+ cells in blood produce IFN-γ, IL-17A and IL-21. The Syk inhibitor block IL-21 production. pSyk+ cells show moderate PD1 expression compared to a second population that express high PD1. Our RNA-seq data show differential expression of lincRNA and microRNA from FcγRIIIa cosignaling that contribute to T cell differentiation. A key finding was upregulation of *mir*1307, a recognized risk allele for SLE in GWAS studies. We propose that FcγRIIIa drives epigenetic changes in CD4+ T cells. Transcription factors c-Maf, FOXO were upregulated. FcγRIIIa cosignal modulated ubiquitination, HSPs, proteasome assembly, and GPCR signaling. Our data provide new insight into the FcR biology in adaptive responses and raises several interesting questions. Does FcRs bearing effector CD4+ T cells superior helper, for the development of autoreactive B cells?

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REGENERAGE SYSTEM: THERAPEUTIC EFFECTS OF COMBINATORIAL BIOLOGICS (MRNA AND ALLOGENIC MSCS) WITH A SPINAL CORD STIMULATION SYSTEM ON A PATIENT WITH SPINAL CORD SECTION

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Westhill University School of Medicine, Mexico

As it has been previously demonstrated that co-electroporation of Xenopus laevis frog oocytes with normal cells and cancerous cell lines in-duces the expression of pluripotency markers, and in experimental murine model studies that mRNA extract (Bioquantine® purified from in-tra- and extra-oocyte liquid phases of electroporated oocytes) showed potential as a treatment for a wide range of conditions as Squint, Spinal Cord Injury (SCI) and Cerebral Palsy among others. The current study observed beneficial changes with Bioquantine® administration in a patient with a severe SCI. Pluripotent stem cells have therapeutic and regenerative potential in clinical situations CNS disorders even cancer. One method of reprogramming somatic cells into pluripotent stem cells is to expose them to extracts prepared from Xenopus laevis oocytes. We showed previously that coelectroporation of Xenopus laevis frog oocytes; with normal cells and cancerous cells lines, induces expression of markers of pluripotency. We also observed ther-apeutic effects of treatment with a purified extract (Bioquantine) of intra- and extra-oocyte liquid phases derived from electroporated X laevis oocytes, on experimentally induced pathologies including murine models of melanoma, traumatic brain injury, and experimental skin wrinkling induced by squalene-monohydroperoxide. The positive human findings for spinal cord injury, and cerebral palsy with the results from previous animal studies with experimental models of traumatic brain injury, respectively. Because of ethical reasons, legal restrictions, and a limited number of patients, we were able to treat only a very small number of patients. These results indicate that Bioquantine® may be safe and well tolerated for use in humans and deserves further study in a range of degenerative disorders. We propose that the mechanism of action of Bioquantine® in these various diseases derives from its unique pharmacology and combinatorial reprogramming properties. In conclusion, these preliminary findings suggest that Bioquantine is safe and well tolerated on patients with Cerebral Palsy and-Spinal Cord Injury, among others. In addition to the regenerative therapy and due to the patient condition, we decided to include the Restore-Sensor SureScan. Based on the of electrical stimulation for rehabilitation and regeneration after spinal cord injury published by Hamid and MacEwan 8-9 , we designed an improved delivery method for the *in-situ* application of MSCs and Bioquantine® in combination with the RestoreSensor® SureScan®. To the present day the patient who suffered a total section of spinal cord at T12-L1 shows an improvement in sensitivity, strength in striated muscle and smooth muscle connection, 11 months after the first therapy of cell regeneration and three month after the placement of RestoreSensor® at the level of the lesion, the patient with a complete medullary section shows an evident improvement on his therapy of physical rehabilitation on crawling from front to back by himself and standing on his feet for the first time and showing a progressively important functionality on the gluteal and legs sensitivity.

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OVERCOMING ADENO-ASSOCIATED VIRUS GENE THERAPY LIMITATIONS IN GENETIC NEUROMUSCULAR DISEASES

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Université Paris-Saclay, France

Neuromuscular diseases represents a major hurdle for patients, families and the society in its entirety. Rare, genetic neuromuscular diseases constitute a bigger challenge given the absence of knowledge on the physiopatological mechanisms and of therapeutic options. In the last years, adeno associated virus (AAV) vector-based gene therapy became a principal actor in the development of therapies for monogenic diseases. Successful human trials of gene transfer in the liver for hemophilia A and B, in the eye for congenital blindness and in the nervous system for spinal muscular atrophy have unveiled the therapeutic potential of this viral vector platform. However, one of the main limitation of AAV gene therapy is the high dose of vector needed to rescue neuromuscular diseases. Doses used in the clinic for these disorders are hardly produced and are likely to induce unwanted secondary effects. Another constraint in the use of AAV vector is their limited size of transgene encapsidation. This is of particular relevance in genetic neuromuscular diseases that frequently involve large transgenes. Here, using glycogen storage disorders as model diseases, we developed some technological tools to overcome the current limitations of AAV gene therapy applied to neuromuscular diseases.

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DRUG TARGET VALIDATION USING RNA INTERFERENCE APPROACH IN *SCHISTOSOMA MANSONI*

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Fundção Oswaldo Cruz, Brazil

The *Schistosoma mansoni* genome project identified 10,852 protein-coding genes of which almost half are annotated with unknown function. Those genes could be parasite-specific and represent genes whose biological functions are of interest for basic and applied science. Despite of great advances in the genomic field, application of technologies for schistosomiasis control have not kept pace; treatment of this disease still relies on a single drug and no vaccines are yet available. Therefore, extracting meaningful functional information from the accumulated genomic data is critical to discovering new chemotherapeutics and other novel approaches to disrupting development within the snail and human hosts. Currently, RNA interference (RNAi) is the most effective reverse genetic tools for manipulating gene expression and determining gene function in schistosome parasites, both *in vitro* and *in vivo* in the association with their hosts. Our group has dedicated efforts to understand the role of schistosome genes and their encoded protein products in the host-parasite interaction, with the goal of identifying and validating promising druggable targets. This talk aims at presenting our work applying the RNAi approach in the different parasite life cycle stages to assess the function of diverse genes such as kinases and histone modifying enzymes, to rationally identify efficient therapeutic targets for schistosomiasis control, as well as understanding the mechanisms by which *S mansoni* survives within its hosts.

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NEW EFFECTIVE THERAPEUTIC APPROACHES TO CONTROL NEUROINFLAMMATION IMPROVE SEVERAL NEUROPATHOLOGIES

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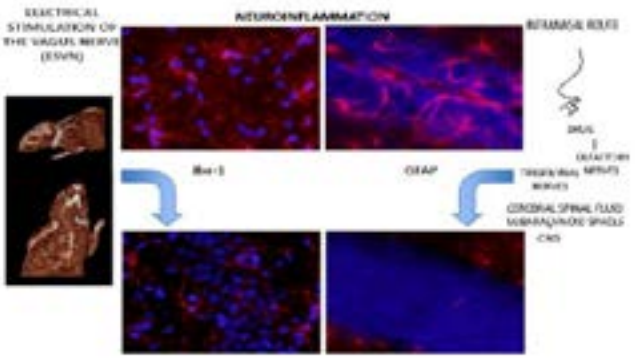
Statement of the Problem: Even though acute, transient neuroinflammation (NI) is a beneficial defensive response to harmful stimuli, sustained NI can lead to pathological conditions. NI is a common trait in many infectious and non-infectious neurological diseases and may promote their onset and progression. Its role in sepsis, Parkinson disease, stroke, and multiple sclerosis places NI as a new common therapeutic target. Controlling subacute and chronic NI may help to restore CNS physiology and homeostasis; however, NI is currently treated only during multiple sclerosis crises, being unattended in other diseases. The absence of an adequate anti-inflammatory response may explain the scarce research on this approach.

Methodology & Theoretical Orientation: The potential of electric stimulation of the vagus nerve (ESVN) and intranasal administration of glucocorticoids were studied in models of sepsis (LPS-treated mice), Parkinson disease (induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, MPTP), ischemic stroke (induced by middle cerebral artery occlusion, MCAO), and multiple sclerosis (autoimmune encephalomyelitis elicited by the myelin oligodendrocyte glycoprotein peptide 35-55).

Findings: Both ESVN and intranasal steroid administration effectively reduced central levels of TNFα, IL-1β, and IL6 (measured by ELISA) and the percentage of CD11b+/CD45 macrophages/microglial cells (measured by FACS). ESVN also reduced the expression of Iba-1 in the cortex and hippocampus. ESVN reduced astrocyte activation (GFAP) and restored the expression of tyrosine-hydroxylase (TH)-positive neurons in the substantia nigra pars compacta (SNc). Intranasal administration of dexamethasone significantly reduced mortality in the stroke model. Moreover, intranasally-treated mice exhibited lower morbidity and central inflammation, and a reduced size of the ischemic lesions. In multiple sclerosis, the intranasal route was more effective than intravenous in improving EAE-associated morbidity.

Conclusion & Significance: Our results highlight the possibility of reducing NI in several neuropathologies, restoring homeostasis more efficiently than current treatments.



Recent Publications

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TARGETING BACTERIAL VIRULENCE TO DEVELOP EVOLUTION PROOF ANTIBIOTICS

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Keeping the antibiotic resistance in mind, it is of greatest need to develop new ways to treat bacterial infections. Evolution-proof antibiotics that disarm the bacterial pathogens without impacting their survival would be an important strategy towards sidestepping the evolution of resistance. Drugs that disarm the pathogen will generate much weaker selection for resistance than traditional antibiotics. Disarming the pathogens is possible by targeting a family of bacterial proteins called AraC family proteins that regulate the bacteria's ability to infect or damage a host, rather than its ability to survive. We tested this exciting hypothesis against Shigella flexneri, a diarrhea causing bacterial pathogen responsible for causing 165 million cases of illness and more than 1.1 million deaths worldwide. We successfully identified several molecules that selectively inhibited an important Shigella protein VirF that is crucial for causing infection. The highly potent molecule SE-1 is found to not impact the growth of the bacteria but prevent bacteria's ability to invade and infect cultured human intestinal cells. SE-1 also inhibits infection pathways in other pathogenic bacteria that cause infections such as diarrhea, pneumonia, and cholera and thus can be developed as a novel agent to treat multiple infections. Targeting such infection pathways may yield non-traditional antibiotics that are more powerful and versatile than our current antimicrobials and would solve the antibiotic resistance issue that has grown to alarming levels.

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TARGETING CD38 ON TUMOR CELLS TO REVERSE THE RESISTANCE TO ANTI-PD-1/PD-L1 IMMUNOTHERAPY OF CANCER

Limo Chen, Lixia Diao, B Leticia Rodriguez, Ignacio I Wistuba, Jing Wang, John V Heymach, F Xiao-Feng Qin and **Don L Gibbons**
The University of Texas MD Anderson Cancer Center, USA

Although strategies incorporating immune checkpoint inhibition are achieving unprecedented successes and rapidly being incorporated into standard of care regimens for lung cancer patients, high rates of therapeutic resistance limit their potential efficacy. Thus, successful immunotherapy of lung cancer requires a thorough understanding of the biological process of resistance. In immunocompetent syngeneic and K-ras$^{LA1/+}$p53$^{R172H\Delta g/+}$ spontaneous animal models of lung cancer, we have explored the resistance mechanisms using pharmacological and genetic approaches (PD-1/PD-L1 monoclonal antibody treatment and CRISPR/Cas9-mediated editing). The molecular and immune profiles of the tumor microenvironment were evaluated. More importantly, to determine the applicability to patients, 793 lung cancer specimens were immunohistochemically stained for CD38, and multiple large independent patient datasets (TCGA, PROSPECT, BATTLE-2) of non-small cell lung cancer (~1430 tumors) were analyzed by using integrated bioinformatics. We identified the up-regulation of CD38 on tumor cells as the marker of resistance to anti-PD-1/PD-L1 treatment. The same resistance mechanism caused by CD38 was also observed in PD-L1 KO mice bearing PD-L1 KO Lewis lung tumors edited with the CRISPR/Cas9 system. *In vitro* and *in vivo* studies revealed that CD38 inhibited CD8 T cell function via adenosine receptor signaling, and that CD38 blockade served as an effective strategy to overcome the treatment resistance to PD-1/PD-L1 axis blockade. In lung cancer patients, 15-23% of cases exhibited positive staining for CD38 on tumor cells, showing a great potential benefit for treatment. Multiple large datasets of lung cancer patients suggested a strong correlation between CD38 and an intratumoral immune signature.

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COMBINED THERAPEUTIC MEDICAL DEVICE AND STEM CELLS FOR REGENERATIVE NANOMEDICINE

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In our group we explore a new generation of smart living implants combining not only active therapeutics but also stem cells, as a novel strategy to regenerate stabilized cartilage and avoid prosthesis, by achieving regeneration of its subchondral bone foundation, requirement which is failing today in the clinic. In our group, a unique nanotechnology strategy is used to entrap, protect, and stabilize therapeutic agents into polymer coatings: nanoreservoirs, covering nanofibres of implantable nanofibrous membranes for bone and cartilage regeneration. Upon contact with cells, therapeutic agents become available through enzymatic degradation of the nano reservoirs. As cells grow, divide, and infiltrate deeper into the porous membrane, they trigger slow and progressive release of therapeutic agents that, in turn, stimulate further cell proliferation. The nano-reservoirs technology enables to reduce the quantities of required therapeutic agent (compared to soaked membranes for instance) thereby reducing costs. Clinical trial: phase 1, (FR, UK, SP, SW) will be submitted. Feasibility and safety assessment of a therapeutic implant based on an active polymeric wound dressing and autologous mesenchymal stem cells derived from bone marrow for the treatment of femoral cartilage isolated lesions.

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ADVANCED APPROACHES FOR CELL THERAPY PRODUCT CHARACTERIZATION

Damian Marshall
Cell and Gene Therapy Catapult, UK

Cell and gene therapy manufacturing process can be complex and have high level of raw material variability. This makes the development of reliable, consistent and cost-effective manufacturing processes a significant challenge. For autologous products, this challenge can be even greater due to the added variability of the patient specific cellular starting material and the lack of real-time process data. These challenges could be addressed through the application of Process Analytical Technologies (PAT) that permit in-line or at-line analysis throughout the manufacturing process. These technologies could allow key variables to be tracked for tighter process control as well as the provision of process information in a time frame enough to allow proactive decision making and the early detection of poor process performance. In this presentation we will show how in-line optical biosensors can be applied for advanced multiparametric monitoring of cell and gene therapy bioprocesses. We will show how real-time process data can be used to support manufacturing decisions and the role these technologies have in supporting a move towards feedback control and adaptive manufacturing.

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EFFECT OF HUMAN UMBILICAL CORD BLOOD-DERIVED MONONUCLEAR CELLS ON DIABETIC NEPHROPATHY IN RATS

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Hoda A El-bahrawy and **Shimaa A El-berashy**
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Diabetic nephropathy (dn) is damage to the kidney which can lead to chronic renal failure, eventually requiring dialysis. Diabetes mellitus is the most common cause of adult kidney failure worldwide in the developed world. The current work was designed to elucidate the effect of mononuclear cells (mncs) injection on reverse dn in rats exposed to streptozotocin (stz) injection compared to metformin as a known hypoglycemic drug, 40 male rats were divided equally into four groups; normal control group, diabetic control group, mncs group were diabetic rats treated with mncs (30×106 mncs/rat once iv dose) in the tail vein of the rat, and metformin group were diabetic rats treated with metformin (100 mg/kg orally daily dose) for four weeks. The results indicated an improvement effect of mncs and metformin on stz-induced dn in rats, which was evidenced by significant decrease in urinary albumin/creatinine ratio, n-acetyl-β-d-glucosaminidase (nag), urinary kidney injury molecule- 1 (kim-1), serum urea, serum creatinine and fasting blood glucose and significant increase in c- peptide level, compared to diabetic control group. Additionally, mncs treated group exhibited pronounced effects in all previous parameters compared to metformin treated group. It is proved that mncs treatment was superior to metformin in controlling hyperglycemia and improving renal function in diabetic rats.

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VIRUSES OF EPIDEMIC

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Foundation de Beaumont Bonelli for Cancer Research, Italy

For the emergency created by the epidemic of influence of the pigs in Mexico it was correct not to create alarmism's being victims of a bad information. The possibility that the virus arrives in other parts of the world is real as for all the types of influence virus. In order that a strain has a wide distribution, its antigenic characteristics must ensure that it escapes the neutralization of antibodies of the host and of the surrounding population. So, the outbreaks will happen with those strains that have dominant antigens that fit the deficiency, or better, the absences of antibody in the population. It seems, in conclusion that the flu virus shows an ability and an aptitude for survival built on the possibility of emergence of new models that allow the virus being confused easily through populations still partly immune to previous antigenic forms. According to this view, the changes in the influenza A can be designed in single meaning, in the context of a principle and of an evolutionary progress, from Burnet said immunological drift or steering immunology. The antiviral drugs (inhibitors of the neuraminidases, receptor of the virus surface) should be assumed within 48 hours by the appearance of the influence symptoms and for the subjects that have had a close contact with people infected by the flu virus. The vaccination against the influence is the most effective method to prevent the illness. From the moment that we find the isolation of a new flu virus, we must wait for the preparation of a new specific vaccine that will be ready for the next Influence season in autumn.