School of Nanomedicine 2022

Wednesday 08 June 2022 - Friday 10 June 2022

CNR, sede centrale

Scientific Programme

Scientific programm

Session 1: Nanomaterials for nanonemedicine, June 8th

14:15 – 15:00 From Tissue Engineering to Regenerative Medicine, Ranieri Cancedda, University of Genova, Italy

15:00 – 15:45 Nanomaterials for the Repair of Spinal Cord Injury, Maurizio Prato, Department of Chemical and Pharmaceutical Sciences, Trieste University, Italy

15:45 - 16:15 Break

16:15 - 16:30 Industrial Clips:Quantum Design Italia,Nanoparticles characterization techniques: dimensions, physical and morphological properties

16:30 – 17:15 The chemistry-biology interplay emerging form molecule-coated nanoparticles, Fabrizio Mancin – University of Padova, Italy

17:15 – 18:00 Nanoparticles meet Organized soft assemblies : Challenges and opportunities for the biomedical field, Debora Berti – University of Firenze, Italy

Session 2: Tissue engineering, June 9th

9:00 – 09:45 3D Bioprinted tissue models by click chemistry approaches
Laura Russo, Università di Milano Bicocca, Italy

09:45 - 10.00 Industrial Clip T.E.E.S. srl, design and manufacture custom mechanical equipment for Scientific Research Laboratories

10:00 - 10:30 Break

10:30 – 11:15 Hybrid nanoparticles for biomedical applications, Luisa de Cola, University of Milano, Department DISFARM and Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milano, Italy

11:15 - 12:00 Functional materials from living organisms, Gianluca Maria Farinola, Chemistry Department – University of Bari, Italy

12:00 – 12:45 Physics, spectroscopy and imaging applied to biology and medicine
Enzo di Fabrizio, DISAT Department, Turin Politech, Italy

Session 3: From bench to bed, June 10th

13:45 - 14:30 From Piazzale Tecchio to Wall Street: the short story of a long polymer hydrogel, Alessandro Sannino – Salento University, Italy

14:30 – 15:15 Supramolecular Approaches to Design Novel Antivirals, Francesco Stellacci – Institute of Materials, Ecole Polytechnique Fédérale de Lausanne (EPFL), Switzerland

Special session, June 9th, h. 16.00 - 18.00

The human-machine relation and AI challenges for nanomedicine in the digital age
Maria Chiara Carrozza – President of CNR & Massimo Durante – University of Torino
moderated by Giacomo Pisani – Euricse Researcher – Trento

Nanomedicine plays an increasingly central role in relevant processes that mainly involve the relation between humans and new technologies. Notably, the use of advanced software, capable of learning and acting in an ever more autonomous way, raises a series of issues that are matter of concern for both science and philosophy. Artificial intelligence has ignited a fruitful dialogue among scholars from different fields. The recognition and implementation of the right to “explanation” based on the GDPR is one of the issues of most concern, along with the limits of the traditional concept of “responsibility” when applied to machine learning algorithms, or the opacity of the so-called “algorithmic governmentality”. Equally troublesome is for individuals to have access, manage and protect their personal data, on the basis of which human autonomy and identity are today mostly build. These are highly topical issues, which also affect relevant aspect of nanomedicine. Think, for instance, of how these issues are deeply entrenched with the human-machine relation, the deployment of enabling technologies, and the progress of science. On the top of that, the construction and protection of our own identity are challenged by current technological surge. Against this backdrop, the seminar intends to encourage dialogue between science and philosophy, discussing some of the main challenges that nanomedicine faces in the new digital era.

https://www.ba.ic.cnr.it/nanomedicine2022/index.php/special-session/

Session 4: Therapeutics nanotechnological approaches, June 10th

9:00 – 09:45 Magnetic nanoparticles and clusters to combine magnetic hyperthermia with different therapeutic approaches, Teresa Pellegrino – Fondazione Istituto Italiano di Tecnologia, Genoa, Italy

09:45 – 10:30 Glycosylated Carbon Nanostructures for Emergent Viruses, Nazario Martin, Departamento de Química Orgánica, Facultad de Química, Universidad Complutense, Madrid, Spain

10:30 - 11:00 Break

11:00 – 11:45 Engineering 3D human tissues equivalent as reliable and predictive tools for clinical implementation of personalized and precision medicine, Paolo A. Netti – Center for Advanced Biomaterials for HealthCare@CRIB Istituto Italiano di Tecnologia, and CRIB, University of Naples Federico II, Napoli Italy

11:45 - 12:30 Current challenges in the understanding and treatment of Alzheimer’s disease: limitation and perspective of nanomedical approaches, Maria Laura Giuffrida, CNR – Istituto di Cristallografia Catania, Italy

12:30 – 13:15 Nanoparticles in BNCT, Simonetta Geninatti, Crich PhD, Dipartimento di Biotecnologie Molecolari e Scienze per la Salute, Centro Imaging Molecolare, Università di Torino

13:15 - 13:30 Concluding remarks

FROM TISSUE ENGINEERING TO REGENERATIVE MEDICINE

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Cell therapy approaches, i.e. transplantation of "ex vivo" expanded autologous stem/progenitor cells, alone or associated to carrier biomaterials can be life/organ saving and allow treatments of very critical patients. However, due to difficult logistics, regulatory issues requiring the adoption of highly sophisticated cell culture facilities, and the high cost of the procedures, these approaches cannot be applied for largely diffuse, difficult to heal tissue deficits such as chronic skin ulcers or osteoarthritis.
To enable a large number of patients to benefit from a Regenerative Medicine approach, new strategies and new products should be considered. The use of media conditioned by progenitor / stem cells or of extracellular vesicles and exosomes released by the same cells is being presently investigated. Alternatively, the treatment of the tissue deficits with platelet derived components has been proposed.

FUNCTIONAL MATERIALS FROM LIVING ORGANISMS

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From the perspective of a synthetic chemist, several living organisms can be envisioned as a plentiful source of micro/nano structures, polymers and molecules useful to access smart functional nanomaterials for photonics, electronics and biomedicine.
Differently from the industrial production, biosynthesis of materials occurs in mild conditions and in the absence of toxic reagents. This approach may open the way to biotechnological sustainable large scale production of functional nanomaterials for biomedicine.
Biosilica, cellulose, lignin, polydopamine, silk are some examples which will be considered in the lecture.
The opportunities and the limits of this approach will be discussed, pointing out possible future directions.

THE CHEMISTRY-BIOLOGY INTERPLAY EMERGING FORM MOLECULE-COATED NANOPARTICLES

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Most of the nanoparticles studied for biomedical applications feature a complex structure, where different topological portions are designed to perform specific functions, as providing stability against aggregation, stealth properties, targeting, accumulate the payload or even perform direct theranostic activity. The realization of systems of such complexity is greatly eased by the use of self-organization based synthetic protocols. The mechanism of most of these protocols can be considered as the controlled formation of surfactant stabilized aggregates, possibly completed by a core polymerization (Figure 1). In this lecture, we will examine in particular the cases of polymer-coated silica and poly(lipoic acid) nanoparticles.1

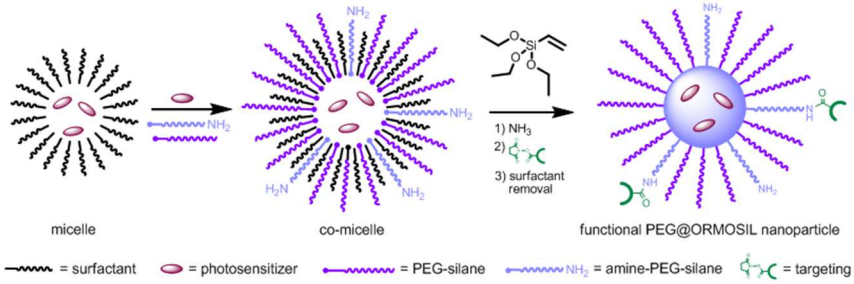

Figure 1. *Synthetic protocol for the preparation of PEGylated ORMOSIL nanoparticles*

The main advantage of these synthetic protocols is that, by taking advantage of the different solvophobic and solvophilc properties, the different nanoparticle precursor can be precisely placed in the site they are desired to be. As an example, water insoluble molecules (dyes, photosensitizers or drugs) locate themselves in the emulsion oil core, amphiphilic species locate at the interface forming a surface functionalization layer, hydrophilic reactive groups, as amines, take position in the outer part of the coating shell, resulting available for further conjugations.2 Such a precise structural organization is not only useful to control and program the functions of the nanoparticles, but it also allow to easily dissect their biological properties in comparative studies. Indeed, taking full advantage of such approach, we prepared nanoparticles densely coated with different hydrophilic polymers (PEG, PMOXA, PEtOXA). Functional studies in serum revealed that the different coatings elicit different, specific and somewhat unexpected interactions with the immune system, activating the complement systems and the innate recognition mechanisms. Molecular recognition processes occurring at the surface of the nanoparticles are hence fundamental in determining the biological role of nanoparticles.

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ENGINEERING 3D HUMAN TISSUES EQUIVALENT AS RELIABLE AND PREDICTIVE TOOLS FOR CLINICAL IMPLEMENTATION OF PERSONALIZED AND PRECISION MEDICINE

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Personalized medicine and precision medicine are the current paradigms steering the changes in medicine practice and healthcare industries. Following these two paradigms, it is expected soon to radically transform medical interventions by providing effective, precise and tailored therapeutic and diagnostic strategies based on molecular (omics) profile adapted to current individual state of a given patience. To operate this revolution, better and personalized therapeutical trial assay must be developed.
Tissue and organ on chip (TOC) devices are microfluidic systems with controlled, dynamic microenvironments in which cultured human in vitro engineered tissues or organs exhibit functions that emulate organ-level physiology. They have been developed to permit the study of human physiology in a tissue-specific context, to enable development of novel in vitro disease models, and to potentially serve as replacements of animals in drug development and toxics testing. ToC device can be 'personalised' to recapitulate individual physiology, for instance by using primary cells harvested from the specific patient or derived from induced pluripotent stem cell (iPSC) patient specific to engineering in vitro autologous pieces of highly competent and patient specific tissue or organ, introducing these engineered tissues in microphysiological systems able to tune key physico-chemical culture microenvironment features based on personal health data. The individual nature of such systems, combined with appropriate molecular and cellular read-outs, provides a powerful tool for person-specific clinical trial by assessing drug efficacy and safety, as well as personalised strategies for treatment, prediction and prevention of disease. All together these devices might contribute significantly towards the practical implementation of precision and personalized medicine.
As today there are several examples of personalized ToC models, with examples including lung-on-a-chip, gut-on-chip, liver-on-chip, skin-on-chip obtained by using primary patient harvested cells, along with multi-organ on chip systems to allow the assessment of the dynamics occurring among organs through their molecular crosstalk. However, for OoC technology to meet the expectation to faithful recapitulate the complex native in vivo behaviour of human tissue and organs, it is mandatory to proceed towards the use of tissue and organs that correctly reproduce in composition and organization the extracellular space. Indeed, while sophisticated microdevices have been designed, the engineered tissues still remain surrogates of the native counterparts. The major challenges for the effective implementation of personalized organs-on-chips in precision medicine are related to obtaining in vitro engineered tissue and organ functionally and structurally competent, as well as to obtaining data on patient outcomes that can confirm the predictive value of personalized organs-on-chips.
In this lecture ToC or OoC devices and their potential utility in personalized medicine will be presented along with their potential to push the clinical implementation of precision medicine. Current and projected use of OoC in different disease and treatment scenarios will be discussed including examples on tumor, rare disease, pulmonary disorder, skin disease where these devices could be integrated into the decision-making process for physicians and healthcare providers. Use of ToC devices in nutraceutical and cosmeceutical field will also be commented.

NANOPARTICLES MEET ORGANIZED SOFT ASSEMBLIES: CHALLENGES AND OPPORTUNITIES FOR THE BIOMEDICAL FIELD

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The combination of inorganic nanoparticles (NPs) with organized natural or synthetic lipid assemblies has the potential to expand both our understanding and the applicative spectrum of these materials in the biomedical field.
This contribution will deal with hybrid systems composed of NPs and extracellular vesicles, (EVs). EVs are a major player in intercellular communication and mediate physiological and pathological processes. I will show how some central colloidal properties of EVs' dispersions can be monitored leveraging the properties of NPs, by introducing a nanoplasmonic assay for fast purity checking and a plasmon-based nanoruler for collectively fingerprinting EVs based on their stiffness.

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3D BIOPRINTED TISSUE MODELS BY CLICK CHEMISTRY APPROACHES

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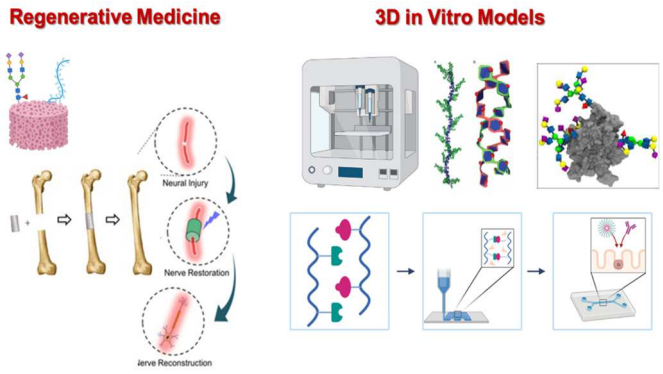
The last advances in 3D printing and bioprinting technologies allows the development of 3D tissue models suitable for tissue engineering and animal free personalized drug screening [1]. To this purpose hydrogels mimicking the Extracellular matrix (ECM) in terms of morphology and biochemical components must be generated. ECM has a key role in the induction of different cell fate modulation and is mediated by specific interactions with cell receptors. These interactions include post translational modification of proteins that are involved in the modulation of cell processes indispensable for the correct functional and structural organs development [2]. The opportunity to mimic in 3D both the physical and the biomolecular features of tissues and organs is leading to the development of 3D tissue mimetics for cell biology studies and drug screening applications. However, the generation of multifunctional polymers employable in the design of functional organ-like constructs still represents an open challenge in the field. Here in this talk, the generation of smart multifunctional biomaterials and their application in tissue engineering applications will be presented.



Acknowledgments: The authors acknowledge funding from the EC, H2020-NMBP-15-2017-GA- 760986, Integration of Nano- and Biotechnology for beta-cell and islet Transplantation (iNanoBIT). They also acknowledge funding from the Italian Ministry of Health (Grant No. RF-2016- 02362946), POR-FESR 2014-2020 Innovazione e Competitività, and Progetti Strategici di Ricerca, Sviluppo e Innovazione, Azione I.1.b.1.3-IMMUN-HUB—Sviluppo di nuove molecole di seconda generazione per immunoterapia oncologica.

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HYBRID NANOPARTICLES FOR BIOMEDICAL APPLICATIONS

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Advancements in the use of nanoparticles for biomedical applications have clearly shown their potential for the preparation of improved imaging and drug-delivery systems. However, only a few successfully translate into clinical practice, because, a common "barrier" preventing nanoparticles from delivering efficiently their payload to the target site after administration, is related to the nanoparticle uptake by macrophages. In my contribution the rationale to design and synthesize nanoparticles will be discussed as well as the problems to reach humans in the clinical trials. Some examples illustrating the difficulties to control the degradation rates, the efficient loading and the lack of targeting ability will be discussed. The size and morphology of the nanoparticles determine not only their biodistribution but also their capacity to escape macrophages. Finally some novel applications of nanomaterials in order to the capture and not release of specific biomarkers will be discussed. In particular combining dyes and the porosity of zeolites a novel class of fluorescent artificial receptors (FARs) has been reported. These FARs can bind the neurotransmitters serotonin and dopamine in a bio-relevant concentration range with unprecedented affinity and selectivity.

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NANOMATERIALS FOR REPAIR SPINAL CORD INJURY

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Spinal cord injury is a most devastating desease, as it causes a permanent loss of motor functions, causing enormous personal, social and economic problems. Neural regeneration has been shown to be a natural process; however, the regeneration mechanisms of the central nervous system are generally ineffective in restoring appropriate function. Therefore, there is tremendous social and medical pressure and research interest to discover new therapeutic strategies for effective repair of spinal cord injury. Repairing spinal cord injuries is far from simple, but new interdisciplinary research approaches through cutting-edge technologies and revolutionary concepts are raising hopes in promoting effective self-repair strategies. Cell- and biomolecule-based delivery strategies and therapeutic strategies based on novel tissue regeneration scaffolds have been developed in this direction. More recently, with a trend towards a combinatorial approach, regenerative/neural engineering therapies, prosthetics, neural engineering, rehabilitation engineering, bio-inspired robotics have been combined to develop advanced intelligent systems that promote spinal plasticity, regeneration and repair. Nanomaterials are increasingly being used in this field, especially due to their size, which allows a particularly efficient control of their physical and chemical properties. In fact, connecting nanostructured materials to biological compartments is a crucial step in prosthetic applications, where the interfacing surfaces should provide minimal undesired perturbation to the target tissue. Ultimately, the (nano)material of choice has to be biocompatible and promote cellular growth and adhesion with minimal cytotoxicity or dis-regulation of, for example, cellular activity and proliferation. In this context, carbon nanomaterials, including nanotubes and graphene, are particularly well suited for the design and construction of functional interfaces. This is mainly due to the extraordinary properties of these novel materials, which combine mechanical strength, thermal and electrical conductivity. Our group has been involved in the organic functionalization of various types of nanocarbons, including carbon nanotubes, fullerenes and, more recently, graphene. The organic functionalization offers the great advantage of producing soluble and easy-to-handle materials. As a consequence, since biocompatibility is expected to improve upon functionalization, many modified carbon nanomaterials may be useful in the field of nanomedicine.
In particular, we have recently shown that carbon nanotubes and graphene can act as active substrates for neuronal growth, a field that has given so far very exciting results. Nanotubes and graphene are compatible with neurons, but, especially, they play a very interesting role in interneuronal communication. Improved synaptic communication is just one example. During this talk, we will discuss about the most recent attempts to regenerate the electrical connection between the fractured sides of the spinal cord, with particular emphasis on the latest and most exciting results obtained in our laboratories in this fast developing field.

PHYSICS, SPECTROSCOPY AND IMAGING APPLIED TO BIOLOGY AND MEDICINE

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We will present some of our activity regarding the use of nanotechnology for exploring different aspects of biological sample preparationand their studyof interest in medicine.The presentation will span from the investigation and detection of several DNA intercalants [1],the generation of protein fibers and their structural studies[2],and last,TEM imaging of ion channels in cell membrane. The presentation will further include the description and the use of an original scanning probe spectroscopy [3] that combines the simultaneous multi probe excitation based on visible enhanced photon generation and hot electrons in order to obtain physical and chemical information on different kind of materials at nanometer scale.

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FROM PIAZZALE TECCHIO TO WALL STREET: THE SHORT STORY OF A LONG POLYMER HYDROGEL

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An innovative class of superabsorbent (SAP) materials was developed to target the raising challenge of creating a completely biodegradable product for industrial applications. Moving forward towards the biomedical applications, the technology platform was changed to create the first superabsorbent material entirely based on food grade products. In particular, our aim was to develop orally administered SAPs, capable of increasing the volume and the elasticity of the ingested foods throughout the entire gastrointestinal (GI) system, without additional caloric value, in a similar manner to raw vegetables. We hypothesized that such biomimetic approach could enable new mechanobiological treatments for the GI tract, with favorable efficacy and safety profile. To this aim, we developed a technological platform to produce novel cellulose-based hydrogels that are exclusively based on carboxymethylcellulose sodium salt (CMC) as the polymer backbone (used as a thickening agent in foods), and citric acid (CA) as the crosslinking agent (found in citrus fruits). By utilizing an in vitro GI model, we show that the SAP can be tuned to function in the wide range of conditions found in the GI tract. In particular, the hydrogel show elasticity levels, when in the stomach and small intestine, remarkably similar to some raw vegetables, while starkly contrasting to functional fibers. Once in the colon, the hydrogels are partially degraded through enzymatic activity thereby releasing the carried water, while the cellulosic material is excreted with the feces. Clinical studies performed on this platform [1, 2] and resulting regulatory clearances, in the US and Europe, show that it represent a useful aid in weight management for the treatment of individuals with overweight and obesity. Moreover, encouraging data from ex vivo and in vivo animal models suggest that the elasticity, in addition to the composition, play a key role in the maintenance of gut tissue health. These findings pave the way to additional indications of the elated to metabolic diseases and gut health. To bring the technology from the research through the clinic, and eventually to the market, a Start up company was incorporated, which completed many rounds of funding till the listing at the NYSE in Wall Street in Jan ’22. The first product, to target obesity, is already on the market in US.

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MAGNETIC NANOPARTICLES AND CLUSTERS TO COMBINE MAGNETIC HYPERTHERMIA WITH DIFFERENT THERAPEUTIC APPROACHES

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Magnetic hyperthermia" (MHT) is based on the magnetic heat losses of magnetic nanoparticles under an alternating magnetic fields (AMF) with the production of heat to 'burn' tumor cells. This treatment is applied on Glioblastoma patients at magnetic field conditions that are clinically safe (100 kHz and up to 24kA/m). The remote actuation by non-harmful magnetic fields enables to provide a more selective heat treatment with less side effects than traditional hyperthermia approaches. This seminar aims at providing an overview of the main research activities of our group to advance MHT and combine it with different therapeutic modalities. I will first focus on our 5 years progress on nonhydrolytic methods for the preparation of magnetic nanoparticles with optimal heat performance in MHT and our attempt to scale up the production of magnetic materials at very high quality for preserving MHT heat performance. I will then focus on the assembly of magnetic nanoparticles in clusters and correlate their heat efficiency under AMF to the assembly configuration. Next, I will discuss our magnetic semiconductor nano-platforms properly synthesized to combine MHT with internal radiotherapy based on Cupper-64. Then, I will introduce the thermo-responsive polymeric based nanocubes and clusters as drug carrier for chemotherapeutic agents and the heat-mediated drug release based on local hot spots or global temperature increase. I will report about our in vitro study on tumor spheroids from cancer cell model to determine the magnetic hyperthermia effects, with or without the association of chemotherapeutic drugs, on different subpopulations of cancer cells. Finally, I will go through our preclinical on xenograft murine tumor model results to evaluate the magnetic hyperthermia efficacy of some of our magnetic materials and the bio-distribution study of some of the best performing materials we have developed.

Keywords: magnetic hyperthermia, magnetic nanoparticles, chemotherapy, nanoparticles alignment, in vivo efficacy study, Cu64-radiolabelling

SUPRAMOLECULAR APPROACHES TO DESIGN NOVEL ANTIVIRALS

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Viral infections are among the main causes of death in the world. When prevention is not an option, antiviral drugs are the last resort to prevent the spread and the mortality of these infections. There are only a few effective drugs on the market, for the most part they prevent intracellular viral replication. Unfortunately, they are too few when compared to the many viruses that threaten humans. In this talk, I will show a new design rule to achieve drugs that fight viruses extracellularly by irreversibly inhibiting their infectivity, i.e. I will show how to create virucidal compounds. The design of these macromolecular virucidal agents starts by a bio-mimic approach and is characterized by the limited toxicity towards host cells that one would expect from such compounds. Yet, I will demonstrate that the multivalent binding to the viruses, coupled with a large hydrophobic contact between the compounds and the virus leads to a loss of integrity of the virion that obviously leads to an irreversible loss of infectivity. Results in and ex-vivo will be illustrated especially for the cases of influenza, herpes, and respiratory syncytial virus.

GLYCOSILATED CARBON NANOSTRUCTURES FOR EMERGENT VIRUSES

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The supramolecular interaction carbohydrate-protein is ubiquitous in a large variety of biological processes. In order to design multivalent peripheral ligands with glycomimetic properties that structurally can attach to the receptor sites of complex biological structures, a broad variety of ‘‘artificial glycoforms’’ have been created with the aim of understanding the mechanisms involved in multivalent binding interactions. There are many examples where multivalency drastically enhances the interactions between biomolecules in comparison to the analogous monovalent binding. In this regard, we have recently shown that hexakis-adducts of [60]fullerene endowed with 12, 24 or 36 mannoses, act as strong inhibitors for DC-SIGN in an Ebola infection assay model.[1] Furthermore, a drastic increase in the inhibition process at the subnanomolar scale has been observed when the size and mannoses´ number are increased in the firstly reported tridecafullerenes endowed with 120 mannose units decorating the periphery of the molecule.[2] From the work carried out by our group on glycofullerenes with globular symmetry, it is possible to bring to light the significance of size and shape of the glycomimetic, being even more determinant that the number of carbohydrate moieties in the glycoparticle. Furthermore, the synthetic approach is simplified, using C_{60} mono-adducts instead of C_{60} hexakis-adducts, without compromising the spherical form of the final glycomimetic, provided by the supramolecular aggregate resulting from the self-assembly of mono-adducts.[3] The efficiency to block DC-SIGN mediated viral infection by an artificial Ebola virus has been tested in a cellular experimental assay finding that, these systems are potent inhibitors of viral infection. In this presentation, a variety of carbon nanostructures endowed with sugars (sugar-balls) will show their effect for inhibiting infection by emergent viruses, namely Ebola, Zika and Dengue[4] and, by modifying organic addend molecules, to other viruses like VIH.[5]

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CURRENT CHALLENGES IN THE UNDERSTANDING AND TREATMENT OF ALZHEIMER'S DISEASE: LIMITATION AND PERSPECTIVE OF NANOMEDICAL APPROACHES

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Alzheimer's disease (AD) is one of the greatest challenges of the 21st century. This common form of dementia is suffered by tens of millions of people worldwide and there are still no treatments available that can cure the disease. A survey of the current understanding of AD pathology and an overview of the old and new strategies proposed will be discussed in light of the main advantages/limitations for future therapeutic applications.

NANOPARTICLES IN BNCT

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Boron Neutron Capture Therapy (BNCT) is an experimental radiotherapy with high selectivity based on a prior selective enrichment of tumor cells with B-10 and subsequent irradiation with a beam of low-energy neutrons. For several years there has been an intense research activity for the development of a new carrier of B-10 able to ensure such selectivity; for this purpose nanoparticles can play an important role. After exposing the basic principles of BNCT and the current world situation of BNCT centers based on new neutron sources installable in hospitals, will be presented some examples of nanoparticles tested in vitro and in vivo and their preliminary results obtained.