Spanish Participation in ERA-Net Cofund Action on Nanomedicine (2016-2021)

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Plataforma Española de Nanomedicina
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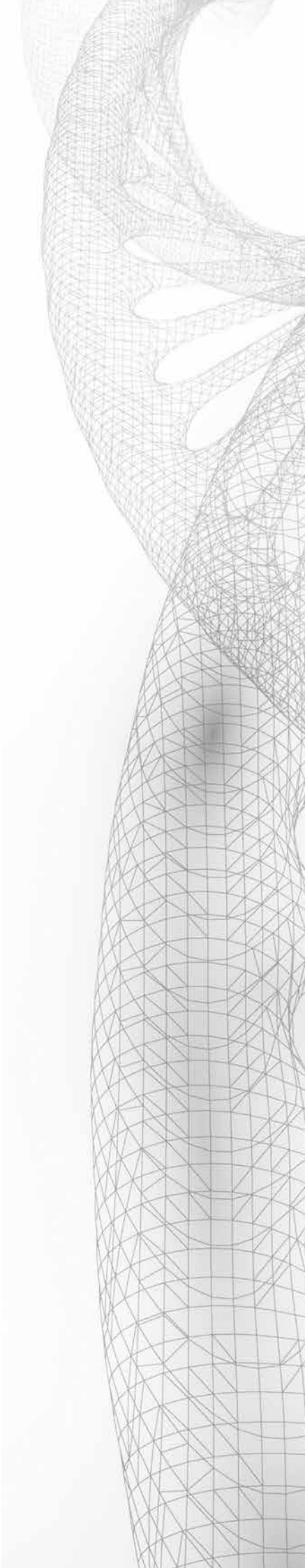

INTRODUCTION

It has been 13 years since the establishment of EuroNanoMed (ENM). During all those years, research and innovation funding organisations in Europe and beyond have been joining forces to fund excellent multidisciplinary and translational research and innovation projects that covered: Regenerative medicine, Diagnostics and Targeted delivery systems.

EuroNanoMed is a platform for funding agencies and ministries established since 2008. National and Regional research funding programmes join together with the goal of creating and funding collaborative research and innovation projects that can convert research in nanotechnology into practical gains in medicine.

Twelve joint transnational calls have been launched and a total of 120 transnational projects have been funded, including 628 research groups from over 21 countries.

EuroNanoMed III (2016-2021) was the last ERA-Net Cofund Action on Nanomedicine under Horizon 2020 that built upon the achievements on its predecessors to support the European Nanomedicine research community.

During this period, ENMIII has successfully funded Projects from a wide range of technical areas such as analytical tools, nanoimaging, nanomaterials and nanodevices, novel therapeutics and drug delivery systems, clinical, regulatory and toxicological issues. The medical domains have changed across the timeline. Most of the Projects are related with oncology/cancer, neurology and infectious diseases but we can also mention projects on dermatology, ophtalmology and/or metabolism.

In this booklet we would like to highlight the very important role that Spanish research on Nanomedicine is playing in the European ecosystem, summarizing the great success that Spanish research groups have had in the 5 Joint Translational Calls that EuroNanoMed III calls has launched since 2016.

Thanks to the crucial support of the State Research Agency (AEI), CDTI and the Carlos III Health Insititute (ISCIII) by cofounding these projects, the participation and the success rate of Spanish entities in these calls have been outstanding.

From a total number of 61 projects that have been funded under EuroNanoMed III 22 have been coordinated by Spanish researchers and 13 more had Spanish representatives as partners. Overall, Spain has participated in almost 60% of all the funded projects. This impressive number is also reflected in the participating research groups. From a total of 309 research groups involved, 58 are from Spain, being the second country with more funded participants just after France.

EuroNanomed III had the goal of creating and funding collaborative research and innovative projects and to convert research in nanotechnology into practical gains in medicine. The participation of ISCIII and CDTI in these calls has for sure strengthen the participation of hospitals, public health institutes and companies which are essential for the translation of the basic research done so far in nanomedicine into the clinics. We can highlight that out of the 68 participating Spanish institutions, 24 are research centers, 24 hospitals or public health institutes and 10 companies.

YEAR	FUNDED PROJECTS	RESEARCH GROUPS	SPANISH COORDINA-TORS	SPANISH PARTNERS	TOTAL NUMBER OF SPANISH GROUPS
2017	16	82	4	8	13
2018	12	57	6	8	14
2019	13	65	3	8	14
2020	10	53	3	4	6
2021	10	52	5	7	11

EuroNanomed III has shown that the Spanish Nanomedicine ecosystem is in very good shape. Excellent research is carried out in the field, and this is proved by the outstanding results obtained in Horizon 2020, not only in the EuroNanomed III calls but also in NMBP calls.

During Horizon 2020, nanotechnology has played an important role as a novel technology with growing application in the field of medicine. Horizon Europe will surely bring new funding opportunities that will help consolidate this role and bring more nanotechnology tools for treatment and diagnosis into the market. Nanomed Spain will continue giving support to all the Spanish stakeholders in the field to make sure that their success in Horizon Europe keeps the same track and Spanish nanomedicine stays at the front of the European research.

NANOMED Spain

The Spanish Platform far Nanomedicine (NANOMED Spain) was created in 2005 and now has more than 180 members, including companies, hospitals, technology centers, research centers and publíc administrations.

Nanomed Spain's main mission is to accelerate the development of innovative medical and pharmaceutical products based on nanotechnology, as well as the translation of nanomedicine from the early stages of research to its arrival in the market and clinic. It does this by encouraging the collaboration of all relevant actors in the sector (academia, industry, hospitals and administration), facilitating a common space for dialogue and cooperation between all these agents.

OBJETIVES

- Encourage public-private collaboration.
- Develop common analyses and strategies in areas of innovaton and knowledge transfer.
- Internationalize Spanish industry thorugh cooperation and coordination between European and Spanish activities.
- Defend Spanish interests and priorities with international funding agencies.

More information about the nanomedicine sector.
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Projects Coordinated by Spanish institutions

NanoGSkin: Transversal tissue engineering and nanomedicine approach towards an improved chronic wound therapy

PROJECT

Current biological technologies for skin diseases aim to provide a matrix and antimicrobial support. However, due to existing limitation it is necessary to develop bioequivalent and cost-effective skin substitutes manufactured in a GMP facility in a relative short period of time.

Granada Health Research Institute has developed a novel biomaterial based on nanostructured fibrin-agarose hydrogel that has proven to be effective for the tissue-engineered construction of artificial human corneas, oral mucosa, peripheral nerve regeneration and skin.

Here we propose a multidisciplinary healthcare approach combining bioengineered skin, growth factor- and antibiotic-loaded nanoparticles (NPs) towards an improved chronic wound therapy.

The NanoGrowSkin project will focus on the development of new advanced therapy tools/technologies in skin regeneration for the treatment of burns, by providing new alternative therapeutic options for many patients with chronic wounds.

The first aim to be accomplished by NanoGrowSkin will be the optimization of human artificial skin models by using pharmaceutical quality products and the implementation of novel methods, such as nanomedicine technologies. This will allow the generation of biomaterials with improved and suitable biomechanical and antimicrobial properties for its therapeutic use in clinical approaches. In order to achieve this first goal, necessary histological, rheological and genetic quality controls are envisaged.

The second aim of NanoGrowSkin will be to adapt the production of these new tools towards an optimal regulatory framework, including GMP regulation and EMA guidelines.

Thirdly, NanoGrowSkin has foreseen a wider exploitation model. It will include the development of a market access approach in order to estimate the benefits of this treatment for the entire society. The envisaged model will include the calculation of cost per patient as well as potential cost-savings and/or cost-effective measures for the affordable introduction of the tissue engineered treatment.

COORDINATOR

Miguel Alaminos, ibs.GRANADA, Spain

PARTNERS

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Loredana Cecchetelli, Istituto Biochimico Italiano, Italy
Muriel Cario-André,Université de Bordeaux, France
Christophe Egles,Université de Technologie de Compiègne, France
Abhay Pandit, NUIG, Irland

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THESIS

Jesús Chato Astrain; Generación y evaluación de modelos biomiméticos de cáncer de piel no melanoma y de sustitutos bio-artificiales de nervio periférico para la evaluación de protocolos terapéuticos, 2021

Anuja Gadekar; Dissertation to obtain the doctoral thesis; On course.

TRANSLATION OF RESULTS

The project allowed a significant improvement of the current model of bioengineered human skin used as ATMP for critically burnt patients

CALL 2017

2-INTRATARGET: Nano-Immunotherapy: Intracellular Targeting of Cancer Cells and TAMs

PROJECT

2-INTRATARGET Improved understanding of tumor cellular heterogeneity and of the dual role of the immune system in the progression of cancer has led to the design of new cancer immunotherapies aimed to target cancer cells as well as immune cells. However, these advanced therapies still have major draw-backs related to their limited access to their cell (cancer cells vs immune cells) and tissue (primary tumor site and metastatic niches) targets, which often result in a poor efficacy/toxicity balance. Moreover, the inability of these therapies (i.e. mAb or siRNAs) to cross the cell membrane makes them unsuitable to reach intracellular targets.

The objective of the 2-INTRATARGET project, has been to address these challenges by engineering Multifunctional Polymeric Nanocarriers (MPNs) aimed to deliver: 1) monoclonal antibodies (mAb) into cancer cells, thus targeting intracellular oncoproteins in the tumor or in their metastatic niches and 2) RNA molecules into the Tumor Associated Macrophages (TAM), to re-educate them and switch the tumor-promoting immune suppressive microenvironment to one that kills tumor cells and promotes adaptive immune responses.

In the frame of this 2-INTRATARGET consortium we have developed and evaluated MPNs with the capacity to deliver different active molecules (i.e. siRNA, dsRNA, small drugs and mAbs) inside cancer cells and TAMs. We have engineered more than 10 prototypes (>100 formulations were screened) loaded with the selected drugs, using different techniques and polymers, which have been screened based on their physicochemical properties (i.e. size, zeta-potential, drug loading) and stability.

To target and reprogram TAMs into M1-antitumor macrophages, we tested 15 MPN prototypes containing different TLR agonists, e.g. imiquimod, resiquimod and Poly (I:C). Finally, we selected the best TLR-loaded-MPNs based on their low toxicity, capacity to deliver the active compounds in the targeted endosomal compartment and to stimulate the anti-tumor cytotoxic activity of macrophages. In vivo, TLR-loaded-MPNs strongly inhibited primary tumor growth in immunocompetent lung cancer models, and lung metastasis in fibrosarcoma murine models.

COORDINATOR

Maria Jose Alonso, University of Santiago de Compostela (USC), Spain

PARTNRS

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Ruth Schmid,SINTEF, Norway
Yilmaz Capan,ILKO, Turkey

To target cancer cells, we have engineered and tested 15 MPNs loaded with siRNAs or mAbs to inhibit KRAS. These prototypes have been optimized in terms of physicochemical characteristics, drug loading and intracellular delivery. Preliminary experiments using anti-KRAS G12V mAb and siRNA anti-KRAS loaded in different MPNs have shown a synergistic effect with gemcitabine in a pancreatic cancer model.

Overall, this 2-INTRATARGET project allowed us to build a solid EU-consortium with complementary expertise in nanotechnology and cancer immunotherapy. In the next years, we will continue working and expanding this line of research, including different antibody combination therapies, in the frame of a recently approved 2^2-INTRATARGET project (2021-2024).

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TRANSLATION OF RESULTS

- Collaboration with the company Sylentis in the context of siRNA anti-KRAS.

- Collaboration of the company Libera Bio in the context of mAb anti-KRAS. The company is now extending the knowledge and facing the advanced preclinical development phase.

Overall, the major innovations are: (i) the possibility to target the KRAS oncoprotein, recognised as an undruggable target until now and, (ii) the design of a new combination immunotherapy targeted to TAM.

NANOpheles: Development of nanovectors for the targeted delivery in Anopheles mosquitoes of agents blocking transmission of Plasmodium parasites

PROJECT

The unmet medical and patient need of malaria eradication will not be achieved unless the targeted delivery of new drugs is vastly improved. The objective of NANOpheles is to design polymeric nanovectors for the delivery of antimalarial agents to Plasmodium stages in the mosquito, and to characterise the efficacy of nanovectors and antimalarial agents to reduce mosquito infectiousness. This objective will be achieved through (i) synthesis of nanocarriers capable of encapsulating antimalarials and preventing their degradation in storage conditions, (ii) engineering targeted nanovectors capable of delivering their antimalarial contents to Plasmodium stages in the Anopheles mosquito, and (iii) evaluating the effect of selected nanovectors (loaded with antimalarial agents) on the mosquito stages of Plasmodium and their transmission capacity in a murine model of malaria. NANOpheles unites leading laboratories with expertise in nanoparticle synthesis, targeted drug delivery to

Plasmodium-infected cells, molecular and cell biology of malaria, mouse models and mosquito vectors of malaria and clinical aspects of malaria.

Main results:

1. Identification of a synthetic polymer capable of solubilizing lipophilic drugs for their delivery to mosquitoes. It can also be applied to diseases other than malaria.
2. Identification of a natural polymer (heparin) with targeting and antimalarial activities towards Plasmodium stages in the mosquito.
3. Identification of a synthetic polymer with targeting to the ookinete stage in the mosquito.
4. Identification of a synthetic polymer with targeting to the mosquito midgut endothelial cells.
5. Discovery of a new antimalarial drug targeting mosquito stages of Plasmodium.

COORDINATOR

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Krijn Paaijmans, Barcelona Institute for Global Health (ISGlobal), Spain
Inga Kiamos-Siden, Foundation for Research and Technology- Hellas (FORTH), Greece
Fatima Nogueira, Universidade Nova de Lisboa, Portugal

PUBLICATIONS

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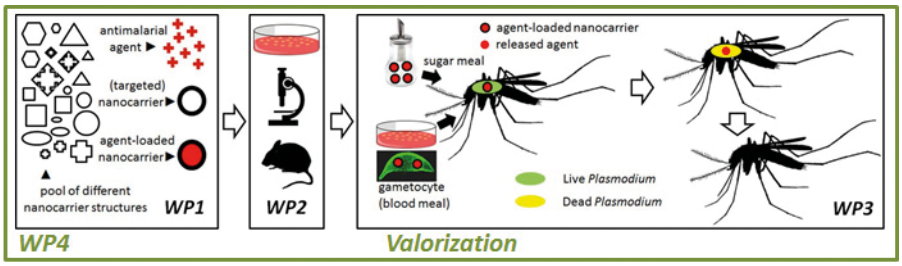

TRANSLATION OF RESULTS

Two patents being currently filed.

MAGBBRIS: New MAGnetic Biomaterials for Brain Repair and Imaging after Stroke

PROJECT

According to the World Health Organization, 15 million persons suffer a stroke worldwide each year, and neuro-repair treatments could offer the opportunity to treat stroke patients by extending the therapeutic time window.

By engineering novel magnetic nano-biomaterials we will achieve tissue repair in the context of an ischemic event. We will take advantage of nanotechnology to deliver therapeutic growth factors, secreted by progenitor cells, into the injured brain. MAGBBRIS aims at demonstrating that growth factors secreted by endothelial progenitor cells can be encapsulated in magnetic biomaterials and safely transplanted into mouse brains with the guidance of magnetic fields, to induce tissue repair.

MAGBBRIS consortium is made up by highly multidisciplinary materials-science, biomedical and clinical research with industrial partnership. The project will provide a new medicinal product ready to be tested in a preclinical multicentric study.

Multimodal nanocapsules made of poly(D,L-lactic-co-glycolic acid, PLGA-NCs) labelled with SPIONs and Cy fluorophores for the imaging tracking and magnetic retention have been designed and successfully produced for the encapsulation of Endothelial Progenitor Cells secretome. The process has been standardized and the characterization shows that reproducibility has been achieved. The average size of the NCs has consistently been under 300 nm. Therapeutic secretome from stroke-derived EPCs has been produced in medium-scale batches in GMP-like protocols by our industrial partner who has provided standardized secretome batches of 15mg/mL free of FBS and fully functional, in vitro. In parallel the magnetic targeting has been achieved with FeNdB focused magnet prototypes for the mouse implantation and a prototype for the human use, developed with appropriate anatomical and functional characteristics.

COORDINATOR

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PARTNERS

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Fabien Gosselet,University of Artois, Faculty Jean Perrin. Lens, France.
Maria Picchio,Ospedale San Raffaele IRCCS. Milano, Italy.
Filip Jelen,Pure Biologics Ltd. Wrocław, Poland.
Peter Kopcansky, Institute of experimental physics, Slovak Academy of Sciences, SAS. Kosice, Slovakia.

We have shown the incorporation of the PLGA-NC into vessel-like structures in vivo and inside endothelial cells of the BBB in vitro. The therapeutic actions of the encapsulated secretome on endothelial cells have been demonstrated in angiogenesis tests and on the BBB models where the secretome protected from the ischemia-induced permeability. In vivo PLGA-NC have been successfully administered in a mouse model of cerebral ischemia with specific brain targeting in the damaged area when administered intraarterially by endovascular procedures further improved by the magnet implantation for a short time. This administration has proved its safety when administered shortly after ischemia while increasing the amount of PLGA-NC in the targeted injured brain, confirmed by MRI and fluorescent molecular imaging taking, advantage of the multimodal imaging properties of our nanocarrier. Finally, the in vivo administration of the therapeutic PLGA-NC with the secretome is being tested to confirm the in vivo efficacy of the produced nanomedical product.

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TESIS

- Yajie Zhang, Nanocapsules as Drug Delivery Carriers for Pro-angiogenic Therapies. 2020.
- Alba Grayston, Advanced medical products for stroke in a pre-clinical model. 2021.

CALL 2018

NANOSIM: Biodegradable Nanoparticles of Simvastatin as new therapeutic tool for chronic liver disease

PROJECT

Liver cirrhosis is the fifth cause of death in adults aged 50 to 70 years and is responsible for 85% of liver transplants. Approximately 29 million people in the European Union still suffer from a chronic liver condition despite major progress in the knowledge and management of liver disease. Unfortunately, there is no treatment (other than the removal of the causing agent) available to stop or slow the progression of this chronic disease.

The purpose of the NANOSIM project is to develop an unprecedented new therapy for chronic liver diseases with safe and specific biodegradable polymeric micelles loaded with simvastatin, precisely directed to liver sinusoidal endothelial cells (LSEC). This will allow increasing drug concentration to maximize its efficacy and reduce its toxicity, becoming a therapeutic tool for hampering progression of liver damage. By the perfect match between nanotechnology, chemistry and hepatology, we will deliver a novel treatment, easy to produce, effective and ready to be assayed in humans.

Statins are considered one of the most promising drugs to change the natural history of chronic liver diseases, by slowing/stopping the progressive inflammation and fibrosis of the liver. However, statins have side effects that increase in patients with advanced chronic liver disease, limiting the use of high doses and preventing their full therapeutic potential. The present project proposes a series of studies aimed at the development and characterization of simvastatin encapsulated in biodegradable nanoparticles, specifically targeted to LSEC, evaluating their toxicity and safety. The project also proposes pre-clinical studies to analyze the efficacy and side effects in an experimental animal model of severe liver cirrhosis as the bile duct ligation model, the most susceptible model to simvastatin toxicity, but also in models of nonalcoholic esteatohepatitis without fibrosis.

COORDINATOR

Joan Genescà, Vall d'Hebron University Hospital (HUVH_COORDINATOR), Spain

PARTNERS

Norman Metanis, The Hebrew University of Jerusalem (HUJI), Israel

Mig Wei, Cellvax S.A., France

PUBLICATIONS

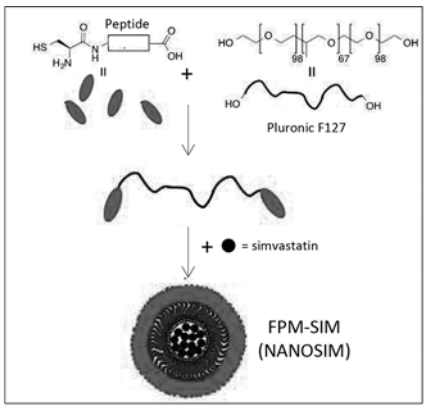
Hide, D., Gil, M., Andrade, F., Rafael, D., Raurell, I., Bravo, M., Barberá, A., Gracia-Sancho, J., Vargas, V., Augustin, S., Genescà, J., Schwartz, S., Jr, and Martell, M. (2020). Simvastatin-loaded polymeric micelles are more effective and less toxic than conventional statins in a pre-clinical model of advanced chronic liver disease. Nanomedicine : nanotechnology, biology, and medicine, 29, 102267. https://doi.org/10.1016/j.nano.2020.102267

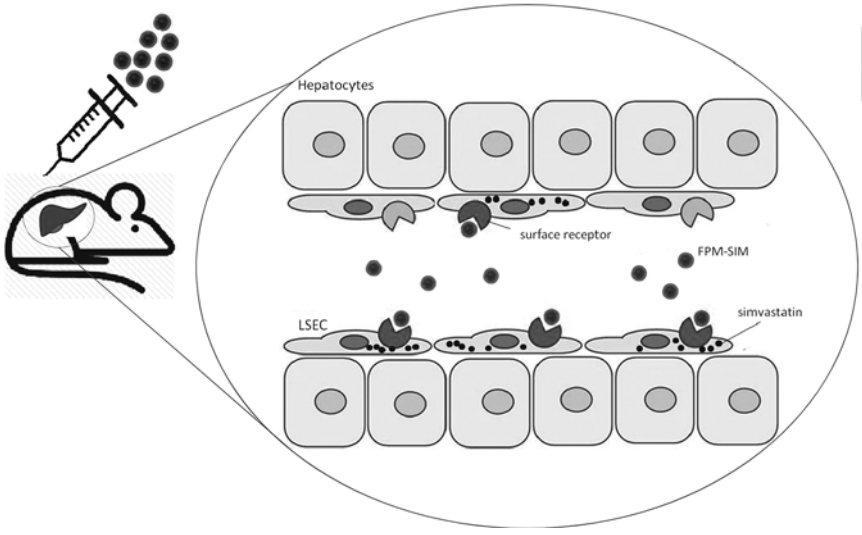
3 COMMUNICATIONS TO CONFERENCES

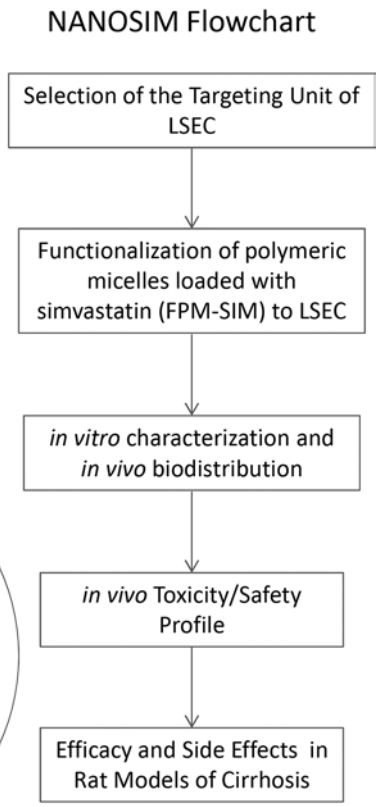
Master Final Thesis. Mar Gil. Study of the effect of Pluronic F127 polymeric micelles (PM-F127) loaded with simvastatin on the different liver cell types in healthy rats (HUVH). 2019.

THESIS

Mar Gil. Targeted biodegradable nanoparticles of simvastatin as new therapeutic tool for chronic liver disease (HUVH). ONGOING.







CALL 2018

CONCORD: Cationic Gold nanoparticles mediated mRNA cytoplasmatic-targeted delivery for production of CAR-T lymphocytes for Chronic Lymphoid Leukemia immunotherapy

PROJECT

Chimeric Antigen Receptor T (CAR T) cell therapy is a type of immunotherapy based on the ex-vivo engineering of patient T-lymphocytes to produce special chimerical receptors on their surface that target specifically tumoral cells when re-introduced in the patient. CAR T cell therapy targeting CD19 is showing very promising results with recurrent and refractory Chronic Lymphocytic Leukaemia. However, modified CAR T lymphocytes stay active indefinitely and consequently patients experience permanent eradication of normal B-cell requiring monthly infusions of immunoglobulins for survival. Besides, T-lymphocytes are modified using lenti- or retroviral vectors, which, though acceptably safe, are not free of oncogenic insertional mutagenesis risk and consequent regulatory barriers.

To overcome the permanent elimination of B-cells, mRNA transfections are more and more used as a tool for transient protein overexpression. However, the use of mRNA as an overexpression tool is challenging since isolated mRNA is easily degraded, and protein levels quickly decline after 24-48h, while the treatment should last for at least 2-3 weeks to eradicate tumoral cells from the patient. Current methods for non-viral mRNA delivery, especially lipofectamine or electroporation, are quite toxic. As an alternative, we propose to bind the mRNA to Au (solid and hollow) nanoparticles (NPs) functionalized with amine-terminated groups as a safer way to transport mRNA to the cytosol via endocytosis and further escape from endosomes through the proton sponge effect.

COORDINATOR

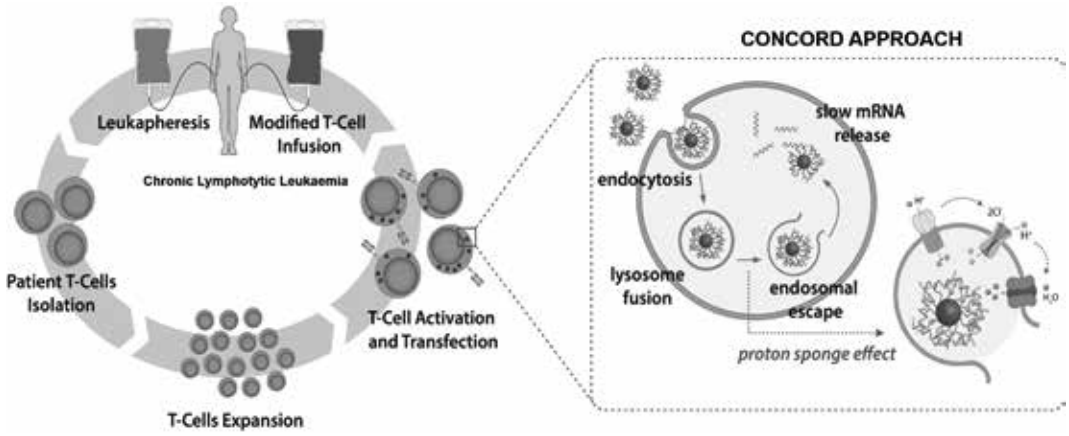
Neus G. Bastús,Institut Català de Nanociència i Nanotecnologia ICN2, Spain

PARTNERS

Manel Juan Otero,Hospital Clínic de Barcelona, Spain.
Giovanna Damia,IRCCS-Istituto di Ricerche Farmacologiche Mario Negri, Italy.
Raf Korenstein,Tel Aviv University, Sackler School of Medicine, Israel
Ignasi Gispert, Applied Nanoparticles S.L., Spain

By adjusting conditions, the slow release of the loaded mRNA inside the cell will be controlled, therefore extending the mRNA half-life and protein expression. AuNPs are of special interest for delivery due to their biocompatibility, tuneable surface chemistry, and their special optical and electronic properties that allow fine monitoring of the evolution, distribution and modifications of them and their chemical environment.

In this context, CONCORD is designing and developing transfection nanovectors for the sustained release of mRNA inside the cell for longer therapeutic levels of CAR expression. This objective involves two different aspects: i) the design of the nanovector: synthesis, functionalization, loading with mRNA, characterization, and dispersion in biological media, and ii) the testing of the nanovector: the study of the molecular mechanisms regulating the interaction cells-nanovectors, evaluation of hazard and risk assessment and evaluation of their efficacy and therapeutic power.



CALL 2018

PANIPAC: Photoactivable nanoparticles to immunostimulate the tumor microenvironment in pancreatic cancer

PROJECT

PANIPAC (Photoactivable nanoparticles to immunostimulate the tumor microenvironment in pancreatic cancer) sets out to tackle a pressing medical need for developing innovative therapeutic approaches that improve the outcome and survival of pancreatic cancer patients. Therapeutic strategies involving the manipulation of the immune system to defeat tumors are gaining momentum in cancer research. Single-agent checkpoint inhibitors, including agents that alter immune suppressive signals in other human cancers, have shown a limited efficacy in pancreatic cancer.

PANIPAC project aims to generate an impact in the treatment of pancreatic cancer, making use of the evidences of immunological responses stimulated by Photodynamic therapy (PDT) treatment, enhanced by appropriate nanoparticles (NPs). We propose to develop nanoparticles able to penetrate and accumulate in pancreatic tumors, and efficiently deliver the associated compounds. This means to develop a tailored nanosystem for the targeted delivery of therapeutic molecules to pancreatic cancer cells, including verteporfin, an antiangiogenic drug that is under clinical evaluation for photodynamic therapy in locally advanced pancreatic cancer.

The main objective of PANIPAC is to make an impact on the treatment of PDAC, making use of the existing evidences for the potential use of nanotechnology to manipulate and/or re-educate the immune cells of the tumor microenviroment (TME), and to locally deliver substances that can stimulate immunological responses, especially photosensitizers for controlled Photodynamic Therapy (PDT), which are also able to induce a potent local inflammatory reaction offering the possibility of boosting an immune response within a re-educated tumor microenvironment to promote the infiltration of effector T (Teff) cells.

COORDINATOR

Rafael López, Consorcio Centro de Investigación Biomédica en Red, M.P. (CIBER), Spain

PARTNERS

Bruno Sainz, Jr Universidad Autónoma de Madrid / Instituto de Investigaciones Biomédicas "Alberto Sols" CSIC-UAM, Spain
Maria Pia Protti, IRCCS Ospedale San Raffaele, Italy
Simona Mura, CNRS, Université Paris-Saclay, France
Serge Calet, STANIPHARM, France

We will meet this objective with the development of nanoparticles activated by light (NALs), composed of bioactive lipids, to induce a controlled inflammatory reaction in the TME of PDAC, and reset the immunogenicity for an improved response to immunotherapies.

The first step is to develop NALs that can efficiently reach PDAC to deliver: 1) verteporfin for PDT, 2) the bioactive lipids, and 3) other active molecules, such as anakinra or IFNd.

In a second phase, we will validate the potential of the developed technology to improve the immunogenicity of PDAC tumors, for the establishment of combinatory therapies with checkpoint inhibitors

Please visit https://metastarg-panipac.ciberonc.es/panipac

PUBLICATIONS

Protti, M. P., and De Monte, L. (2020). Thymic Stromal Lymphopoietin and Cancer: Th2-Dependent and -Independent Mechanisms. Frontiers in immunology, 11, 2088. https://doi.org/10.3389/fimmu.2020.02088

11 COMMUNICATIONS TO CONGRESSES

CALL 2018

METASTARG: Targeted multifunctional nanoemulsions to interrupt metastasis progression

PROJECT

METASTARG (Targeted multifunctional nanoemulsions to interrupt metastasis progression) is an innovative solution relying on nanotechnology for the early detection and treatment of occult micrometastases to cause a direct impact in patient survival, quality of life, and health-economics.

METASTARG is set to explore the full potential of nanotechnology to detect and eliminate occult micrometastases, interrupt metastasis progression and improve cancer survival.

From a technological point of view, the main challenges are related to the targeting capacity of the proposed nanotechnology to efficiently reach occult micrometastases, by definition small clusters of cells poorly vascularized, and to avoid possible toxic effects that could worsen the situation of cancer patients.

Bearing this in mind, we follow an innovative approach that merges pharmaceutical innovation and a deeper molecular understanding of the metastatic process.

Objectives

-To optimize the technology to allow detection of occult micrometases, and simultaneous delivery of anticancer drugs.

-To understand the biophysics of targeting metastasis to improve nanoparticles interaction with occult micrometastases.

-To generate a solid proof-of-concept of the potential of nanoparticles in oncology.

-To advance in the translation of nanoparticles to a clinical setting.

PLEASE VISIT https://metastarg-panipac.ciberonc.es/metastarg

COORDINATOR

María de la Fuente, Consorcio Centro de Investigacion Biomedica en Red, M.P. (CIBER), Spain

PARTNERS

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Serge Calet,STANIPHARM, France
Speranta Valeria Tanasescu, “Ilie Murgulescu” Institute of Physical Chemistry of the Romanian Academy, Romania

PUBLICATIONS

Tanasescu, S., Gheorghe, D., Precupas, A., Botea Petcu, A., Sandu R., Popa, V. T. (Thermodynamic descriptors of the interaction at the bio/nano interface. In Nanomaterials functional properties and applications vol. 28, Series Micro and nanoengineering. Ed. Academiei Romane, Bucuresti. 2020. ISBN 978 973 27 3290 8

Grimaudo, M. A., Herreros Pomares, A., Alonso, M., Calabuig Fariñas, S., Jantus Lewintre, E., de la Fuente, M. Biofabrication of 3D tumor models in cancer research. In Biomaterials for 3D Tumor Modeling chapter 3 Materials Today. Elsevier, USA. 2020:67-90. ISBN: 9780128181287

THESIS

Abi Judit Vázquez Ríos. Development of targeted therapeutic strategies for metastatic lung cancer. 2020

In Januray 2021 we included 17 communications to congresses

CALL 2018

TARBRAINFEC: Nanosystems conjugated with antibody fragments to target/treat brain infections

PROJECT

Infectious diseases affecting the central nervous system (CNS) remain an important source of morbidity and mortality. A major obstacle for curing brain diseases is the blood-brain barrier (BBB), which impedes therapeutic agents to reach the brain and target the related pathogens. In this project, we want to develop a drug delivery nanosystem coated with antibody fragments, also called nanobodies (Nbs) as a proof of concept for crossing BBB and combating brain infections caused by bacteria, virus and parasite. To do this, we will generate nanobodies (Nbs) against neurotropic pathogens using two bacterial (Neisseria meningitides and Borrelia burgdorferi), herpes simplex virus (HSV) and the protozoan parasite Trypanosoma brucei as the model systems. These Nbs will be further engineered to bear the transferrin receptor ligand in order to overcome BBB via the receptor-mediated transcytosis. The so-created Nbs will be then conjugated to the drug-loaded nanoparticles constructed with polymer or dendrimer nanovectors. The obtained nanotherapeutics will be characterized for their size, morphology, surface charge and stability as well as drug loading and release profile etc.

The ability of these nanotherapeutics to across BBB will be assessed using an in vitro model of BBB, and their biological activity against the neurotropic pathogens N. meningitides, B. burgdorferi, herpes simplex virus (HSV) and T. brucei will be assessed in vitro using cell based experiments and in vivo using animal models. The success of this project will validate the proof-of-concept study to combine the nanobody technology with the nanotechnology based drug delivery for effectively overcoming BBB and treating brain infections. We expect to generate, in this project, clinical useful pilot results for the best performing candidates for future translation, and at the same time, research data of general scientific interest useful to the broad scientific community.

COORDINATOR

Jose A. García-Salcedo,Fundación para la Investigación Biosanitaria de Andalucía Oriental (FIBAO) - Instituto de Investigación Biosanitaria de Granada (ibs.GRANADA), Spain

PARTNERS

Ling Peng,Centre Nationale de Recherche Scientifique (CNRS), France
Sylwia Czarnocka-Śniadała, Nanosanguis, Poland
Antonio Alcamí, Centro de Biologia Molecular Severo Ochoa, Spanish Research Council, (CSIC), Spain
Mangesh Bhide,Institute of Neuroimmunology, Slovak academy of Sciences (SAS), Slovakia
Aristidis Tsatsakis, University of Crete, Greece

PUBLICATIONS

Lyu, Z., Ding, L., Tintaru, A., and Peng, L. (2020). Self-Assembling Supramolecular Dendrimers for Biomedical Applications: Lessons Learned from Poly(amidoamine) Dendrimers. Accounts of chemical research, 53(12), 2936-2949. https://doi.org/10.1021/acs.accounts.0c00589

Chen, J., Ellert-Miklaszewska, A., Garofalo, S., Dey, A. K., Tang, J., Jiang, Y., Clément, F., Marche, P. N., Liu, X., Kaminska, B., Santoni, A., Limatola, C., Rossi, J. J., Zhou, J., and Peng, L. (2021). Synthesis and use of an amphiphilic dendrimer for siRNA delivery into primary immune cells. Nature protocols, 16(1), 327–351. https://doi.org/10.1038/s41596-020-00418-9

Sarandi, E., Kruger Krasagakis, S., Tsoukalas, D., Rudofsky, G., and Tsatsakis A. (2021) A Clinical Trial for the Identification of Metabolic Biomarkers in Hashimoto's Thyroiditis and in Psoriasis: Study Protocol. Pathophysiology.; 28(2):291-306. https://doi.org/10.3390/pathophysiology28020019

CALL 2018

ABISens: Monitoring of Acquired Brain Injury and recovery biomarkers by the combined label-free nanoSensing of multiple circulating molecules

PROJECT

The evaluation of patients after brain injuries remains a primary unmet clinical need. The current diagnosis, prognosis, and rehabilitation efficacy are mainly assessed by clinical examinations, neuroimaging, and electrophysiological tests during prolonged hospital stays. Our proposal aimed to offer as an alternative a novel nanobiosensor platform to selectively quantify multiple brain injury and recovery biomarkers (miRNAs and proteins) in biofluids with high sensitivity and in a short time. The nanophotonic biosensor platform employs silicon interferometric nanowaveguides combined with oligonucleotide bioreceptors to selectively recognize the biomarkers. To reach the final goal, ABISENS is aimed to carry out the following milestones:

-Receptor synthesis for the detection of protein and miRNA targets. Oligonucleotides were the bioreceptors envisioned for target detection: aptamers for protein detection and complementary oligonucleotide probes for miRNAs detection. Aptamer selection and screening have been made by UNIBO (France). So far, they have prepared SELEX libraries for three candidates and found and characterized one promising aptamer candidate for one protein biomarker. On the other hand, ICAQ-CIBER (Spain) has already accomplished the design and selection of complementary oligonucleotide probes to detect the selected miRNAs. Different probes have been synthesized, carrying amino groups and biotin groups to facilitate the sensor biofunctionalization.

-Nanodevice production. ICN2-CIBER (Spain) has already accomplished the design and manufacturing of a multiplexed 8 channel photonic sensor and a polymeric microfluidic cartridge to flow the samples over each of the sensors surface. A silicon sensor chip carrying a beam splitter to propagate the light to 8 different sensing waveguides was designed, fabricated and optically characterized. A microfluidic cartridge was designed and fabricated containing microchannels to flow the sample independently to each waveguide sensor. This task is currently in progress.

COORDINATOR

Laura M. Lechuga,Consorcio Centro de Investigación Biomédica en Red, M.P. (CIBER), Spain

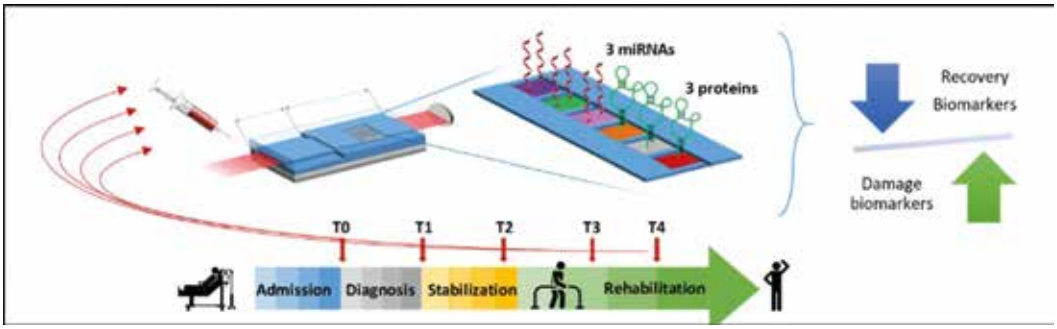
PARTNERS

Caterina Pistarini, Instituti Clinici Scientifici Maugeri Spa Società Benefit (ICSM), Italy

Carmelo Di Primo, Institut Européen de Chimie et Biologie, University of Bordeaux (UNIBO), France

Another task carried out was the nanobiosensor optimization for the detection of single and multiple biomarkers. Different protocols were selected to immobilize the oligonucleotide probes on the sensor surface. From all of them, biotin-functionalized probes showed the most sensitive and reproducible protocol, and currently calibration curves are being produced for miRNA detection. Furthermore, biofunctionalization protocols are being developed for the attachment of antibodies for the protein biomarkers quantification.

-Sample collection and sensor validation. ICSM (Italy) has already enrolled the patients and collected the serum and plasma samples at different times after the brain injury. These patient samples have already been evaluated for two of the selected protein biomarkers BDNF and NFL, using SiMOA and ELISA as orthogonal techniques. In the future, these samples will also be evaluated with the nanobiosensor for its validation.



CALL 2018

nAngioDerm: Ion-release materials to promote angiogenesis on dermal regeneration

nAngioDerm will develop nanostructured ion-release platforms and devices that promote the in situ regeneration of damaged skin without the need of cells or growth factors. Within the consortium, we have developed CaZn nanoparticles and collagen-gelatin scaffolds that can recruit cells for wound re-vascularization and regenerate skin injuries.

PROJECT

COORDINATOR

Elisabeth Engel,Institute for Bioengineering of Catalonia (IBEC),The Barcelona Institute of Science and Technology, Spain

PARTNERS

Dimitrios Zeugolis, Technological Education Institute of Epirus, (TEI of Epirus), Greece
Joan Pere Barret,Hospital Universitario Vall d'Hebron (HUVH), Spain
Olivier Stéphane,Université Grenoble Alpes, Service Courrier Université Grenoble Alpes (UGA),France
Denis Barbier, MicroLight3D SAS, France

PUBLICATIONS

Blanco-Fernandez, B., Cano-Torres, I., Garrido, C., Rubi-Sans, G., Sanchez-Cid, L., Guerra-Rebollo, M., Rubio, N., Blanco, J., Perez-Amodio, S., Mateos-Timoneda, M. A., and Engel, E. (2021). Engineered microtissues for the bystander therapy against cancer. Materials science and engineering. C, Materials for biological applications, 121, 111854. https://doi.org/10.1016/j.msec.2020.111854

Blanco-Fernandez, B., Gaspar, V. M., Engel, E., and Mano, J. F. (2021). Proteinaceous Hydrogels for Bioengineering Advanced 3D Tumor Models. Advanced science (Weinheim, Baden-Wurttemberg, Germany), 8(4), 2003129. https://doi.org/10.1002/advs.202003129

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Perez-Amodio, S., Engel, E. Engineering Cell-Derived Matrices:

From 3D Models to Advanced Personalized Therapies (2020)

Advanced Functional Materials, 30(44), 2000496. https://doi.org/10.1002/adfm.202000496

Perez-Amodio, S., Rubio, N., Vila, O. F., Navarro-Requena, C., Castaño, O., Sanchez-Ferrero, A., Marti-Munoz, J., Alsina-Giber, M., Blanco, J., and Engel, E. (2021). Polymeric Composite Dressings Containing Calcium-Releasing Nanoparticles Accelerate Wound Healing in Diabetic Mice. Advances in wound care, 10(6), 301-316. https://doi.org/10.1089/wound.2020.1206

DrNanoDAll: Nanodiagnosis for Betalactam Hypersensitivity

PROJECT

Betalactam (BL) allergy is self-reported by approximately 10% of the population with adverse drug reactions (ADR), being most frequently induced by an IgE mediated mechanism. This ADR has implications for patients safety and Health Systems costs since prescription of alternative antibiotics could induce bacterial resistance, could be more expensive and could potentially be more toxic. IgE-mediated BL allergy varies among patients, with some reacting only to one BL and others to several of them; it tends to change over time and differs between European countries, depending on BL consumption.

BL allergy diagnosis is challenging, relying on patient clinical history, in which previous BL-ADR evidence are often inaccurately reported; and on drug provocation and/or skin tests, which are not risk-exempt and require specialized healthcare professionals for results interpretation and patient management.

In vitro testing stands out as the more rational alternative diagnostic method, showing however various limitations, such as low sensibility. Immunoassay for quantifying specific IgE is the most used one, although limited to few BLs. Basophil activation test is also used, although the lack of knowledge about the activation mechanisms has hampered a wider clinical application. Thus, nowadays these tests do not fulfil the clinician's needs.

DrNanoDAll proposes the development of nanoparticles decorated with BL dendrimeric antigens, innovative solutions to surpass the current limitations. In order to offer new in vitro tools for BL-allergy accurate diagnosis, this proposal will combine nanotechnological and immunological approaches with BL-allergy clinical expertise, implementing a multi-omics workflow and involving the industry for scaling up nanomaterials and clinical test validation steps.

Major developments of our project include the preparation of different particles and their preliminary immunological evaluation with patients' samples, with the following outcomes so far: (i) Radio Immunoassays using nanoparticles, which improve protocol management and the sensitivity of current available techniques. (ii) Basophil activation test using nanoparticles, improves the sensitivity of this test compared when performed with the free drug.

COORDINATOR

Maria José Torres, Universidad de Málaga-BIONAND, Spain.

PARTNERS

Jean Louis Gueant, Inserm and University of Lorraine, France.
Rosa Pettinato, IRCCS Associazione Oasi Maria SS. – ONLUS, Italy.
David Rodriguez, DIATER Laboratorio de Diagnósticos y Aplicaciones Terapéuticas, S.A, Spain.

This European-wide collaboration will be crucial to generate a new BL-allergy diagnosis tool suitable for personalized medicine, which will impact positively on the European Health Systems.

PUBLICATIONS

Martín-Serrano, Á., Gonzalez-Morena, J. M., Barbero, N., Ariza, A., Sánchez Gómez, F. J., Pérez-Inestrosa, E., Pérez-Sala, D., Torres, M. J., and Montañez, M. I. (2020). Biotin-Labelled Clavulanic Acid to Identify Proteins Target for Haptenation in Serum: Implications in Allergy Studies. Frontiers in pharmacology, 11, 594755. https://doi.org/10.3389/fphar.2020.594755

Bogas, G., Mayorga, C., Martín-Serrano, Á., Fernández-Santamaría, R., Jiménez-Sánchez, I. M., Ariza, A., Barrionuevo, E., Posadas, T., Salas, M., Fernández, T. D., Torres, M. J., and Montañez, M. I. (2020). Penicillin and cephalosporin cross-reactivity: role of side chain and synthetic cefadroxil epitopes. Clinical and translational allergy, 10(1), 57. https://doi.org/10.1186/s13601-020-00368-1

Martin-Serrano, A., Perez-Inestrosa, E., Mayorga, C., Torres, M. J., and Montañez, M. I. (2021). Recent patents in allergy and immunology: New pyrazinones for the diagnosis of allergies to aminocephalosporins. Allergy, 76(4), 1288–1291. https://doi.org/10.1111/all.14673

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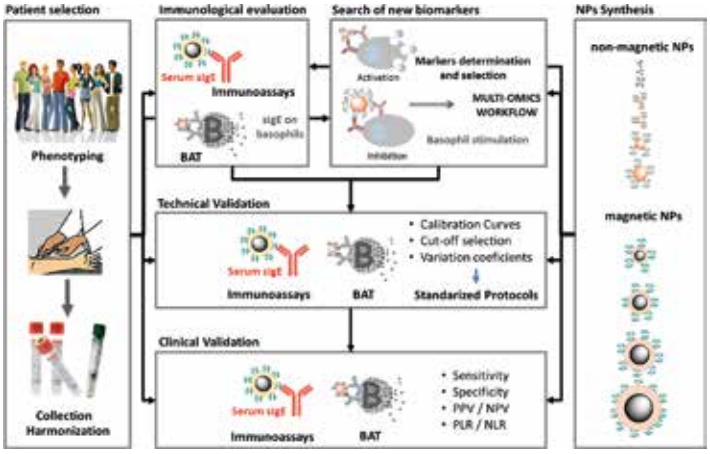
Mayorga, C., Perez-Inestrosa, E., Rojo, J., Ferrer, M., and Montañez, M. I. (2021). Role of nanostructures in allergy: Diagnostics, treatments and safety. Allergy, 76(11), 3292–3306. https://doi.org/10.1111/all.14764

Tesfaye, A., Rodríguez-Nogales, A., Benedé, S., Fernández, T. D., Paris, J. L., Rodriguez, M. J., Jiménez-Sánchez, I. M., Bogas, G., Mayorga, C., Torres, M. J., and Montañez, M. I. (2021). Nanoarchitectures for efficient IgE cross-linking on effector cells to study amoxicillin allergy. Allergy, 76(10), 3183–3193. https://doi.org/10.1111/all.14834



CELLUX: CeO2 Nanoparticles-assisted stem cell-based therapy: an innovative nanopharmaceutical approach to treat retinal degenerative diseases.

PROJECT

Chronic inflammation is now regarded as a major pathogenic pathway common in many different pathologies. Age-related Macular Degeneration (AMD) is a neuro-degenerative and complex disorder with multifactorial etiology, currently inevitable and orphan of treatment, that represents a major cause of blindness in people over 50 and affects millions of people worldwide. Its progression is associated with an increase of oxidative stress and inflammatory response in the eye leading to retinal cell death. Recently, a new agent has been added to the group of antioxidant/anti-inflammatory substances with therapeutic properties: cerium oxide nanoparticles (CeO2NPs). CeO2NPs have a unique electronic structure that when reduced to the nanoscale, oxygen defects appear at their surface, behaving as sites for free radical scavenging. Thus, the main objective of CELLUX is to develop a novel pharmaceutical-based CeO2NPs eye drops to treat AMD that in combination with stem cell-based therapeutic strategies, will not only stop degeneration but restore vision-

Despite the COVID-19 global situation, the progress of the CELLUX project is going as planned. Although it is true that we had some delays in several deliverables, all partners are committed to making an effort to achieve each task on time, now that the situation is getting better. One of the first goals of the project was to test whether our newly CeO2NP and eye drops were safe. We tested it using different models, from the ocular microbiome, biological media, cells, invertebrate animals, to mice and rats. We did not observe any cytotoxicity, increased cell death, immune response, or irritation in any of these systems.

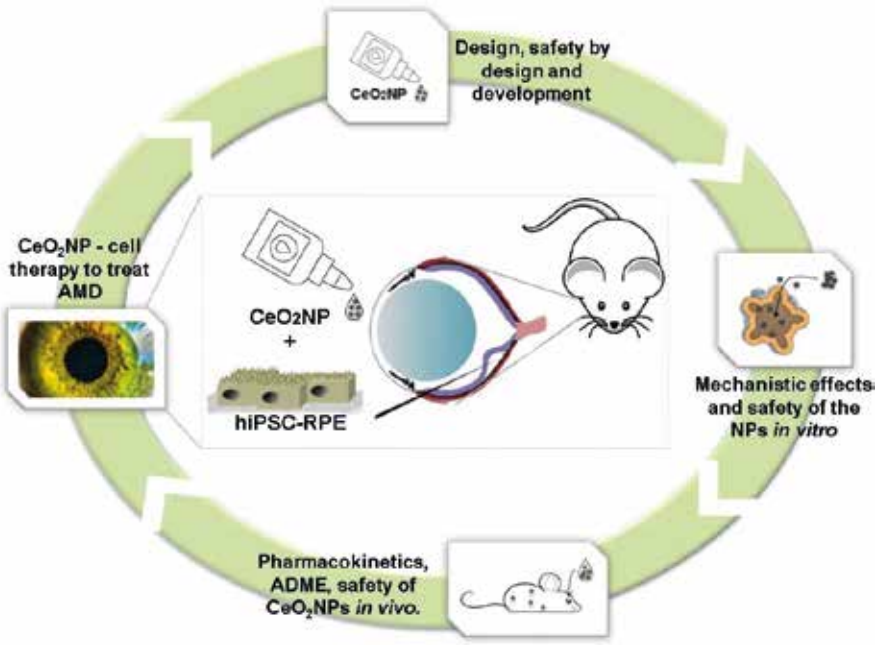
COORDINATOR

Anna Duarri, Vall d'Hebron Institut de Recerca, Spain

PARTNERS

Maria Dusinska, NILU-Norwegian Institute for Air Research, Norway
Luisa Diomede, Istituto di Ricerche Farmacologiche "Mario Negri" IRCCS, Italy
Alena Sevcu, Technical University of Liberec, Czech Republic
Els Verhoeyen, Centre International de Recherche en Infectiologie (CIRI)/ INSERM U1111, France
Ignasi Gispert, Applied Nanoparticles, Spain

Moreover, regarding another goal on whether the CeO2NP could act as a potent antioxidant, this was also proved in cells and animal models. However, this part is still ongoing. We also described a new potential particularity of our CeO2NP eye drops. We observed that using in vitro models and in vivo ocular treatment in mouse models of neovascular AMD, CeO2NP inhibits neovascularization, making these NP even more interesting for further clinical applications.



TRANSLATION OF RESULTS

Patent: Ophthalmic topical composition with Ceria nanoparticles for treating diseases of posterior segment of the eye (EP21382320.6)

NANO4GLIO: Nanomedicine for glioblastoma therapy

NANO4GLIO

1. Nanoparticle synthesis.

During the development of the project, several nanoparticles have been synthesized including:

a. -cyclodextrin derivatives. Two of them were selected for further studies following siRNA interaction and toxicity experiments.

b. Nine phosphodendrimers in the first round. After testing for siRNA interaction and toxicity, a second round comprising 7 phosphodendrimers was synthesized . Four of them were selected to proceed with transfection efficiency studies.

c. Several additional nanoparticles were prepared allowing them to be transformed in situ as glyconanodendrimersomes.

d. Twelve peptides with a site modification or sequence deletion from the lead peptide (DEA). The sequence-activity-relationship will be studied later. In addition, 12 branched peptides with divalent, trivalent, tetravalent or octavalent structures which were obtained by conjugating DEA on multidentate skeletons; and 15 amphiphilic dendrimers of different generations with 4 to 32 amino groups on the surface (called N-terminus) for siRNA interactions, and with C18 chains or BBB crossing carrier on its C -terminus were also synthesized and characterized.

e. Eight dihydropyridine derivatives were synthesized and tested for interaction with siRNA and toxicity. All of them showed a good toxicity pattern.

2. Toxicity on neurons and astrocytes

Two -cyclodextrin , 4 phosphodendrimers, and 10 dihydropyridine-based nanoparticles that showed ability to bind siRNA and to protect it from degradation by RNAses were tested for toxicity in primary mouse cortical neurons and astrocytes, in human glioblastoma T98G cell line, and in 2 cell lines generated by partner 6 from glioblastoma tissue obtained from patients. These studies allowed to identify the concentration range that is not toxic for neurons and astrocytes that are the cell types sharing anatomic space with glioblastoma cells in vivo. In addition, neither of the tested nanoparticles was toxic up to 15 µM for either T98G glioblastoma cells or the patient-derived glioblastoma cells.

COORDINATOR

Valentín Ceña, CIBERNED, ISCIII. Spain

PARTNERS

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Maria Angeles Vaz, Hospital ramón y Cajal. Spain
Aiva Plotniece, State Education Development Agency. Latvia

Toxicity studies for glyconanodendrimersomes, the peptide-based, and amphiphilic dendrimers are under way.

3. Transfection efficiency in glioblastoma

The nanoparticles tested for toxicity on neurons, astrocytes, the cell line T98G, and the patients-derived cell lines were tested for their ability to efficiently transfect siRNA aimed to knockdown the protein p42-MAPK which is involved in proliferation and survival of glioblastoma cells. From the nanoparticles studied, two -cyclodextrins and 6 dihydropyridine-derived nanoparticles showed a high transfection efficiency (reduction of p42-MAPK protein levels of more than 70%). The phosphodendrimers tested did not show high transfection efficiency. Thus, they will be further modified and studied to achieved the desired transfection efficiency level.

PUBLICATIONS

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INTREPIDUS: Nanoporous-Membranes for Intrathecal (Pseudo) Delivery of Drugs

PROJECT

Drug delivery to the Central Nervous System (CNS) is limited by complex biological barriers generally termed the blood-brain barriers (BBB).The nanotechnology-enabled innovation to be developed in INTREPIDUS is a drug delivery system that will lay the foundations for a new route of administering drugs to the CNS. This new concept is called pseudodelivery and is based on a patented implantable device able to put in touch target molecules present in the Cerebrospinal Fluid (CSF) with drugs infused inside of the device. This is achieved by means of a smart architecture of selectively-permeable nanoporous membranes that allow the influx of small molecules (targets) at the time of preventing the efflux of therapeutics of larger molecular size (nanosieve). Acting directly on the CSF is expected to be highly effective while no immune responses are expected from biological drugs as they do not enter in contact with cells (immunoisolation). Thus, the ultimate aim is to change the paradigm of route of administration of drugs for a wide number of neurological conditions: from peripherally delivered to intrathecally pseudodelivered. Specifically in this project, we will develop and test an intrathecally implantable device to be used in combination with two types of drugs: enzymes and antibodies. The project is composed of interconnected work packages aimed at refining the design of the device, manufacturing all components, and assembling the prototype. Proof-of-concept is being shown at multiple levels: in vitro, ex vivo (human and mice CSF) and in vivo. Strategies to optimize biocompatibility and biofouling of nanoporous membranes are implemented throughout the project since membranes need to be fully biocompatible and remain operational for the long term.

COORDINATOR

Manuel Menéndez González,FINBA, Spain

PARTNERS

Mihail Barboiu, Institut Européen des Membranes (CNRS), France
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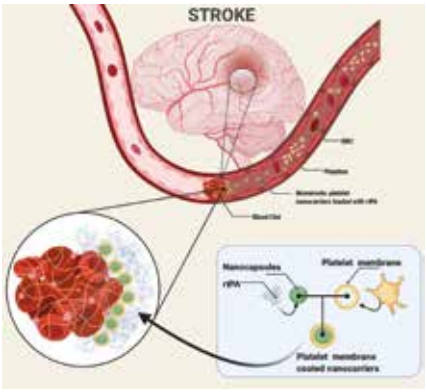
Tomasz Ciach,Warsaw University of Technology (WUT), Poland
Katarzyna Leczycka-Wilk, NanoSanguis Ltd., Poland
Mabrouk Mostafa, Egypt National Research Centre (ENRC), Egypt

CALL 2020

PLATMED: Biomimetic platelet-derived nanomedicines for treatment of thromboembolic stroker

PROJECT

Stroke is a disease that occurs unexpectedly and has a disastrous outcome. Approximately 15 million people will experience a stroke episode every year worldwide, of which 33% are left with a permanent disability, whereas 40% of cases will result in death. Thrombolysis with intravenous recombinant tissue plasminogen activator (rtPA) is the only approved drug treatment for patients with acute ischemic stroke, but its use is limited by a narrow therapeutic window, selective efficacy, and haemorrhagic complications.The main ambition of the PLATMED project is to fabricate a new model of "smart" nanomedicines in order to improve the thrombolytic efficacy of rtPA, reduce the risk of systemic bleeding and haemorrhage, and evaluate the recanalization rate by imaging techniques. This innovative strategy is expected to improve the outcome of rtPA-treated stroke patients, increase the therapeutic time-window, and thus the number of stroke patients that can benefit from this treatment.



COORDINATOR

Francisco Campos Pérez, Health Research Institute of Santiago de Compostela (IDIS), Spain.

PARTNERS

Beatriz Pelaz, University of Santiago de Compostela (USC), Spain.
Denis Vivien, University Caen-Normandy, GIP Cyceron, France.
Dusica Maysinger: McGill University, Canada.
Op2Lysis company, France.

PUBLICATIONS

Correa-Paz, C., da Silva-Candal, A., Polo, E., Parcq, J., Vivien, D., Maysinger, D., Pelaz, B., and Campos, F. (2021). New Approaches in Nanomedicine for Ischemic Stroke. Pharmaceutics, 13(5), 757. https://doi.org/10.3390/pharmaceutics13050757

2^2-INTRATARGET: Nanocarriers to deliver antibodies towards intracellular targets in cancer cells/TAMs at primary/metastatic sites

PROJECT

2^2-INTRATARGET The use of antibodies in clinical oncology has represented a key breakthrough for the treatment of cancer. More than 30 mAb are already in the market, including immune checkpoint blockade (ICB) treatments. Despite the advances, these new treatments have failed to deliver according to the expectations. This is in part due to the inadequate tissue biodistribution of mAb and, hence, to their associated side effects. In addition, the use of mAbs has been so far restricted to extracellular targets, whereas hundreds of important intracellular oncoproteins inside cancer cells or immune-related cells, still remain "undruggable". In this context, we envisage the implementation of nanotechnology as great opportunity to make these targets druggable by facilitating the intracellular delivery of antibodies in the target tissues.

Thus, the objective of this 2^2-INTRATARGET proposal is to address these challenges by engineering Multifunctional Polymeric Nanocarriers (MPNs) with the capacity to deliver antibody-based entities inside cancer cells or tumor associated macrophages (TAMs) in two different tissue compartments, the primary tumor and its metastatic niche (i.e. lymph nodes). The selected active candidates are full monoclonal antibodies (mAb), minibodies (mini-Abs) and nanobody-fused-proteins (nAb-FP) against specific targets, KRAS, STAT3 and TGF-b, which represent key pathways for tumor proliferation, metastatic spread and immune evasion. Some on-going clinical trials have been initiated to block extracellularly TGF-b or to inhibit KRAS or STAT3 using small molecule inhibitors or siRNA approaches, however their effective inhibition has still not been successfully achieved. We expect that the effective implementation of these combination therapies will have a dramatic impact towards the cure of lung tumors resistant to immunotherapy and in metastatic cancer.

COORDINATOR

María José Alonso Fernández, Instituto de Investigación Sanitaria de Santiago de Compostela (IDIS), Spain

PARTNERS:

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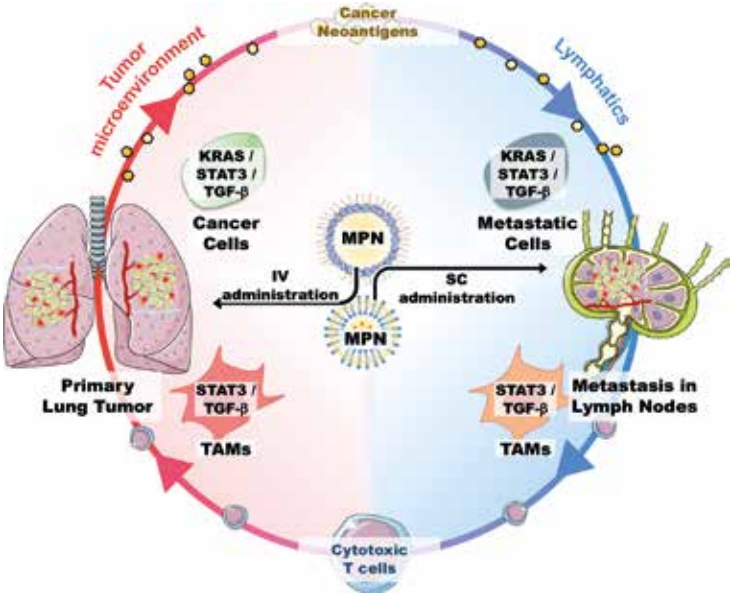
Alfonso Calvo, University of Navarra (UNAV), Spain
Ruth Schmid, SINTEF Industry, Norway
Jean-Christophe Rain, HYBRIGENICS SERVICES, France

In the first year of the project, we have synthesized the first antibodies for the relevant targets. Plasmids have been validated and antibody selection is ongoing. We have also progressed on the formulation of nanostructures with model-nanobodies, showing promising results in terms of cellular internalization both in cancer cells and macrophages in vitro. We are also working on the optimization of the in vivo models of lung cancer for the subsequent phases of the project.

This 2^2-INTRATARGET project allowed us to build a solid EU-consortium of 5 partners with complementary expertise in the fields of Nanomedicine, Antibodies and Cancer Immunotherapy. We have designed a working plan comprising: (i) development of antibody-based entities, mAb, miniAb and nAB-FP against selected targets; (ii) engineering and characterization of MPNs loaded with antibody-based entities; (iii) in vitro screening of MPNs using 2D and 3D models; (iv) in vivo antitumoral efficacy; (v) in vivo PK/BD studies and preliminary toxicology studies.



TRANSLATION OF RESULTS

Collaboration of the company Libera Bio in the context of mAb anti-KRAS. The company is now extending the knowledge and facing the advanced preclinical development phase

Overall, the major innovations are related to the provision of new nanotechnological formulations allowing the intracellular activity of antibodies. As a proof of concept, we expect to develop therapeutic entities to target and inhibit KRAS, STAT3 or TGF-b intracellularly in cancer cells or the last two inside TAMs, with implications for the treatment of solid tumors.

RAIN - Radiotherapy-Activated Immunomodulating Niches

PROJECT

Glioblastoma (GBM) is one of the deadliest types of cancer, and new treatments in the last decades have had little impact on patient survival. Immunotherapy tries to activate the host immune system against the tumor and it is considered a key opportunity to provide a real breakthrough in glioblastoma treatment. Unfortunately, GBM is poorly immunogenic and is characterized by an immunosuppressive environment, rendering immunotherapy ineffective and highlighting the urgent need for innovative approaches.

The RAIN project starts from the understanding that radiotherapy, used in the first-line treatment of glioblastoma, has a direct immune effect caused by the release of tumor antigens in the tumor microenvironment by dying cells. Still, this immune stimulation alone is insufficient to provide anticancer effects due to the profound immunosuppression of the GBM microenvironment. RAINs are delivery systems for local implantation at the GBM resection cavity consisting of nanoparticle-delivered immune stimulating molecules and RNA inhibitors against immunosuppressive pathways aimed at boosting the antitumoral effects of radiation and immune checkpoint inhibitors. The delivery of these molecules in nanostructured formulations is a critical element, because these drugs, although very potent, have important pharmaceutical limitations: (a) they can be toxic if spread around the bloodstream, (b) they require stabilization of long-term effects and (c) they have to reach intracellular targets.

The RAIN team will first identify photon radiotherapy protocols that generate the most effective immune responses and simultaneously design different types of nanomedicines for immune activation. Then, the team will study the antitumoral effect of the prototypes in combination with radiotherapy and with the immune checkpoint inhibitor anti-PD-1 in different glioblastoma models in an effort to move these nanomedicines towards a clinical translation.

COORDINATOR

Marcos Garcia-Fuentes, Instituto de Investigaciones Sanitarias de Santiago de Compostela (IDIS), Spain.

PARTNERS

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Long-Sheng Lu, Taipei Medical University and Taipei Medical University Hospital, Taiwan
Bernard Gallez, Université Catholique de Louvain (UCLouvain), Belgium
Ilaria Marigo, Istituto Oncologico Veneto-IOV-IRCCS, Italy

GLEBioassay - Nano-Monitoring of Cancer Immunotherapy Efficiency: The Graphene Lateral Electrophoretic Bioassay platform

PROJECT

GLEBioassay aims to develop a multiplexed point of care nanobiosensing platform to monitor the efficacy of the naxitamab-based immunotherapy in neuroblastoma. Naxitamab is a humanized anti-GD2 monoclonal antibody elicitor of the complement dependent toxicity and the antibody dependent cellular cytotoxicity. It is less immunogenic and more effective than previous chimeric antibody-based immunotherapies and FDA has recently approved its use against refractory/relapsed high-risk neuroblastoma. Some patients can develop human anti-human antibodies (HAHAs), thus provoking the deferment or suspension of the therapy. Conversely, this treatment induces in some patients a vaccine effect, when they start producing their own anti-GD2 antibodies. Currently, there is no standardized and accurate method to determine naxitamab, HAHAs and anti-GD2 in patients undergoing therapy. In this context, the main goal of the project is to develop a novel platform to monitor the pharmacodynamics and pharmacokinetics of naxitamab in real samples, yielding the results in one step.

Based on our previous expertise and two recently patented technologies, GLEBioassay will bring an electrophoretical paper-based portable platform with an electrochemical readout for multiplexed immunosensing. In contrast to lateral flow systems where the sample runs through capillarity with optical detection; in our approach the mobility is ruled by electrophoresis enabling a continuous flow, separating its components and cleaning the whole pad. On the other hand, we will use a fast stamping method of laser scribed graphene nanofilms. This technique allows an electrochemical detection using antibodies tagged with electroactive nanoparticles with the advantage of a lower limit of detection and more accurate results. Due to the versatility of the proposed platform, the outcome of the project can also be applied to different scenarios or other immunotherapies where a fast and efficient point of care biosensor is needed.

COORDINATOR

Arben Merkoçi Hyka, Fundació Institut Català de Nanociència i Nanotecnologia, Spain.

PARTNERS

Carlos Javier Rodriguez Hernández, Fundació Privada per a la Recerca i la Docència Sant Joan de Déu (FSJD), Spain

Serhat Sev.Nehir Biyoteknoloji Ltd., Turkey

Michal Otyepka, Palacký University Olomouc (UP), Czech Republic

QUPID - Quantitative and storage-stable point-of-care diagnostic device

PROJECT

Malaria, a parasitic disease caused by different species of Plasmodium, is a leading cause of mortality in many developing countries and a public health concern worldwide. The World Health Organization (WHO) has launched an ambitious plan to eradicate malaria that will require population screening, which is not feasible with current diagnostic tools. Nowadays, malaria point-of-care (POC) testing relies on rapid diagnostic tests (RDTs), which are easy to use but display insufficient sensitivity. Other unmet needs are the generation of a quantitative response, a robust and reproducible production path, and long-term stability under a wide range of temperatures and humidity conditions.

Responding to this challenge, this project aims to develop a cost-effective analytical system that, by exploiting synthetic receptors and tags, will exhibit long-term storage stability, and fast and quantitative malaria diagnosis with minimal user intervention, facilitating remote interpretation.

A multidisciplinary consortium has been assembled to tackle this goal by integrating the know-how of its members. Magnetic nanobeads (MNB) will be used to optimize fast and sensitive single-step bioassays, in which: i) synthetic receptors selected and produced in vitro will substitute antibodies (Ab) to improve room temperature storage stability, and ii) electroactive nanotags (ENT) will substitute enzyme labels to reduce sample matrix interference and provide rapid direct detection. Handling will be minimized by using economical paper microfluidic electrodes to automate the assay, while a customized hand-held electrochemical platform will deliver quantitative and robust results.

The system, which should reach TLR4 by the end of the project, will provide a fast diagnosis from whole blood and include the elements for automated operation with little user handling. Moreover, although initially oriented to malaria diagnosis, similar technology could be employed in future in other medical fields.

COORDINATOR

Eva Baldrich, Vall d'Hebron Hospital Research Institute (VHIR), Spain

PARTNERS:

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Una Rieksina, University of Latvia, Latvia
Sibel Ozkan, Ankara University, Turkey
Pierre-Emmanuel Doulain, SON - Synthesis Of Nanohybrids, France

ECM-CART- LDL-like nanoparticles for CAR-T-based glioblastoma immunotherapy

PROJECT

This project aims to demonstrate that the targeted delivery of exogenous antigens to the extracellular matrix (ECM) of brain tumors provides a safe and specific target for chimeric antigen receptor T-cell (CART) for the treatment of glioblastoma (GBM). GBM is the most common brain tumor in adults and despite all the advances combining surgery, chemotherapy and radiotherapy, it is still a disease with no cure. CART therapy is one of the most promising approaches in the treatment of GBM. The main obstacle limiting CART efficacy is the scarcity of highly expressed tumor antigens in GBM. In this regard, the ECM could provide a niche for abundant antigens suitable for activating CART; nonetheless, as these antigens are also present in healthy tissues, including the brain, a direct target by CART would lead to severe side effects.

In this project, we hypothesize that the components of the ECM could become ideal targets for CART therapy if labelled with FITC-peptides, enabling a tumor treatment using CART directed to FITC (FITC-CART). Therefore, we propose to deliver FITC-peptides to the ECM by incorporating these conjugates in small nanoparticles that mimic low-density lipoproteins (LDLNP), taking advantage of the known capacity of LDL to accumulate into brain tumors. The nanoparticle-based delivery of exogenous antigens will promote local accumulation of antigens in the tumor avoiding unspecific antigen build-up in healthy organs, which will result in the activation of CART only at the ECM of brain tumors.

This project describes an original approach for the treatment of GBM using CART therapy. Building upon the collective expertise of the consortium, this project will 1) Identify new peptides with selective affinity for the ECM of brain tumors; 2) synthesize FITC-peptide loaded LDLNP 3) deliver and release the FITC-peptides at the tumor ECM 4) produce and deliver FITC-CART to ECM 5) study the efficacy of the CART activated by FITC-peptides in GBM animal models.

COORDINATOR

Pablo Hervella, Health Research Institute of Santiago de Compostela, Spain
PARTNERS:
Anat Globerson Levin, Tel Aviv Sourasky Medical Center (TAS), Israel
Jacobo Cruces, GalChimia S.A., Spain
Dinorah Friedmann- Morvinski, Tel Aviv University (TAU), Israel
Tambet Teesalu, University of Tartu, Estonia

OASIs - Targeting OsteoArthritis with Senolytic and anti-Inflammatory peptide-loaded nanopharmaceuticals

PROJECT

Osteoarthritis (OA) is the most common form of arthritis and a leading cause of pain and disability worldwide. Current treatments are limited to symptom relief. There is an urgent need to develop innovative therapeutic strategies that aim to restore joint function for the benefit of millions of people worldwide. Major limitations relate to the complexity of the underlying pathogenic mechanisms for the different clinical phenotypes, and even more for the unmet need for efficient delivery strategies. OA treatment might be attained by personalizing care, accompanied by the development of targeted therapeutics that can successfully be delivered making use of nanotechnology.

We aim to develop innovative nanopharmaceuticals based on the association of peptides that target senescence and inflammation to nanoemulsions that can safely be administered to the synovial joint via intra-articular injection, and provide sustained and long-lasting, symptom and structure modification, for the enhanced treatment of OA.

Interfering peptides targeting senescent cells can modulate tissue regeneration and response to injury. Anti-inflammatory peptides from biological venoms have shown to reduce inflammation and pain. In this proposal we will develop new combinatorial targeted therapies by loading these peptides into biocompatible and biodegradable, safe-by-design and versatile, lipid nanoemulsions. The most promising combinations will be assessed in vitro, ex vivo and in vivo. Optimization of critical formulation parameters, nuclear imaging tracking, and pharmacokinetic studies, will allow to select a nanopharmaceutical composition for preclinical evaluation. The results obtained in this proposal will help us to make state-of-the-art advances in order to successfully advance our research to the clinic. Attention to critical manufacturing processes, exploitation, dissemination and managerial activities will ensure translatability of the candidate nanopharmaceuticals.

COORDINATOR

María de la Fuente, Fundación Instituto de Investigación Sanitaria de Santiago de Compostela, Spain

PARTNERS

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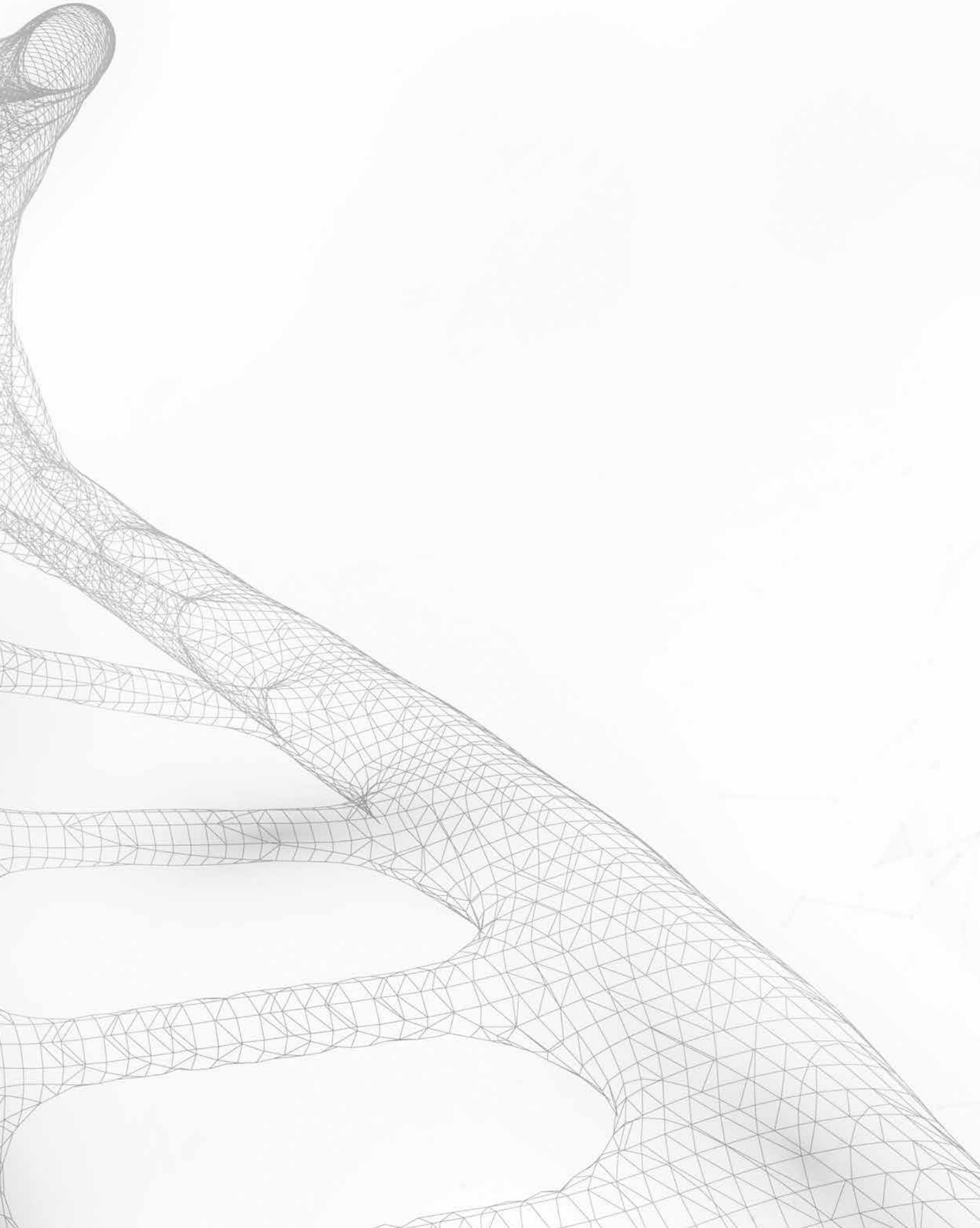
Franck Pavan, V-NANO, France
Luminita Labusca, NATIONAL INSTITUTE OF RESEARCH AND DEVELOPMENT FOR TECHNICAL PHYSICS (NIRDTP), Romania



Projects with Spanish partners

CALL 2017

AMI: Antidrug-antibody and drug Molecular detection in Inflammatory diseases with organic electronics platform

PROJECT

The vision of AMI is a nanoscale label-free platform for the assessment of the immune reaction against biologicals targeted at inflammatory pathologies. The AMI platform is based on arrays of label-free electrolyte-gated organic field effect transistors with multiple gates functionalized either with the target biomarker for specific antidrug-antibody (ADAs) recognition, or with ADAs for dosing the circulating drug in patient fluids. The role of LEITAT in the project has aided the integration of a user-friendly microfluidic interface (also called microfluidic cartridge) to enable the non-specialist to operate the platform. LEITAT has also developed a portable and ergonomic device to improve the acceptance by potential end users. This point-of-care device incorporate a pre-programmed series of micropumps and microvalves to carry out the sequential recognition and rinsing of the ADAs in whole blood. LEITAT has improved the portability of the whole system and has developed an aliquot dispensing system to control it. Based on the results obtained during the project and the feed-baked collected from all the partners, LEITAT has tested the portable device outside of the laboratory to be tested in real hospital situation employed by the practitioners, medical staff and other end-users.

COORDINATOR

Fabio Biscarini, Università degli Studi di Modena e Reggio Emilia, Italy

PARTNERS

Jordi Ricart Campos, LEITAT, Spain
Paolo Samorì, Université de Strasbourg, France
Pablo Fanjul Bolado, DropSens S.L, Spain
Robert Zimmer, ImmuPharma, France

PUBLICATIONS

We have 3 posters presentation in conferences.

TRANSLATION OF RESULTS

Provide microfluidic cartridges and the automated point-of-care device to the partners for the hospital implementation

EXIT: Exosomes Isolation Tool with nanofluidic concentration device

PROJECT

Around 2 million patients in Europe, Japan and the US are annually diagnosed with Alzheimer's disease (AD). At present, there is no effective therapy. There is an urgency to improve our understanding of the early pathogenesis of AD. Evidence is growing that transcriptomic, metabolic and immunologic changes are preceding the amyloid and tau pathology characterizing AD. One of the major hurdles hampering progression of research is that there is a paucity of brain tissue in early stages of disease. Recently exosomes have gained a significant interest in the research community due to their ability to pass the blood-brain barrier. The presence of these nanoparticles in body fluids such as blood, urine and saliva make them an appealing resource for non-invasive etiologic and diagnostic research that can be translated into preventive and therapeutic interventions. Technology for precise, high-throughput isolation of exosomes from complex body fluids is pre-requisite, but is currently lacking. The aim of this project is to develop a beyond the state-of-the art nanotechnology driven analytical platform for isolation of exosomes and use this platform to investigate metabolic, proteomic, immunologic and transcriptional changes in AD. Our novel electrodriven separation and fractionation method ? nanochannel induced ion depletion zone isotachophoresis ? will be employed for fully controllable isolation of exosomes and their use for biomarker discovery in Alzheimer's disease. EXIT will integrate nanotechnology, transcriptomics, genetics and metabolomics with large existing EU biobanks, enabling to investigate large sample cohorts of blood and paired cerebrospinal fluid (CSF) and blood. Within EXIT nanotechnologists, analytical chemists, biologists, geneticists, epidemiologists and clinicians will work together to make the long-awaited breakthrough in exosome isolation and rapidly translate this breakthrough into etiologic, preventive and therapeutic applications.

COORDINATOR

Thomas Hankemeier, Leiden University, The Netherlands

PARTNERS

Elizaveta Vereshchagina,SINTEF, Norway
Antonio Chiesi, HansaBioMed Life Sciences, Estonia
Cornelia Van Duijn, Erasmus Medical Center Rotterdam, The Netherlands
Agustín Ruiz, Fundació ACE. Institut Català de Neurociències Aplicades, Spain

CALL 2017

ARROW-NANO: New Approaches to Rare Respiratory Orphan fibrotic diseases With locally administered targeted NANOparticles

PROJECT

The present project aims at developing a new treatment of two rare severe respiratory disorders, bronchiolitis obliterans syndrome (BOS) and Systemic Sclerosis-Interstitial Lung Disease (SSC-ILD) by using nanovectors loaded with drugs and targeted specifically to diseased cells. Conventional systemic treatments of these fibrotic disorders are poorly effective due to insufficient drug accumulation, limited efficacy and high toxicity. We have demonstrated in vitro that drugs loaded into specifically targeted (coated with anti CD44 antibody) gold nanoparticles (GNPs) were more effective in inhibiting primary pathological cells (from BOS and SSC-ILD) than lone drugs, without affecting normal airway epithelium. The same GNPs administered to normal mice by inhalation selectively localized in the lungs without peripheral toxicity. When tested on a mouse model of pulmonary fibrosis (intratracheal administration) these GNPs were effective in preventing pulmonary fibrosis. However, long-term treatment might result in accumulation of GNPs in macrophages suggesting that chronic administration may cause excessive gold store. The aim of this project is to engineer novel, fully biocompatible targeted nanovectors (liposomes) that can be safely and repeatedly administered by inhalation. To do this, consortium will: 1) manufacture liposomes functionalized with ligands targeting CD442) screen in vitro efficacy/toxicity of the novel liposomes compared with lone drugs or drug loaded-GNPs3) determine biodistribution, efficacy, and toxicity of the novel liposomes in animal models of BOS and SSc-ILD4) plan a translation from the bench results to phase I clinical trials in both diseases. This project takes advantage of the complementary competences of the partners and their already existing collaboration. The design and fabrication of nanovectors bears high innovation potential and the consortium has already foreseen intellectual property rights protection and commercialization.

COORDINATOR

Federica Meloni,IRCS Policlinico San Matteo Foundation, Italy

PARTNERS

Elias Fattal, Centre National de la Recherche Scientifiques (CNRS), France
Santos Castañeda, Hospital Universitario de la Princesa, IIS-IP, Madrid, Spain
Walter Klepetko, Medical Universiy of Vienna, Austria

TEMPEAT: Temperature-responsive polypeptide nanocarriers for abdominal therapies

PROJECT

We envisioned that an ELP-micelle with encapsulated chemo-drugs in combination with photosensitizers can further induce synergetic effects compared to a mono-therapy, especially in in vivo treatments. Together with a selected nanobody for a specific tumor, functionalized ELPs can recognize and selectively destroy the target while limiting damage to other normal tissues. The rational strategy can be described as: (1) intraperitoneally administered ELP micelles, with the decorated VHHs, will localize at the targeted tumor, allowing close contact of photosensitizers with cells. (2) Tumor sites will be irradiated by NIR light to induce the production of oxygen radicals that selectively kill the cancer cells that the ELP particles are binding. (3) Further washing steps with cold solutions will induce the disassembly of ELP micelles to release chemo-drugs for further treatment.

In the final report we describe our achievements in creating these responsive ELP micelles. In section A the development of suitable photosensitizers is described which can be integrated with the ELP micelle system. B reports on the successful conjugation of the photosensitizer to the ELP. C deals with the selection and incorporation of suitable targeting ligands. Section D and E, finally, describe the integration of the different components and the in vitro and in vivo assessment of the efficacy of these multifunctional and responsive particles.

COORDINATOR

Jan C.M. van Hest, Eindhoven University of Technology, The Netherlands

PARTNERS

Leon Masuger, Radboud UMC/Radboud University, The Netherlands
Tomas Torres,UNIVERSIDAD AUTONOMA DE MADRID, Spain
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Catelijne Stortelers, Ablynx, Belgium

PUBLICATIONS

Ibrahimova, V., González-Delgado, J. A., Levêque, M., Torres, T., Garanger, E., and Lecommandoux, S. (2021). Photooxidation Responsive Elastin-Like Polypeptide Conjugates for Photodynamic Therapy Application. Bioconjugate chemistry, 32(8), 1719–1728. https://doi.org/10.1021/acs.bioconjchem.1c00251

Ferreira, J. T., Pina, J., Ribeiro, C., Fernandes, R., Tomé, J., Rodríguez-Morgade, M. S., and Torres, T. (2020). Highly Efficient Singlet Oxygen Generators Based on Ruthenium Phthalocyanines: Synthesis, Characterization and in vitro Evaluation for Photodynamic Therapy. Chemistry (Weinheim an der Bergstrasse, Germany), 26(8), 1789–1799. https://doi.org/10.1002/chem.201903546

Lo, P. C., , Rodríguez-Morgade, M. S., , Pandey, R. K., , Ng, D., , Torres, T., , and Dumoulin, F., (2020). The unique features and promises of phthalocyanines as advanced photosensitisers for photodynamic therapy of cancer. Chemical Society reviews, 49(4), 1041–1056. https://doi.org/10.1039/c9cs00129h

TRANSLATION OF RESULTS

Inventors: Lecommandoux,S., Garanger, E., Ibrahimova, E., Torres Cebada,T., and González Delgado, J. A.

Title: Bioconjugate comprising a photosensitizer unit, method for its preparation and use thereof.

Organization: European Patent Office

Code: EP21305116.2

Date: 29/1/2021

Priority country: Europe

Extended countries: Europe

CALL 2018

NANO-VERTEB: Next generation Antibacterial Nanostructured Osseointegrated customized VERTEBRAL replacement

PROJECT

Vertebral body replacement represents one of the most challenging and invasive procedures. Even though modern surgical techniques for en bloc resection of vertebral body are consolidating, this procedure is burdened by high complication rates (45.5%) as surgical site infections, that are critical and difficult to treat, poor bone regeneration and mechanical instability, also correlated with infections.

NANO-VERTEBRA project proposes a breakthrough approach to realize customized prosthesis to replace vertebral bodies affected by tumors or major traumatic events, specifically engineered to reduce infections and increase patients' surgical options.

The project proposes to implement personalized vertebral prosthesis, by combining nanostructured antibacterial and ceramic coatings to prevent infections and to promote fast and effective bone regeneration. An optimization of implant architecture by 3D modeling and additive manufacturing technologies will be also performed to maximize coverage of the prosthesis by nanocoatings, boost integration, and guarantee suitable mechanical properties and to be patient specific.

COORDINATOR

Milena Fini, IRCCS-IOR Istituto Ortopedico Rizzoli, Italy

PARTNERS

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Tung-Wu Lu, National Taiwan University, Taiwan

PUBLICATIONS

Girolami, M., Sartori, M., Monopoli-Forleo, D., Ghermandi, R., Tedesco, G., Evangelisti, G., Pipola, V., Pesce, E., Falzetti, L., Fini, M., and Gasbarrini, A. (2021). Histological examination of a retrieved custom-made 3D-printed titanium vertebra : Do the fine details obtained by additive manufacturing really promote osteointegration?. European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society, 30(10), 2775–2781. https://doi.org/10.1007/s00586-021-06926-w

TRANSLATION OF RESULTS

Development of a custom-made implants service for vertebral body replacement

CALL 2019

NAN-4-TUM: Development of CXCR4 targeting-nanosystem-probes for molecular imaging of cancer cells and tumor microenvironment

PROJECT

Molecular tumor imaging still faces criticisms in sensitivity, specificity, spatial resolution and depth penetration. The use of nanoparticles as imaging agents overcomes cancer-imaging limitations. Nanoparticles offer an important additional advantage compared to traditional imaging agents, i.e. theranostic capability to combine diagnosis and therapy. CXCR4 is a key factor for tumor growth and metastasis in several types of human cancers. The development of a PET-nanosystem probe targeting CXCR4 in solid tumors with higher sensitivity will allow praecox detection of primary and secondary lesions of CXCR4 overexpressing tumors. The selected probe is a selective antagonistic peptide leading to CXCR4 signaling blockade, which allows the specific targeting of solid tumors, but regression of malignant lesions as well. The members of the consortia have designed and produced self-assembly supramolecular dendrimers and pegylated liposomes with excellent physicochemical properties for the in vivo delivery, which are currently being conjugated to the CXCR4 antagonistic peptide and PET tracer. We have selected breast, colorectal, gastric and pancreatic cancer tumor types to be targeted with the nanoparticles according CXCR4 expression and tumor burden (incidence and mortality). Accordingly, we are testing the cell autonomous (epithelial tumor cells) and non-cell autonomous (immune system) therapeutic potential of CXCR4 antagonistic peptide both in vitro an in vivo in these tumor types.

COORDINATOR

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PARTNERS

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TRANSLATION OF RESULTS

The results from this project have the potential to improve cancer diagnosis and treatment. Cancer continues to be a major health problem for the European population, with about three million new cases diagnosed every year. The translation of the results is considered by means of the First in Man clinical trial in patients with solid tumors using CXCR4-PET-NAN probe (project aim 3, work package 3).

Additionally, the exploitation will be evaluated during the scope of the project and will include a prior patentability analysis and a valorization plan. Patenting will be the first protection option to be considered and will be performed after a proper freedom-to-operate analysis. This work will be conducted with the legal departments of the respective partners, who will evaluate the patentability of the project outcomes and will provide full consulting services to ensure that the project exploitability is maximized. After intellectual property protection, different transferability actions will be considered, depending the TRL achieved after project closure. In case the consortium is not able to directly market the resulting technology, licensing will be sought to a third entity which is capable of pushing the results to the next level, including regulatory approval, large scale manufacturing and commercialization. Alternatively, the interaction with potential investors or interested stakeholders could provide additional financing to complete de development. Finally, the creation of a spin-off company to raise capital could also be considered with the same purpose.

CALL 2019

ENAMEP: Exosomes as innovative Nanomedicine Approaches to reverse obesity and its MEtabolic and Psychotic complications with specific targeting of the hypothalamus

PROJECT

This program will establish an innovative exosome-based nanomedicine approach challenging obesity-related diseases. Controlling central regulation of obesity through this approach would spawn the definition of new strategies to monitor efficacy of therapy with minimal side effects. The use of these exosomes is the only way to target specific hypothalamic area by intravenous delivery, making them affordable for therapeutic use.

Genetic ablation or loss of function of AMP-activated protein kinase alpha 1 (AMPK1) in steroidogenic factor 1 (SF1) neurons of the ventromedial nucleus of the hypothalamus (VMH) induces feeding-independent resistance to obesity due to sympathetic activation of brown adipose tissue (BAT) thermogenesis. Here, we show that body weight of obese mice can be reduced by intravenous injection of small extracellular vesicles (sEVs) delivering a plasmid encoding an AMPK1 dominant negative mutant (AMPK1-DN) targeted to VMH-SF1 neurons. The beneficial effect of SF1-AMPK1-DN-loaded sEVs is feeding-independent and involves sympathetic nerve activation and increased UCP1-dependent thermogenesis in BAT. Our results underscore the potential of sEVs to specifically target AMPK in hypothalamic neurons and introduce a broader strategy to manipulate body weight and reduce obesity.

COORDINATOR

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PARTNERS

López Pèrez Miguel Antonio, University of Santiago de Compostela, Spain
Johan Anders Fernø, Haukeland University Hospita, Norway
Marc Gregòire, INSERM, France

PUBLICATIONS

Milbank, E., Dragano, N., González-García, I., Garcia, M. R., Rivas-Limeres, V., Perdomo, L., Hilairet, G., Ruiz-Pino, F., Mallegol, P., Morgan, D. A., Iglesias-Rey, R., Contreras, C., Vergori, L., Cuñarro, J., Porteiro, B., Gavaldà-Navarro, A., Oelkrug, R., Vidal, A., Roa, J., Sobrino, T., ... López, M. (2021). Small extracellular vesicle-mediated targeting of hypothalamic AMPK1 corrects obesity through BAT activation. Nature metabolism, 3(10), 1415-1431. https://doi.org/10.1038/s42255-021-00467-8

TRANSLATION OF RESULTS

Inventors: Milbank E, Martínez MC, Andriantsitohaina R and López M
Title: Populations of small extracellular vesicles for use in the treatment of obesity
Organization: European Patent Office
Code: P201130250
Date: 17/8/2021

CALL 2019

GLIOSILK: Nano-trampa implantable de fibroína de seda para el tratamiento del glioblastoma

PROJECT

Brain-tumor glioblastoma (GB) is still considered as one of the worst unmet clinical need in spite of implementation of the therapeutic arsenal available and recent developments in nanomedicine and immunotherapy. With inevitable relapse its prognosis remains devastating. The reasons behind this failure are the tumor heterogeneity and the peritumoral infiltrative niche. A complex interaction between the initial tumor location, its attraction by the peritumoral microenvironment defines a heterogeneous pathway that is probably the more relevant target if we want to develop more curative therapies. In contrast with direct targeting of infiltrated cancer cells for their elimination, GLIOSILK aims to evaluate new bio-interactive interventional silk-fibroin (SF)-based nano-implants in their capability to recruit in controlled brain areas the cells submitted to a chemo-attractant SDF-1 signal. By developing biocompatible SF-based nano-scaffold and use of well mastered cross-cutting methods, the capability of newly built bio-interactive deposits to define a confined in situ gradient and to effectively trap GB cells before elimination (eg. by radiations) while ameliorating the evolution of the disease will be determined. Overall, this multidisciplinary work's purpose is to make significant breakthrough in overcoming treatment resistance in GB, and other solid tumors toward clinical transfer.

COORDINATOR

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PARTNERS

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PUBLICATIONS

Molina-Peña, R., Haji Mansor, M., Najberg, M., Thomassin, J. M., Gueza, B., Alvarez-Lorenzo, C., Garcion, E., Jérôme, C., and Boury, F. (2021). Nanoparticle-containing electrospun nanofibrous scaffolds for sustained release of SDF-1. International journal of pharmaceutics, 610, 121205. https://doi.org/10.1016/j.ijpharm.2021.121205

CALL 2019

GOTTARG: Glutamate Oxaloacetate Transaminase Nanoparticles targeted to the Brain for Neuroprotection in Ischemic Stroke

PROJECT

This project will develop and test the first targeted and long-acting nanomedicine with neuroprotective properties for ischemic stroke, and with potential application in other neurological diseases related with glutamate excitotoxicity. The Team will demonstrate that the targeted delivery of a long-acting glutamate oxaloacetate transaminase (GOT) nanoparticle to- or near to- the brain enhances the neuroprotection in a model of ischemic stroke. In addition to the design and synthesis of the nanomedicine, this project will investigate the mechanism of neuroprotection to conclude pre-clinical studies and place the Team in a position to embark upon clinical testing.

COORDINATOR

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PARTNERS

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Espen Mariussen, Norwegian Institute for Air research, Norway

PUBLICATIONS

Zaghmi, A., Dopico-López, A., Pérez-Mato, M., Iglesias-Rey, R., Hervella, P., Greschner, A. A., Bugallo-Casal, A., da Silva, A., Gutiérrez-Fernández, M., Castillo, J., Pérez, F. C., and Gauthier, M. A. (2020). Sustained blood glutamate scavenging enhances protection in ischemic stroke. Communications biology, 3(1), 729. https://doi.org/10.1038/s42003-020-01406-1

CALL 2019

nanoLight: Photosensitive nanotools for neuronal stimulation and rescue of degenerative blindness

PROJECT

The goal of nanoLight is to compensate for nervous system pathologies in which neuronal degeneration has induced a specific loss of function. Novel photosensitive nanotools (PNTs) that can be delivered to the tissue with minimally invasive microinjections and anchored target to neurons to convert light stimuli into an electrical stimulation. The project will focus on three parallel strategies exploiting both organic and inorganic PNTs.

Poly(3-hexylthiophene) (P3HT) nanoparticles (synthesized by IRCSS) have been employed as a photosensitive tool for the restauration of visual functions in a rat model of Retinitis Pigmentosa (RP). The nanoparticles have been injected in the subretinal space of the dystrophic rats with an ongoing retinal degeneration at the level of the photoreceptors. In vivo electrophysiological characterization depicted a recovery in the amplitude of visually evoked potentials and an improved visual acuity up to 240 days.

In addition to the above P3HT nanoparticles synthesized by IRCSS, P3HT nanowires, (Au-terminated poly(3,4-ethylenedioxythiophene) (PEDOT) nanowires and Au-P3HT nanorods has been developed,

iPNTs. Silicon microdiodes in suspension fabricated at CSIC has been sent to IRCCS for biocompatibility studies. In order to maximize the light trapping efficiency, the photogenerated charges separation, and the charge injection into the electrolyte solution, combining finite-difference time-domain (FDTD) simulations and semiconductor band engineering.

COORDINATOR

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PARTNERS

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Anne Labouret, SOLEMS S.A. , France
Daniel Pérez, Nanoimmunotech S.L., Spain

PUBLICATIONS

Maya-Vetencourt, J. F., Manfredi, G., Mete, M., Colombo, E., Bramini, M., Di Marco, S., Shmal, D., Mantero, G., Dipalo, M., Rocchi, A., DiFrancesco, M. L., Papaleo, E. D., Russo, A., Barsotti, J., Eleftheriou, C., Di Maria, F., Cossu, V., Piazza, F., Emionite, L., Ticconi, F., ... Benfenati, F. (2020). Subretinally injected semiconducting polymer nanoparticles rescue vision in a rat model of retinal dystrophy. Nature nanotechnology, 15(8), 698-708. https://doi.org/10.1038/s41565-020-0696-3

Munteanu, R. E., Moreno, P. S., Bramini, M., and Gáspár, S. (2021). 2D materials in electrochemical sensors for in vitro or in vivo use. Analytical and bioanalytical chemistry, 413(3), 701-725. https://doi.org/10.1007/s00216-020-02831-1

Polonschii, C., Gheorghiu, M., David, S., Gáspár, S., Melinte, S., Majeed, H., Kandel, M. E., Popescu, G., and Gheorghiu, E. (2021). High-resolution impedance mapping using electrically activated quantitative phase imaging. Light, science and applications, 10(1), 20. https://doi.org/10.1038/s41377-020-00461-x

Thesis: Yue Zhang, Opto-Magneto-Electrical Nanoactuators for Wireless Cell Stimulation, December 2020, UAB

TRANSLATION OF RESULTS

Inventors: Milbank E, Martínez MC, Andriantsitohaina R and López M

Title: Eye-injectable polymeric nanoparticles and method of use therefor

Organization: USA Patent Office

Code: US PCT 16/005,248

Date: 12/12/2019

CALL 2020

NANO4STROKE: Anti-inflammatory miRNA nNanoshuttles as therapeutic strategy for stroke

PROJECT

The goal of NANO4STROKE is to generate an innovative nanomedicine for stroke based on therapeutic miRNA carried by synthetic vesicular nanoshuttles. The strong inflammatory reaction triggered by the ischemic cascade contributes to exacerbate tissue damage. Bio-inspired artificial nanoshuttles of cerebroprotective/anti-inflammatory miRNA will be merged in one smart drug delivery nanoplatform to target the injured neurovascular unit(NVU)/blood-brain-barrier, thus releasing therapeutic miRNA where the brain microvascular endothelial cells reside and influence secondary neuroinflammatory responses. NANO4STROKE will build on the miRNA-associated therapeutic efficacy showed by biologic nanovesicles toward brain ischemia. 1/ promising subsets of therapeutic miRNA will be drawn from the miRNome of biologic nanovesicles. 2/ selected miRNA will be loaded into ad hoc brain-targeting liposomes by cutting-edge microfluidics-associated strategy. 3/ synthetic vesicular nanoshuttles will be validated in a NVU-on-chip model. 4/ the biodistribution, toxicity and functional recovery will be addressed in an aged co-morbid model of stroke. The first part of our contribution as partners in this project has been: a) the characterization of the effect of natural exosomes obtained from endothelial cells under hypoxic or normoxic conditions in vitro in a model of inflammation; b) RNAseq data of endothelial cells to identify putative targets for nanoshuttle functionalization.

COORDINATOR

Lorenza Lazzari, Department of Transfusion Medicine and Hematology, Laboratory of Regenerative Medicine - Cell Factory, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Italy

PARTNERS

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Anna M. Planas, Consorci Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Spain
Aurel Popa-Wagner, University of Medicine and Pharmacy of Craiova, Romania

CALL 2021

LIPARCI - Pre-clinical development of an acylceramide nanostructured delivery system to rescue the skin barrier in patients with ichthyosis

PROJECT

Inherited ichthyoses are rare genetic diseases (prevalence 13.3 per million people in Europe) that occur at birth. They cause abnormal thickening of the skin, dryness, scaling, redness, itching and painful skin fissures involving life-long disfigurement and social ostracism. All forms of ichthyosis lead to a defective epidermal barrier and more than half of patients shows Autosomal Recessive Congenital Ichthyosis (ARCI) in which the metabolism of ?-O-acylceramides is impaired. This lipid species and, more precisely, linoleic acid (LA) esterified to ?-hydroxyacyl sphingosine (CerEOS), are essential for building a healthy stratum corneum (SC), the outermost epidermal layer responsible for the skin barrier. Current treatments of the ichthyoses are mainly symptomatic, untargeted, often minimally effective and with significant side effects. Thus, replacement of the missing ceramides is a promising therapeutic approach. The peculiar structure of the CerEOS quintessentially containing esterified LA seems fundamental for proper skin repair. However, the low solubility and extreme lipophilicity of CerEOS are challenging for its chemical synthesis and delivery to deeper SC to reach full effect. Moreover, the nanoscale organization of the SC makes difficult the entry of substances. This justifies an approach based on nanotechnology that allows the delivery of the mentioned lipids in the place where they have their biological function. The aim of LIPARCI is to develop an innovative lipid substitution system based on synthetic LA-esterified CerEOS and LA-esterified ?-hydroxy fatty acids included in nanostructured lipid systems that will be validated for rescuing the epidermal barrier using pre-clinical in vitro and animal models of ichthyosis. LIPARCI should thus allow the future development of highly efficient pathogenesis-based therapy of ichthyoses exhibiting impaired CerEOS metabolism as a primary defect.

COORDINATOR

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PARTNERS

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Ángela Hernández-Martin, Hospital Infantil Niño Jesús, Spain

Katerina Vavrova, Charles University, Faculty of Pharmacy in Hradec Kralove, Czech Republic

Deniz Ceylan Tuncaboyl, Bezmialem Vakif University, Turkey

CALL 2021

NANOEAR - New DX243-conjugated nanoparticles as a neuroprotective drug for hearing loss

PROJECT

Because of their high prevalence, 5% of the population worldwide, an untreated decline of hearing impairments, has a profound negative impact on the affected individuals' quality of life, impeding communication, and leading to social isolation, depression, reduced physical and cognitive functions. Impaired synaptic transmission, degeneration of auditory neuron neurites, and neuronal loss characterize most of these disorders. Despite the major recent progress on hearing loss mechanisms, treatment options are mostly missing, and the economic and societal burden on healthcare systems worldwide keeps increasing. To date, the cochlear implant, which bypasses the damaged hair cells by providing direct electrical stimulation of the primary auditory neurons, is used to restore functional hearing in many patients who were profoundly deaf. However, their beneficial outcomes vary significantly among patients, often impacted by the number and functional state of auditory neurons. A therapeutic approach would allow the prevention or delay of degenerative processes is thus urgently needed.

We previously identified a new drug that is promising to restore cochlear synaptogenesis. Local administration of this drug through the tympanic membrane is a preferable option. Still, the efficacy of such a way of administration relies on the drug's capacity to remain long enough at the cochlear round window level. The objective of NANOEAR is to develop a novel nanoparticle-based pharmacologic strategy for treating deafness caused by auditory synaptopathy in a well-defined group of deaf patients suffering from Clarin-1 mutation.

WP1: Develop a unique nanoparticle formulation with DX243 and in vitro characterization

WP2: Validate the efficacy of drug-loaded nanoparticles on human-derived inner ear organoids

WP3: Provide in vivo proof of concept of the drug-loaded nanoparticles in synaptopathy preclinical models

COORDINATOR

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Coordinated by:

IBEC

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