MEDICAMENTOS INNOVADORES
Plataforma Tecnológica Española

farmaindustria

Acción experimental para el fomento de la cooperación entre compañías farmacéuticas y empresas y grupos de investigación en el ámbito de la biotecnología

XVIII Encuentro de Cooperación Farma-Biotech

Proyectos avanzados

Martes, 29 de octubre de 2019

La jornada tiene por objeto establecer un punto de encuentro para la cooperación entre compañías farmacéuticas nacionales e internacionales, empresas españolas de biotecnología y grupos de investigación, en torno al desarrollo de nuevos medicamentos innovadores.

La iniciativa diseñada por FARMAINDUSTRIA se propone a través de estas jornadas que empresas españolas y grupos de investigación de centros especializados, previamente seleccionados, expongan, ante las compañías farmacéuticas interesadas, productos en desarrollo con el potencial suficiente (***innovador, eficaz, protegido***) que pueda representar una oportunidad de cooperación para ser explorada por ambas partes.

Tras un cuidadoso estudio de necesidades expresadas por las compañías farmacéuticas y del estado de desarrollo de las investigaciones en curso en las empresas biotecnológicas y los grupos de investigación, se han seleccionado **siete propuestas** para que realicen su presentación en la jornada del martes día 29 de octubre en Madrid.

En Farmaindustria venimos siguiendo el **desarrollo de proyectos avanzados** de investigación en nuevos fármacos, tanto en centros de investigación como en pequeñas empresas biotecnológicas, y consideramos que los **siete que han sido seleccionados** para su presentación en esta jornada han alcanzado un **grado de madurez óptimo**, lo que permite estudiar posibles **acuerdos de cooperación** con la industria farmacéutica en condiciones ventajosas técnico-económicas. Consecuentemente, pensamos que esta jornada reviste especial interés para las compañías farmacéuticas invitadas, incluyendo responsables de sus **unidades de desarrollo de negocio** e inversiones.

El grado de información manejado durante la jornada se clasifica como "no confidencial" por lo que no se requiere ningún acuerdo previo al respecto.

La jornada se configura como un foro individualizado no abierto a terceras partes, y en donde se desea generar un **clima de interacción** suficiente que permita identificar el valor añadido derivado del intercambio de información entre demanda y oferta, con suficiente contenido diferencial e innovador en el ámbito de las nuevas terapias y los medicamentos avanzados.

Para cualquier duda o aclaración sobre esta jornada por favor contactar con:

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Agenda

La organización de la jornada pretende dar énfasis tanto a las *presentaciones* como a la *interacción personal* entre los asistentes, de acuerdo con la siguiente agenda:

Hora	Presentación	Estado de Desarrollo	Ponente
09:15 09:30	Recepción, contactos informales, café		
09:30 09:45	*Bienvenida y presentación de la jornada*		***Javier Urzay*** FARMAINDUSTRIA
09:45 10:15	*"Uso de agonistas selectivos de receptores Beta-3 adrenérgicos para el tratamiento de hipertensión pulmonar"*	Ensayo clínico en Fase II	***Inés García-Lunar*** CNIC-CLINIC
10:15 10:45	*"PRP-HO7: un nuevo inmunomodulador biológico"*	Validado en modelos animales	***Josep M. Aran*** Idibell (Barcelona)
10:45 11:15	*"Eficacia de nuevos antimicrobianos contra cepas resistentes de Helicobacter pylori"*	Validado en modelos animales	***Javier Sancho*** Unizar
11:15 11:45	*"Nuevo agente para tumores con desregulación transcripcional pediátricos y de adultos"*	Preclínica terminada en diciembre 2019	***Francisco Moris*** Entrechem
11:45 12:15	Café, refrescos, contactos directos		
12:15 12:45	*"Nanoconjugado humanizado antimetastático selectivo para el tratamiento del cáncer colorrectal"*	Validado en modelos animales	***Ramón Mangues*** Nanoligent (Barcelona)
12:45 13:15	*"Vacuna multivalente tuberculosis, listeriosis y neumonía basada en nanopartículas de oro cargadas con péptidos"*	Validado en modelos animales	***Carmen Álvarez*** IDIVAL
13:15 13:45	*"Método no invasivo para el diagnóstico y monitorización de pacientes diagnosticados con glioblastomas"*	Pruebas de validación en pacientes	***Inmaculada Ibáñez*** IdiPAZ (Madrid)
13:45- en adelante	*Aperitivos y refrescos. Contactos directos*		

Todas las presentaciones se harán en español, si bien la documentación escrita se dispondrá en inglés para facilidad de circulación interna entre los órganos de las compañías internacionales

Lugar de celebración: **Sede de Farmaindustria en Madrid. Calle María de Molina nº 54. 7ª planta**
Fecha: **Martes día 29 de octubre de 2019**

La Plataforma Tecnológica Española Medicamentos Innovadores cuenta con apoyo financiero del Ministerio de Ciencia, Innovación y Universidades a través de la Agencia Estatal de Investigación

PRESENTACIONES QUE TENDRÁN LUGAR EN ESTA JORNADA

CNIC

PROFILE

CNIC and **Fundació Clinic** per la Recerca Biomèdica are both co-owners of the described invention. Our research is focus on the development of new therapies and the use of noninvasive imaging (particularly magnetic resonance) for the treatment, diagnosis and monitoring of Pulmonary Hyopertension PH.

SPEAKER

Dr. Inés García-Lunar is a cardiologist trained at the Hospital Puerta de Hierro (Madrid 2007-2013) and further specialized in advanced cardiovascular imaging at the Mount Sinai Hospital (New York 2012) and translational research at the CNIC (2013-present). She currently combines her clinical work as a cardiologist at the Cardiac Imaging Department from Quirón University Hospital (Madrid) with her role as a translational researcher at the Translational Laboratory for Cardiovascular Imaging and Therapy, in collaboration with Drs. Ana García-Álvarez and Borja Ibáñez. Her research has focused on pulmonary hypertension and evaluation of right ventricular function using imaging techniques.

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PRODUCT

β3-adrenergic receptor agonists

MECHANISM OF ACTION

There are two major classes of β3AR agonists, the phenylethanolamines (comprising BRL37344, SR58611A, and CL316243) and aryloxypropanolamines (including mirabegron, cyanopindolol and CGP12177A). Distinctive pharmacodynamic properties of β3AR, such as their upregulation in disease and resistance to desensitization, suggest that they may be attractive targets for therapeutic intervention.

Like other adrenoreceptors, β3AR are coupled to G proteins. The downstream pathway activated by β3AR includes nitric oxide synthase (NOS), NO-activated guanylyl cyclase and cGMP synthesis, and increased cAMP synthesis. Loss of cGMP and cAMP signaling is a hallmark in PH. Within the pulmonary circulation, cyclic nucleotides are responsible for mediating endothelin-dependent dilatation, thereby maintaining pulmonary vascular homeostasis, but they also have salutary actions on pulmonary vascular remodeling, fibrosis, and right ventricular (RV) function.

TARGET INDICATIONS

Our research focuses in the use of β3AR agonists for the treatment of chronic pulmonary hypertension, while β3AR agonists, particularly mirabegron (Betmiga®), are currently used for the treatment of hyperactive bladder syndrome.

CURRENT STATUS

- Several experimental studies have shown that in vivo treatment with BRL37344, a β3AR agonist, improves cardiac performance and ameliorates myocardial injury in experimental

models of heart failure and ischemia-reperfusion through a nitric oxide-mediated mechanism. In pulmonary vessels from dogs and rats, ex vivo β3AR agonists produces vasodilatation.

- An experimental study in pigs (n=34) with chronic PH created by pulmonary vein banding was designed to evaluate the acute hemodynamic effect and the long-term effect of β3AR agonists on hemodynamics, vascular remodeling and RV performance in chronic PH.
- Ex vivo human experiments were performed to explore the expression of β3AR mRNA and the vasodilator response of β3AR agonists in pulmonary arteries. Single intravenous administration of the β3AR agonist BRL37344 produced a significant acute reduction in PVR, and two-week treatment with two different β3AR selective agonists, intravenous BRL37344 or oral mirabegron, resulted in a significant reduction in PVR associated with a significant improvement in magnetic resonance-measured RV performance.
- Histological markers of pulmonary vascular proliferation (p27 and Ki67) were significantly attenuated in β3AR agonists-treated pigs. β3AR was expressed in human pulmonary arteries and β3AR agonists produced vasodilatation. We are currently conducting a multicenter randomized clinical trial to assess the beneficial effect of mirabegron in patients with PH due to left heart disease.

INNOVATIVE ASPECTS

- Few therapies with high cost and limited beneficial effect are currently available for pulmonary arterial hypertension (group 1 in the current PH classification), and no pharmacological therapy has been demonstrated to have a consistent effect in PH due to left heart disease (group 2), which is the most frequent causes of PH.
- If proven beneficial, β3AR agonists would be the first pharmacological treatment for PH due to left heart disease. As previously commented, distinctive pharmacodynamic properties of β3AR, such as their upregulation in disease and resistance to desensitization, suggest that they may be attractive targets for therapeutic intervention.

IPR

Members of the consortium have a related patent, entitled "Beta-3 adrenoceptor agonists for the treatment of pulmonary hypertension" (PCT/ES2013/070611) currently granted in Japan and close to be granted in USA and Europe.

PARTNERING OPPORTUNITIES

We are interested in the collaboration with Industry to continue the development of this new therapeutic use and patent.

IDIBELL

PROFILE

Bellvitge Biomedical Research Institute (IDIBELL) is a research center in biomedicine participated by l'Hospital Universitari de Bellvitge, l'Hospital de Viladecans, the Institut Català d'Oncologia, Universitat de Barcelona and Ajuntament de l'Hospitalet de Llobregat. The research focuses of IDIBELL are cancer, neuroscience and translational medicine.

The "*Immune-inflammatory Processes and Gene Therapeutics*" team, headed by Dr. Aran, is a dynamic group integrated in the Molecular Genetics Laboratory, with specific training in the areas of human genetics, biochemistry, and molecular and cell biology, interested in translational biomedical research and focused to the study of the molecular basis of the immune-inflammatory processes.

SPEAKER

Dr. Josep M. Aran has a wide experience in the areas of molecular and cell biology, gene transfer and therapy, gained during a six year stay in USA scientific Institutions. Nowadays he is a senior researcher and Group Leader in the Molecular Genetics Laboratory (IDIBELL). He has worked extensively uncovering the molecular basis of the immune-inflammatory processes, and developing novel gene and cell therapy strategies to mitigate immune-inflammatory pathology in several animal models. He was co-founder and partner of the biotechnology company "Zyrnat Biotherapeutics, S.L." (2011-2015)

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PRODUCT

PRP-HO family: novel biologic immunomodulators

MECHANISM OF ACTION

Recently, we identified a novel biomolecule (PRP-HO7) showing powerful anti-inflammatory and tolerogenic properties. PRP-HO7-based immunomodulation acts selectively over inflammatory phagocyte precursors and is able to "reprogram" them promoting operational tolerance. Moreover, analogously to antibodies, it has a robust structure very stable in the circulation, showing high specificity, binding affinity (KD= 5-10 nM) and avidity interacting with specific receptor(s) in inflammatory mononuclear phagocytes.

Thus, PRP-HO7 and analogues, administered by subcutaneous injection at the appropriate dose and schedule, should halt inflammatory pathology, restore immunological tolerance and achieve long-term remission of established autoimmune diseases without immunosuppression. These biologics enable performing pharmacological therapy (direct PRP-HO7 administration), or cell therapy using ex vivo PRP-HO7-conditioned dendritic cells.

TARGET INDICATIONS

Acute and chronic immune-inflammatory processes and, particularly, autoimmune diseases (systemic lupus erythematosus, diabetes mellitus type I, inflammatory bowel diseases, asthma, rheumatoid arthritis, multiple sclerosis, autoimmune skin diseases (psoriasis,…), etc, and alloimmune diseases (ischemia-reperfusion injury, GvHD, rejection after organ transplantation)

CURRENT STATUS

- We have confirmed the immunomodulatory activity of both PRP-HO7 on inflammatory DCs and macrophages. In addition, we have successfully demonstrated the safety and the efficacy of low-dose, subcutaneous administration of PRP-HO7 to ameliorate autoimmune lupus nephritis in three autoimmune disease pre-clinical models: lupus nephritis (manuscript submitted), inflammatory bowel disease (IBD) and rheumatoid arthritis (unpublished results).
- Along with PRP-HO7, we are also developing a new, smaller and non-glycosilated analogue, PRP6-HO7, which shows enhanced efficacy, specificity and easier/cheaper production.
- Thus, the unique mechanism of action, specificity and efficacy of both PRP-HO7 and PRP6-HO7 shown both in in vitro studies with human immune cells (where we have developed a predictive efficacy endpoint assay for prospective clinical trials), and in pre-clinical assays (e.g., PRP-HO7 efficacy probed superior to minocycline in the IBD model, and to the anti-TNF biologic Enbrel (etanercept) in the rheumatoid arthritis model), makes them particularly suited for medical treatment to achieve and maintain remission in autoimmune diseases.

INNOVATIVE ASPECTS

- Standard anti-inflammatory medications for autoimmune diseases include anti-inflammatory drugs (corticosteroids and aminosalicylates) and immunosuppressors (cyclosporine, mercaptopurine, methotrexate). Nevertheless, none of these has proved curative and all of them have shown relevant side effects/toxicity.
- Recently, last-generation antibody-based biologics (infliximab, adalimumab, ustekinumab,...) have also been introduced. However, primary nonresponse is observed in 20–30% of patients, and another 30% of patients become refractory due to secondary loss of response.
- Thus, newer, more efficacious and safer drugs are urgently needed to significantly change the course of autoimmune conditions in many therapy-refractory patients. In that sense, PRP-HO7 and analogues are novel and stable biologic immunomodulators that have proved highly effective.
- PRP-HO7 has shown superior anti-inflammatory and tolerogenic activities, and null toxicity by periodic intradermal administration in our preclinical assays and involves a distinct mechanism of action respect to the therapeutic antibodies present in the market for autoimmune diseases.

IPR

We already have issued two European patents involving PRP-HO7 immunomodulation (EP11382240 and EP17382187). We recently requested a new European patent application for the PRP6-HO7 analogue.

PARTNERING OPPORTUNITIES

During next 3 years, we aim to overcome regulatory pre-clinical trials and reach IND file presentation. GMP standards production will be ensured for at least one of the studied analogues for the planned clinical trials (I and IIa). Thus, we will explore co-development partnership with major pharmaceutical/biotechnological companies. Once reached the clearance of Phase IIa milestone, licensing the technology to pharmaceutical companies will be explored to continue the development to reach the market.

BIFI

PROFILE

The Institute for Biocomputation and Physics of Complex Systems (BIFI) is a research center of the University of Zaragoza devoted to the study of complex systems from a multidisciplinary perspective. In this Institution, biochemists, physicists, mathematicians, computer scientists and researchers from other fields study complex systems, as well as different phenomena and processes related to them (protein folding, interacting diseases, epidemic spreading, multilayer networks, collective social phenomena, etc.)

SPEAKER

Dr. Javier Sancho is a Ph D in Chemistry (University of Zaragoza). Postdoctoral researcher (University of Cambridge: Chemical Laboratory, and Cambridge Center for Protein Engineering). Full professor of Biochemistry and Molecular Biology (University of Zaragoza). Promoter of the Institute for Biocomputation and Physics of Complex Systems (BIFI). BIFI Director in 2015-2018.

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PRODUCT

Novel antimicrobials specific against Helicobacter pylori

MECHANISM OF ACTION

We are dealing with novel small molecules that are effective in vitro against Hp-resistant clinical strains and that in a mouse model of Hp-infection reduce the bacterial load and in some mice eradicate the infection. The compounds were primarily discovered as inhibitors of Hp-flavodoxin, a protein essential for the bacteria.

TARGET INDICATIONS

Helicobacter pylori infection erradication in peptic ulcer, MALT lymphoma, atrophic gastritis, after gastric cancer resection and in first-degree relatives of individuals with gastric cancer.

CURRENT STATUS

- The compounds are effective in vitro against Hp-resistant clinical strains.
- In a mouse model of Hp-infection, they are able to reduce the bacterial load and, in some mice, to eradicate the infection, when they are administered for one week in a single daily dose uncombined with any other therapeutic agent.

INNOVATIVE ASPECTS

- The compounds are specific for Helicobacter pylori. Thus, they might not damage the microbiota as broad spectrum antibiotics do.
- So far, no resistance exist against them.
- They have shown partial efficacy when administered as a single daily dose for 7 days in absence of additional antibiotics or inhibitors of the proton pump (no combinations or more

sophisticated dosing regimens have been attempted). In contrast, standard Hp eradication regimes used worldwide simultaneously combine 2-3 broad-range antibiotics/antimicrobials with 1 inhibitor of the proton pump in optimized dosing regimens lasting for about 2 weeks and nevertheless failing in 30 % of the individuals treated.
IPR Patent recently filed
PARTNERING OPPORTUNITIES We are open to different models of beneficial cooperation.

ENTRECHEM

PROFILE

EntreChem SL is the only company in the world leveraging the power of synthetic biology and combinatorial biosynthesis with drug candidates close to clinical trials. EntreChem SL brings the promise of "polypharmacology in a single drug" closer to clinical realization, since our drugs address multiple targets and pathways, both in tumor and cancer stem cells. Drug candidates: EC-70124: next-generation Midostaurin for AML with superior metabolic and PPB profile; EC-8042: novel in class transcription reprogramming agent for tumors with transcriptional deregulation.

SPEAKER

Francisco Morís, Ph.D. in Organic Chemistry from the University of Oviedo and postdoct in The Scripps Research Institute in La Jolla (USA), worked in small US biotech companies as well as at Bristol-Myers Squibb before he co-founded EntreChem in 2005. Francisco is co-author of over 50 scientific international publications, co-inventor in over 15 patents and has raised more than 9MEUR to date from local Business Angels, Family Offices and Public Agencies.

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PRODUCT

EC-8042 - first in class agent for pediatric and adult tumors with transcriptional deregulation

MECHANISM OF ACTION

EC-8042 is a next-generation, best in class Mithramycin analog, intravenous transcription modulation agent. It has been selected from a family of mithralogs discovered by combinatorial biosynthesis of aureolic acid biosynthetic genes and produced by fermentation of a recombinant bacterial strain. EntreChem has selected EC-8042 based on its antitumoral in vitro and in vivo activity in mice xenograft models (70-90% TGI, and regressions depending on the tumor), and in the NCI hollow fiber assay as well (one of the most active compounds on record).

EC-8042 mechanism of action consist of selective binding to GC-rich DNA sequences, specifically to the site of union of transcription factors overexpressed in tumor cells, therefore exerting a synergistic effect by hitting deregulated networks and its genes. In Ewing sarcoma, however, the main target is the validated tumor driver, the transcription factor EWS-FLI1. EC-8042 brings back to normal levels the expression of key genes altered by EWS-FLI1. In liposarcoma, EC-8042 inhibits Sp1 and downregulates the Cancer Stem Cell gene signature.

TARGET INDICATIONS

Main therapeutic area is related to sarcomas: Ewing, Rhabdoid (pediatric tumors), liposarcoma (adults). Additional indications are: Prostate cancer ERG-positive and Lung cancer non-small cell.

CURRENT STATUS

- The main recent milestones consist on industrialization of the supply (recombinant strain fermentation up to 400L, downstream processing and purification by chromatography); PoC in animal models of human solid tumors (sarcomas, lung, prostate), optimized iv

schedule; 2-week toxicology studies completed (Dose Range Finding) and Pivotal toxicology studies ongoing in rat and dog.

- Pending to enter FIH trials: 28-days toxicology studies in dogs and GMP production following the industrialization protocol.

INNOVATIVE ASPECTS

- EC-8042 was selected since it shows one order of magnitude less toxicity in regulatory species than Mithramycin, providing a wider therapeutic window and opening the door to viable clinical applications of this chemical class (Mithramycin is a drug subject of intense research, including recent clinical work sponsored by the NCI). Animal PK data projects a human dose of EC-8042, with plasma levels well above those needed for therapeutic action.
- Importantly, EC-8042 downregulates the Cancer Stem Cell gene signature, while widely used anthracycline doxorubicin upregulates such signature. Targeting stem cells is an important feature that sets apart EC-8042 from traditional chemotherapy.

IPR

US: patent awarded (US 8,772,253) on Feb 28, 2014 (in force), protecting composition of matter until July 23rd, 2029. EU: patent awarded (EP2457921) on March 19th, 2014. Validated in ES, DE, FR, GB, IT, BE, DK, SE, NL, CH and IE (all in force), protecting composition of matter until July 23rd, 2029.

PARTNERING OPPORTUNITIES

Co-development until PoC in humans in exchange of an upfront fee. From PoC until approval EntreChem won´t be involved in clinical development (only in CMC if needed), and will be compensated by advanced clinical development milestones and royalties.

NANOLIGENT

PROFILE

Nanoligent SL is a recent spin-off Biotechnological Company of the IIB-Sant Pau and Autonomous University of Barcelona (UAB). The researchers that created Nanoligent intend to develop nanonjugates for the selective elimination of metastatic stem cells (MetSCs) in solid tumors and hematological neoplasias, as well as their use in the neoadjuvant setting and metastasis prevention. They are also involved in a very active collaboration with the Pharmaceutical Industry in Industrial Transfer, including Merck & Co., Lilly, Laboratorios Esteve, Pharma Mar (Zeltia) and Argon Pharma.

SPEAKER

Dr. Ramón Mangues is a Clinical Pharmacist, Postdoctoral Fellow at New York University Medical Center, Researcher of the National Health System and Translational Coordinator of the Nanomedicine Network CIBER-BBN, Member of the Scientific Committee for Clinical Translation of the French National Cancer Institute and the Internal Scientific Committee of the Josep Carreras Research Institute.

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PRODUCT

Nanoconjugate for selective antimetastatic effect in colorectal cancer treatment

MECHANISM OF ACTION

The nanconjugate (NC) T22-hProtein-oligo-FdU is an antimetastatic nanomedicine that achieves selective elimination of CXCR4+ CRC MetSCs (colorectal metastatic stem cells that overexpress the CXCR4 receptor (CXCR4+), responsible for metastatic dissemination). The targeting vector is a recombinant fusion protein produced in bacteria, containing a CXCR4 peptidic ligand, a human Protein, and terminal tags for auto-assembling as 12 nm targeting vector. The maleimido-functionalized vector is covalently bound to the genotoxic drug Floxuridine (FdU) (pentameric oligonucleotic form, thiol-functionalized). Its synthesis has been optimized for high scale production, to initiate regulatory preclinical toxicology before clinical testing. Its humanized form avoids immunogenicity.

The NC blocks metastatic dissemination by its selective internalization through the CXCR4 receptor in MetsSCs that show 20-200 fold overexpression as compared to levels of hematopoiteic stem cells (normal cells with higher CXCR4 expression). As compared to free-FdU injection, the NC increases the genotoxic damage and apoptosis, and selectively eliminates CXCR4+ MetSCs, blocking trafficking functions (peri-tumoral CXCR4+ emboli intravassation) and tumor-reinitiation capacity (spheroid culture or in vivo re-implantation after treatment) without associated toxicity, validating MetSCs as targets for clinical therapy. Its in vitro killing of CXCR4+ cells is CXCR4-dependent, whereas its antimetastic effect is higher with higher CXCR4 cancer cell overexpression

TARGET INDICATIONS

Control and prevention of metastases development in advanced colorectal cancer

CURRENT STATUS

- As compared to free FdU, repeated NC i.v. administration NC induces higher regression of established metastases and prevention of metastases in cell line and patient-derived CRC

cancer models. This yields a high % of mice completely free of metastases; while achieving in the rest of mice high reduction in foci number and size in liver, peritoneal or lung metastases, with negligible distribution, DNA damage, apoptosis or toxicity in normal tissues, including hematopoietic stem cells.

- The NC blocks MetSC trafficking functions, reducing the number of intravassated CXCR4+ tumor emboli primary tumor peri-tumoral vessels. NC treatment also reduces tumor re-initiation capacity (assess by spheroid culture or in vivo re-implantation). Both, in vitro and in vivo killing is CXCR4 dependent since cells exposed to the NC is blocked by a CXCR4 inhibitor, whereas its antimetastic effect is higher when CXCR4 cancer cell overexpression levels are higher.

INNOVATIVE ASPECTS

- This is the first selectively antimetastatic drug aimed to solve the main cause of death in colorectal cancer (CRC) patients, either as neoadjuvant therapy for metastasis prevention in CXCR4+ cancer patients with limited disease or treatment of established metastases in advanced disease, since CXCR4+ tumors associate with metastatic dissemination, relapse after treatment and poor survival.
- This NC improves the therapeutic index of targeted drugs (e.g. mAbs or low MW inhibitors of CXCR4), through highly selective drug delivery leading to selective killing of the CXCR4+ CRC MetSCs to induce potent antimetastatic effect in the absence of toxicity (classical CXC4 inhibitors induce hyperleukocytosis). No Antibody-drug conjugates targeting CXCR4+ cells have reached the market.

IPR

The protein-based nanoconjugates and nanoparticles for targeted drug delivery are protected by three patents licensed to Nanoligent. One patent protects targeting drugs to CXCR4+ cells whereas the others protect CXCR4+ cell-targeted therapeutic nanoconjugates or polypeptidic nanoparticles.

PARTNERING OPPORTUNITIES

We have public funds to initiate NC preclinical regulatory studies (RETOS). We need additional private investment to complete preclinical requirements and to initiate a Phase1 trial in CXCR4+ CRC patients. We are willing to explore collaboration with pharma companies: co-development, licensing or partnership. There is also the opportunity to develop our technology in additional tumor types among the 23 cancers showing CXCR4-dependent metastatization.

IDIVAL

PROFILE

Within Valdecilla Hospital, in Cantabria, this research group at IDIVAL has two main research topics: (1) Prepare Listeria based vaccines for prevention of infectious diseases as listeriosis, tuberculosis or pneumonia, caused by intracellular bacteria. (2) Design Listeria based nanovaccines as immunotherapies for solid tumours.

SPEAKER

Dr. Alvarez-Dominguez has a PhD in Bioch. & Mol. Biol. (UAM, Madrid, 1993). She worked as Research Associate at Washington University (Saint Louis, MO, USA, 1994-99) and Centro de Biología Molecular "Severo Ochoa" (Madrid, 1999-01). She obtained the Ramon y Cajal award (2001-06, HUMV) and a tenure-track position as Research Faculty at Instituto de Investigación Marques de Valdecilla (IDIVAL, 2006-current)

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PRODUCT

Multivalent vaccines based in gold nanoparticles coupled to peptides: tuberculosis, listeriosis and pneumonia.

MECHANISM OF ACTION

Gold nanoparticles coupled by covalent chemical linkages to two ligands, beta-D-glucose" and a short peptide 1-15 of the bacterial enzyme glyceraldehyde-3-phosphate dehydrogenase (GAPDH) (GNP-GAPDH1-15 nanovaccines). The size of the nanoparticles is 2 nm and they have homogeneous distribution on size and shape. They are non-toxic and confer stability to the two ligands, especially enzymatic stability to the peptide. This GAPDH1-15 peptide is common to three bacterial genus, Listeria, Mycobacterium and Streptococcus.

These GNP-GAPDH1-15 nanovaccines target to dendritic cells and due to common enzymatic activity and structural homology of three-bacterial genus, Listeria, Mycobacterium and Streptococcus, behave as a common virulence factor of pathogenic strains of these bacteria and presented multivalent vaccine abilities. Therefore, GNP-GAPDH1-15 nanovaccines protect against experimental models of the pathogenic strains of Listeria, Mycobacterium and Streptococcus. These multivalent nanovaccines are targeted to protect adults and especially, the elderly. They are the first example that a multivalent vaccine can simultaneously protect against three bacteria genera.

TARGET INDICATIONS

Infectious Diseases, Oncology, Reumatology, Immunology, Vaccinology.

CURRENT STATUS

- Proof of concept were performed in vivo using mice vaccinated with GNP-GAPDH1-15 of Listeria, Mycobacterium or Streptococcus and next challenged with either pathogenic strain intravenously.
- GNP-GAPDH1-15 nanovaccines and a larger peptide design GNP-GAPDH1-22 nanovaccines of Listeria presented high capacity to protect against experimental listeriosis, cutaneous (M. marinum) or lung models of mycobacteria (M. smegmatis) as well as against pneumonia caused by S. pneumoniae.

- Protection was achieved because they targeted to dendritic cells and macrophages, inducing a Th1 pro-inflammatory response and pathogen specific cytotoxic T cells.
- In vitro monocyte derived dendritic cells from listeriosis patients were activated by GNP-GAPDH1-15 nanovaccines and shifted Th2 response to a TH1 response, indicating they might be effective in experimental mice models and also in humans.

INNOVATIVE ASPECTS

- There are not available vaccines against listeriosis, neither are vaccines that can protect against cutaneous or tuberculosis mycobacteria or pneumonia caused by Streptococcus in adults.
- There are not peptide and chemically synthetic vaccines against these three bacterial genera.
- There is no multivalent vaccine able to protect against different pathogenic bacteria of Listeria, Mycobacterium or Streptococcus genera for adults and especially for the elderly.

IPR

Patent application has been presented to OEPM (P201830628) on 22/06/2018. After the year of priority, it was international extended with a PCT treaty (PCT/ES2019/070413) on 13/06/2019. We are pending for receiving the IPER to recognized the novelty and innovation capacity of the invention.

PARTNERING OPPORTUNITIES

We need a partner to invest in the developement of the product and perform a phase I clinical assay.

IdiPAZ

PROFILE

Hospital La Paz Institute for Health Research (IdiPAZ) was constituted on December 15th 2009 as a place for biomedical research between La Paz University Hospital (HULP), Fuenlabrada University Hospital (HUF), the Autonomous University of Madrid (UAM), and the Foundation for Biomedical Research of La Paz University Hospital (FIBHULP). IdiPAZ includes 55 research groups distributed in six strategic areas (Neurosciences Area, Cardiovascular Area, Infectious Diseases and Immunity Area, Organ System Pathologies Area, Cancer and Human Molecular Genetics Area, Surgery, Transplant and Health Technologies Area).

SPEAKER

Dr. Ibanez has completed her PhD from UCM, Madrid; 6 years of Post-doctoral studies from FCCC (Phil, USA) and IIB/CSIC from the National Research Council. She coordinates the experimental therapies and biomarkers group at The Sanitary Research Institution IdiPAZ, and is the Head of the Cancer Epigenetics Group at U. H. La Paz. She has published more than 30 papers in reputed journals, is the main author of five patents based on biomarkers of clinical use, (one already licensed and under exploitation)

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PRODUCT

Non-invasive method for diagnosis and monitoring of glioblastoma

MECHANISM OF ACTION

Gliobastomas are brain tumours of glial cells with an incidence of ~3-5/100,000 inhabitants. They are fast-growing tumours with a high level of malignancy and a 5-year survival rate of less than 5%. The standard treatment of patients diagnosed with glioblastoma includes surgery, radiotherapy and chemotherapy with temozolamide. Recurrence is common in this type of tumor and there is no clear indication for second-line treatment. Studies on predictive markers of response of this malignancy to alkylating agents have identified the enzyme O6-methylguanine-DNA methyltransferase (MGMT) as responsible for the elimination of alkyl groups from the O6 position of guanine (effect of alkylating agents).

The O6-methylguanine-DNA-methyltransferase (MGMT) gene located at 10q26 encodes a DNA repair protein that eliminates alkyl groups from the O6 position of guanine. Elevated levels of the protein in tumour cells would lead to a lower cytotoxic effect of drugs whose mechanism of action is based on the alkylating effect of DNA, such as temozolamide (TMZ), causing resistance to them. The MGMT gene is subject to epigenetic regulation and its silencing through the methylation of CpG islands of the promoter region of the gene is associated to a better response to the treatment and therefore to a greater survival (prognostic and predictive biomarker)

TARGET INDICATIONS

Diagnosis, monitoring, prediction of the response to treatment and determination of the progression of the disease of those patients diagnosed with glioblastomas (GB1, GB2, Giant Cell Glioblastoma, Gliosarcoma). This invention could be extended to other tumor types in which methylation of the MGMT gene was also present as a tumor marker, for example colorectal cancer.

CURRENT STATUS

- Based on the extraction of plasma circulating exosomes from patients, the subsequent extraction of DNA and the evaluation of methylation, the biomarker was detected in blood with a sensitivity of 100% and specificity of 92%. This indicates that the biomarker meets requirements to be extended to clinical practice. In addition, the presence of methylation in the exosomal content of 5 healthy donors was also evaluated, without finding the presence of methylated molecules in any of them.
- The invention could also be used as a follow-up marker and for the monitoring of treatment effectiveness, since in those patients who presented from the beginning basal methylation at diagnosis in tumor tissue as well as in liquid biopsy, the methylation of the biomarker disappears from the blood at the same time as the disease radiologically remits, and remains elevated in those patients in which the disease is still present. In this way, the biomarker also acquires a role in the monitoring and detection of patient recurrence.
- To date the research group has recruited 75 patients to fine-tune the quantitative technique, 25 tumor/blood paired patients and 4 patients with follow-up serial samples. The next steps needed to bring technology to market require significantly more funding and the resources and infrastructure available to pharma companies.

INNOVATIVE ASPECTS

- This is the first time that it has been possible to describe a rapid and non-invasive method of diagnosis of glioblastoma, which also involves overcoming the problem of diagnosis in tissue due to tumour heterogeneity, which means that a biopsy of the tumour is not representative of all the tumour tissue, or that it is a necrotic region that prevents the molecular diagnosis of the biopsy. Therefore, this methodology not only finds application for diagnosis but would also be applicable to the monitoring or determination of disease progression, obtaining a global diagnosis, with 100% of the molecular representation of tumor DNA.The glioblastoma diagnostic techniques published so far fail to detect with sufficient sensitivity the methylation of MGMT in blood. This new diagnostic method based on the measurement of MGMT methylation levels presents a high sensitivity and specificity, surpassing the diagnostic techniques described so far.
- This great superiority with respect to current techniques is explained by the extract on which MGMT methylation levels are measured, this being the exosomal extract which can cross the blood-brain barrier and reach the blood more easily, making it possible to find a greater concentration of tumor DNA inside and quantify the presence of methylation with high sensitivity and specificity.

IPR

The technology is protected by the patent "Method for determining the percentage of methylation of the promoter of the gene O6-methylguanine-DNA methyltransferase(MGMT) in circulating exosomes", owned by the Foundation for Biomedical Research of La Paz University Hospital, European patent registration number EP19382299.6, filed on 16 April 2019.

PARTNERING OPPORTUNITIES

We are interested in any type of collaboration with the industry, whether through the signing of a license (licensing-out type agreements), an investor who finances the project, a partner interested in getting involved in any of the different phases up to market launch or co-development agreements.