XX Encuentro de Cooperación Farma-Biotech

Investigación avanzada de medicamento innovadores, en laboratorios del CSIC

Miércoles, 28 de abril de 2021

El Programa Farma-Biotech 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 presente jornada, que hace la número 20 desde que se inició el programa en el año 2011, está enfocada a la presentación de proyectos de medicamentos innovadores desarrollados en distintos laboratorios de investigación del CSIC, que han sido seleccionados por su gran potencial y avanzado estado de desarrollo, dentro del ámbito de la investigación preclínica temprana.

En esta jornada se presentarán y discutirán **siete propuestas** que se considera han alcanzado un **grado de madurez suficiente**, 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.

Debido a las circunstancias especiales originadas por la pandemia del Covid19, esta jornada se organizará en formato online. Se **enviará con antelación la documentación de cada proyecto**, en inglés, incluido el PowerPoint de cada presentación, a todos los participantes inscritos, a fin de que puedan analizar mejor cada proyecto y formular dudas y preguntas a través del correo-e los días previos a la celebración de la jornada. Este mecanismo permitirá **una mayor flexibilidad en las presentaciones**, de modo que los ponentes no usarán su tiempo simplemente para repetir lo que ya está escrito en la documentación enviada, sino que podrán hacer más énfasis en los aspectos concretos de mayor interés de los representantes de las compañías farmacéuticas participantes. Por lo tanto, la presencia online durante toda la jornada suministrará más valor añadido que la mera lectura previa de la documentación.

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

Amelia Martín Uranga

amuranga@farmaindustria.es

Tfno. 915159350

Agenda

El programa Farma-Biotech, patrocinado por FARMAINDUSTRIA*, pretende dar énfasis tanto a las presentaciones como a la interacción personal entre los asistentes, para lo cual todas las jornadas hasta la aparición de la Covid19 se han realizado de modo presencial. Sin embargo, las circunstancias actuales derivadas de la necesidad de controlar la pandemia aconsejan que esta jornada tenga lugar de modo telemático. Aunque este formato plantea ciertas barreras para la interacción interpersonal, haremos lo posible para obtener el máximo provecho del desarrollo de la jornada.*

Hora	Desarrollo en curso	Ponente
09:00	Se abre la sesión online para ajustes de acceso	
09:30 09:45	*Bienvenida y presentación de la jornada*	***Javier Urzay*** (FARMAINDUSTRIA) ***Ana Castro*** (CSIC)
09:45 10:00	*Indicaciones para la operativa de la jornada*	***A. Martín/J. Villoslada*** FARMAINDUSTRIA
10:00 10:30	*Inhibidor de CDC7 como mecanismo para disminuir la fosforilación de TDP43. Pruebas in vivo para su aplicación a ELA y demencia frontotemporal.*	***Ana Martínez*** CIB
10:30 11:00	*Aproximación innovadora, basada en incrementar del número de sinapsis, para el tratamiento de enfermedades neurodegenerativas. Nueva molécula.*	***María José Sánchez*** CIB / IQF
11:00 11:30	*Uso de enzimas codificados por bacteriófagos, contra bacterias gram-resistentes, como tratamiento alternativo a antibióticos.*	***Pedro A. García*** CIB
11:30 12:00	*Método de combinación para vencer resistencia a antibióticos betalactámicos. Patente de uso extendida a Europa y EE.UU.*	***Daniel López*** CNB
	DESCANSO	
12:15 12:45	*Inhibidores de la tirosina hidroxilasa para el tratamiento del aneurismo aórtico abdominal, alternativo a la cirugía.*	***José Martínez*** IIBB / Hospital Sant Pau
12:45 13:15	*Anticuerpo monoclonal humanizado para el tratamiento del cáncer colorrectal metastásico. Eficacia demostrada in vivo.*	***Juan Ignacio Imbaud*** ProAlt / CIB
13:15 13:45	*Inmunoterapia basada en la transfagocitosis para el tratamiento de tumores sólidos. Pruebas in vivo para cáncer de colon y melanoma.*	***Esteban Veiga*** CNB
	FINAL. Desconexión de la sesión online	

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: **Formato telemático por videoconferencia. Se facilitará la conexión con suficiente antelación.**

GOBIERNO DE ESPAÑA MINISTERIO DE CIENCIA E INNOVACIÓN

La Plataforma Tecnológica Española Medicamentos Innovadore con apoyo financiero del Ministerio de Ciencia e Innovación a t la Agencia Estatal de Investigación

PRESENTACIONES QUE TENDRÁN LUGAR EN ESTA JORNADA

PROFILE

Researchers at **CIB Margarita Salas** study the structure and organization of living matter and its processes, seek to understand the bases of disease and discover experimental treatments. Translational Medicinal and Biological chemistry group is focused on the design, synthesis, biological evaluation, study and further optimization of structurally diverse chemical entities as innovative drugs with novel mechanism of action Our group applies medicinal chemistry programs combining classical and computational medicinal chemistry to discover and develop new candidates for unmet severe pathologies such as neurodegenerative and infectious diseases.

SPEAKER

Prof **Ana Martinez**'s research is focused on drug discovery and development for neurodegenerative and infectious diseases since more than 30 years ago, caring the close contact with biopharmaceutical companies for technology transfer. She has been NeuroPharma's R&D Director for six years and more recently, founder of ANKAR PHARMA. She is author of more than 275 scientific publications and thirty active patents in the field. She is the head of Translational Medicinal and Biological Chemistry group..

ana.martinez@csic.es

PRODUCT

CDC7 inhibitors for ALS and FTD therapy

MECHANISM OF ACTION

Our candidates are CDC7 inhibitors, a conserved ser/thr kinase involved in cell cycle, and recently identified to be involved in in vivo TDP-43 phosphorylation. Candidates have IC50 values in submicromolar range and are AT-competitive but selective in a panel of 40 structural related kinases. They are able to cross the blood brain barrier.

Brain permeates small molecules able to recover TDP-43 homeostasis (phosphorylation decrease and nuclear localization) in celular models, including human lymphoblast from ALS and FTD patients.

TARGET INDICATIONS

Neurodegenerative diseases, mainly amyotrophic lateral sclerosis and frontotemporal dementia, but also CDC7 inhibitors can play an important therapeutic role in other diseases where homeostasis of TDP-43 is lost. These may include rare disease such as Alexander' and Perry' diseases but also the prevalent limbic-predominant age-related TDP-43 encephalopathy (LATE)

CURRENT STATUS

The following are last tasks already done and main achieved goals:

- Reverse chemical genetic approach to identify hits able to inhibit CDC7

- Med Chem program to optimize the hit. Focus on increase biological potency and blood brain barrier penetration. More than 50 different heterocyclic related small molecules with submicromolar potency.
- Recovery of TDP-43 homeostasis (reduction of hyperphosphorylation and recovery of nuclear localization) both in neuroblastoma cell lines and lymphoblasts from ALS and FTD patients.
- Decrease of TDP-43 phosphorylation in vivo (C. elegans model)
- Confirmed in vivo penetration into CNS and spinal cord TDP-43 phosphorylation reduction after chronic administration in a transgenic TDP-43 murine model.

INNOVATIVE ASPECTS

- Up to now, only some antibodies targeting TDP-43 are under clinical evaluation as a strategy to alleviate TDP-43 pathology. In preclinical stage, CK1 inhibitors have shown also important biochemical changes in a TDP-43 transgenic ALS model but no modification of phenotypic behaviour. By the moment, phenotypic differences among these two different families of compounds are unknown. We are studying muscle changes looking for these differences.
- The advanced candidate is able to decrease TDP-43 phosphorylation in two different TDP43 transgenic animal models: C. Elegans and mice. Chronic administration for 21 days of our candidate in the PrTDP43 A315T mice ameliorates phenotypic behaviour and decrease TDP-43 phosphorylation in spinal cord.

IPR

Compounds are protected by two independent patents. The first one (ES20170322) is now granted in Spain (ES2686909 (B1)) and under study in national phases (AU2018240527(A1); US2020093828 (A1) and EP3604310(A1)). The second one (ES20180921) is also granted in Spain (ES2749743(B2) and just published in international phases (WO2020058558 (A1)).

PARTNERING OPPORTUNITIES

We are looking for a partner to work in co-development (private-public collaboration) or some company interested in licencing the patent and develop the technology.

PROFILE

The research group at **Rocasolano Institute** uses Crystallography together with Molecular, Biophysical and Biochemical approaches to understand the function of the Neuronal Calcium Sensor 1 (NCS-1) at molecular and atomic level to understand how the protein triggers distinct coordinated cellular responses based on the interaction and regulation of their target proteins.

IRYCIS (Hospital Ramón y Cajal) also participates in the project, where Dr. Alicia Mansilla works on the research as a Biologist.

SPEAKER

Dr **María José Sánchez** has a Master Degree in Chemistry (2000) and a PhD in Crystallography (2005). She has carried out a 3-year postdoc at the MRC-LMB (Cambridge, UK) working on cancer-related proteins combining structural, biochemical and cellular approaches to understand their function. In 2009, she moved back to Spain as a Ramón y Cajal Fellow. Since then, she lead projects at Institute Rocasolano (CSIC) on calcium signaling processes in mammals and in plants with biomedical and biotechnological interest.

xmjose@iqfr.csic.es

PRODUCT

Synapse modulators targeting the NCS-1/Ric8a complex for neurodegenerative disorders

MECHANISM OF ACTION

The product is a small molecule, 3b, that binds to the neuronal calcium sensor NCS-1 and strengthens the interaction between NCS-1 and its target protein Ric8a (a G-protein activator) has been found (Canal-Martín et al., Nat. Comms 2019). Tests performed in fly and mouse models of Alzheimer´s and Huntington´s diseases, have shown significant improvement in synapse number and cognitive characteristics associated with these neuronal disorders. Structural studies have shown at atomic level how 3b is recognized by NCS-1 and has allowed to propose a mechanism of action.

The NCS-1/Ric8a complex regulates in an antagonistic manner synapse number and probability of neurotransmitter release. The formation of this complex is essential to raise up synapse number in normal brain. Given that during neuronal degeneration there is a loss of synapses, a molecule able to enhance the protein complex, would increase synapse number to correct certain deficits associated with the loss of neuronal connections and therefore, improve cognitive abilities. We have demonstrated that this is the case of compound 3b, it targets NCS-1 and stabilizes a conformation that favours the interaction with Ric8a, enhancing complex formation. This is translated to an increase in synapse number, as shown with Alzheimer´s flies, and an improvement in cognitive characteristics both in Alzheimer´s (flies) and Huntington´s (mice) disease models.

TARGET INDICATIONS

Treatment of neurodegenerative disorders such as Alzheimer's, Huntington's or Parkinson's diseases characterized by a decrease in the number and efficacy of synapses that precedes neuronal death.

CURRENT STATUS

- Proof of concept in an animal model of Drosophila with pathology hallmarks reminiscent of Alzheimer's disease including defective locomotion, memory loss or reduced longevity.
- Compound 3b increases the number of synapses to normal levels, exclusively in the presence of a synaptic pathology, which is an essential requirement for any treatment directed to synapses.
- Proof of concept in Huntington's mice (HD). Promising preliminary experiments showed an improvement in locomotor activity in HD mice treated orally with compound 3b.
- Currently working on improving Blood Brain Barrier permeability of compound 3b. New compounds are currently being tested and will be validated in animal studies.

INNOVATIVE ASPECTS

- Despite the best efforts, neurodegenerative diseases do not have effective treatments. Research has focused on specific targets that are relevant for each pathology.
- This new approach is novel and general, as it focuses on the functional unit of a neuron, the synapse, which is altered in all these disorders. NCS-1/Ric8a is the first target known to control the probability of neurotransmitters release by each synapse, as well as the synapse number.
- This makes it the first strategy tackling both neuronal features at the same time.

IPR

This technology is protected by P201830933 "Acylhydrazones for the treatment of neurological diseases". Spanish priority granted on 03.12.2020 and published with reference ES 2 750 924 B2. Owned 80% CSIC and 20% FIBioHRC. The patent protects a group of compounds and their use for the treatment of neurological diseases.

PCT/ES2019/070649 requested on the 25th October 2019. Owned 70% CSIC and 30% FIBioHRC. The ISR issued is favourable. It enters phases on 03/27/2021. CSIC and FIBioHRC will enter on EU, USA, AUS, CA.

PARTNERING OPPORTUNITIES

In our commitment to develop this therapy we will seek funding and partnering with pharma and biotechs, to carry out the preclinical studies. Due to the contribution of Ramon y Cajal Research Institute we are able to manage and run clinical trials. We are also having conversations with international Venture Capital firms for funding.

PROFILE

The main line of the Research Group at **CIB Margarita Salas** has focused on the pneumococcal "Choline Binding Proteins", or CBPs. Some of these proteins are peptidoglycan hydrolases and play relevant roles in bacterial physiology. In recent years he has studied phage lytic enzymes as novel antimicrobials, also called endolysins or enzybiotics. In particular, those targeted against several bacterial respiratory pathogens, including Gram-positive pneumococcus and Gram-negative Pseudomonas aeruginosa

SPEAKER

Dr Pedro García González is a Research Scientist at Centro de Investigaciones Biológicas Margarita Salas (CIB-CSIC). He is head of the group "Host-parasite interplay in pneumococcal infection" at CIB.

pgarcia@cib.csic.es

PRODUCT

Polypeptides with antibacterial activity

MECHANISM OF ACTION

Phage lysins, or enzybiotics, are enzymes that degrade specific bonds of the bacterial peptidoglycan, which leads to the lysis and death of the targeted bacteria. Normally, enzybiotics against Gram-positive bacteria are modular proteins that contain an enzymatically active domain, which determines the bond to be excised, and a cell wall binding domain, which recognizes the cell wall structure to be anchored. Enzybiotics against Gram-negative bacteria are usually monomodular with an enzymatic domain.

Enzybiotics represent an alternative to standard antibiotics, since the target is the bacterial peptidoglycan, a well conserved polymer that acts as a protective barrier against the inner osmotic pressure. When these enzymes are exogenously added, the rapid binding to the susceptible peptidoglycan and breaking of such polymer, leads to the lysis and death of the targeted bacteria

TARGET INDICATIONS

The compounds are conceived against respiratory infectious diseases produced by certain Gram-negative bacteria like Pseudomonas aeruginosa, Acinetobacter baumannii and Moraxella catarrhalis, particularly against those multiresistant strains. The synergistic activity between these polypeptides and some antibiotics is an additional therapeutic advantage

CURRENT STATUS

- We have constructed several polypeptides (wild type enzymes, fusion proteins, and peptides derived from the same enzybiotics) that have an in vitro killing effect against Pseudomonas aeruginosa, Acinetobacter baumannii and Moraxella catarrhalis.
- In addition, preliminary experiments with P. aeruginosa suggest an important synergistic effect between the tested peptides and some antibiotics.

- These data are obtained with only ¼ of the corresponding MICs for the peptides and antibiotics, increasing the rate of mortality by several orders of magnitude.

INNOVATIVE ASPECTS

- These phage-based antimicrobials form part of the so called "phage therapy", and constitute an alternative to standard antibiotics.
- But enzybiotics present several advantages over antibiotics and entire phages (virions), among them: specificity, low chance of resistance, killing effect against multiresistant strains, synergistic effects with some antibiotics or other enzybiotics, easy handling to clone the corresponding genes and the subsequent protein expression and purification, absence of severe side effects.
- Nowadays, the possibility to construct a "tailor made enzybiotic" against any bacterial pathogen is closer.

IPR

This technology is protected by EP20382666 with date of receipt on 24th July 2020 and title "Polypeptides with antibacterial activity". Owned 100% CSIC. The patent protects a group of polypeptides and their use as an antimicrobial agent against certain pathogenic bacteria.

PARTNERING OPPORTUNITIES

As the promising results summarized here still lack several in vitro and in vivo experiments, we would like to collaborate with any pharmaceutical company interested in these remaining assays and in the eventual formulation of the better compounds..

PROFILE

Within CNB, the Research Group uses the pathogen methicillin-resistant Staphylococcus aureus (MRSA) to investigate the contribution of bacterial cell organization to the development of infections. This Research Group is a pioneer in the discovery of functional membrane microdomains in bacteria, similar to eukaryotic lipid rafts, where protein complexes related to infections and resistance to antibiotics are organized. The group has developed techniques and protocols that are used globally by laboratories interested in exploring the complexity of the microbial world.

SPEAKER

Dr Daniel López started his laboratory at the University of Würzburg (Germany 2010-2015) and he is currently at CNB (Spain 2015-present). Previously, he was a postdoc at Harvard University (USA) and completed his PhD at the University of Murcia (Spain). His work is published in the most prestigious journals. Daniel Lopez is elected member of the European Academy of Microbiology (since 2018). He obtained the Banco Sabadell Foundation Award for Biomedicine (2018) and the Caja Granada Foundation Health Award (2018).

dlopez@cnb.csic.es

PRODUCT

Anti-raft therapies to fight multi-drug resistant infections

MECHANISM OF ACTION

Anti-raft molecules perturb the architecture of bacterial lipid rafts by inhibiting the production of the membrane lipids that constitute the rafts. Bacterial lipid rafts are membrane lipids of isoprenoid nature; their biosynthetic pathway resembles that of cholesterol synthesis in humans. Anti-rafts molecules inhibit key enzymes of raft lipids production. In the absence of these lipids, many raft-associated proteins lose their functionality causing a severe perturbation of bacterial survival. As several antibiotic-resistant proteins, such as PBP2a, are raft-associated proteins, the inhibition of raft lipids synthesis also compromises bacterial antibiotic resistance.

The protein PBP2a responsible for penicillin resistance in MDR Staphylococcus aureus (MRSA), serves as case study. These "anti-raft" compounds are non-toxic to humans; some of them are commercially available as cholesterol-lowering drugs. Nanomolar concentrations of these compounds inhibited raft-associated proteins, including PBP2a, resulting in inhibition of antibiotic resistance thus rendering MRSA infections susceptible to penicillin. Anti-rafts molecules combined with conventional penicillins eliminate MRSA infections and open up the possibility of recycling penicillins in disuse due to multi-drug resistance.

TARGET INDICATIONS

The alarming increase of multi-drug resistant (MDR) pathogens represents an unprecedented global health problem. MDR pathogens threaten our ability to treat common infections, causing severe complications for medical or surgical procedures. Our anti-raft technology can be implemented in healthcare systems to fight MDR infections that cannot be treated otherwise. This technology will reduce risks of medical procedures as well as the cost of

hospital stays and intensive care. Anti-raft technology opens up the possibility of reusing antibiotics currently discarded due to the rising of MDR pathogens.

CURRENT STATUS

- We demonstrated that perturbation of bacterial rafts assembly using anti-rafts compounds results in MRSA infections susceptible to penicillin treatment.
- To test the versatility of our anti-raft therapy, we developed a mouse pneumonia infection model to recapitulate distinct infection scenarios common in ICU.
- The main outcomes are: 1) Anti-raft therapy prevents the progress of already ongoing MRSA infections, to recapitulate patients with complicated pneumonia. 2) Anti-raft pre-treatment prevents the development of MRSA infections, to protect patients that will require risk procedures (e.g., surgery). 3) Anti-raft therapy is active against all MRSA clinical isolates tested. We tested isolates from pandemic, multi-resistant, chronic and acute infections). 4) Anti-raft therapy works against other pathogens such as Listeria monocytogenes or Pseudomonas aeruginosa (in vitro). 5) In collaboration with several Spanish hospitals (e.g., Hospital Virgen de Rocio, Seville) we correlated our laboratory results with prospective clinical studies in patients

INNOVATIVE ASPECTS

- We target bacterial lipid rafts to fight bacterial infections by simultaneously inhibiting many raft-associated proteins related to infection and antibiotic resistance.
- The current antibiotic crisis teaches us that new antibiotics become ineffective soon after they are introduced into the clinic due to rapidly evolving resistance in pathogenic bacteria.
- In the current scenario, our anti-raft therapy provides benefits that cannot be achieved with the available antibiotics: to eliminate MDR infections that show resistance to clinically available antibiotics, our therapy can be used to treat infections that cannot be treated otherwise.
- In addition, this therapy is able to recover currently discarded antibiotics. This can alleviate the antibiotic crisis, to circumvent large investments in cost and time for the discovery and development of new antibiotics.

IPR

Patented in 2017. Patent of applicability extended to Europe and USA.

PARTNERING OPPORTUNITIES

We look for the impulse of the industrial sector to implement this product in hospital environments.

PROFILE

The Research Group investigates, at **IIBB-CSIC** and **Hospital Sant Pau**, the cellular and molecular mechanisms involved in the onset, progression and complication of atherotrombotic diseases (ischemic heart disease and peripheral artery disease) and abdominal aortic aneurysm. His research is centered on the role of NR4A nuclear receptors, in particular NOR-1, and lysyl oxidases (LOX) in these pathologies. His ultimate goal is to identify novel therapeutic targets and biomarkers to better manage these highly prevalent diseases.

SPEAKER

Dr José Martínez González graduated and PhD in Pharmacy from the University of Barcelona. He leads the Atherosclerosis and Vascular Biology group at the IIBB-CSIC, and a multidisciplinary group which is one of the 40 Spanish research groups integrated in the Biomedical Research Networking Center on Cardiovascular Diseases (CIBERCV). He has been devoted to research in cardiovascular diseases for more than 25 years.

jose.martinez@iibb.csic.es

PRODUCT

Tyrosine hydroxylase inhibitors for the treatment of aortic aneurysm

MECHANISM OF ACTION

The formation of abdominal aortic aneurysm (AAA) is associated with the up-regulation of the enzyme tyrosine hydroxylase in the aortic vascular wall, while the systemic administration of a drug that competitively inhibits tyrosine hydroxylase activity attenuates the main pathophysiological mechanisms involved in AAA disease, including oxidative stress, inflammation and elastic fiber breakdown, thereby preserving vascular wall integrity and preventing the formation of aneurysms.

A therapeutic strategy for the medical management of abdominal aortic aneurysm, addressed to slow aneurysm progression and to prevent aneurysm dissection and rupture, based on the pharmacological inhibition of the vascular activity of the enzyme tyrosine hydroxylase by means of treatment with a-methyl-p-tyrosine (AMPT).

TARGET INDICATIONS

The product applies to abdominal aorta aneurysm (AAA), a life-threatening disorder characterized by a focal and permanent dilation of the abdominal aorta, whose diameter progressively grows increasing the risk of aortic rupture. AAA prevalence increases with age (up to 8% of men aged >65 years), and AAA rupture is a devastating condition with a high fatality rate that accounts for more than 16,000 deaths each year in the United States. Additionally, the treatment method could be useful for the clinical management of thoracic aneurysm.

CURRENT STATUS

- Microarray expression profiling shows the up-regulation of the rate limiting enzyme of catecholamine biosynthesis (tyrosine hydroxylase, TH) in an experimental model of AAA.

- TH is up-regulated in aneurysmal aorta from both AAA patients and preclinical animal models, mainly co-localizing with sympathetic nerve and inflammatory cells.
- The TH inhibitor a-methyl-p-tyrosine (AMPT) protects against the formation of AAA induced by angiotensin II infusion in two animal models of AAA.
- AMPT treatment significantly attenuates vascular oxidative stress and inflammation, reduces the activity of metalloproteinases that degrade extracellular matrix and preserves elastin integrity.
- AMPT treatment is well tolerated and improves the level of circulating markers of renal function.
- Studies to assess the effect of AMPT on pre-established aneurysms are ongoing.

INNOVATIVE ASPECTS

- There are no pharmacological treatments for abdominal aortic aneurysm (AAA) able to slow progression or to prevent aneurysm dissection and rupture.
- Elective surgical or endovascular repair of high-risk aneurysms is currently the only effective way to treat the disease.
- Guidelines recommend intensive risk factor modification in AAA patients, who are commonly treated with statins, β-blockers, antihypertensive or antithrombotic drugs, but no clinical trials have shown a significant effect of these treatments on AAA growth or rupture.

IPR

A patent application has been filed "Use of inhibitors of Tyrosine hydroxylase for the treatment of aortic aneurysm" (Appl. Nº ES201830607), owned by CSIC (80%) and FIRHSCSP (20%). International PCT extension published as WO2019243653. Currently, the patent is in National phases, filed in USA (App. Nº US17252677) and Europe (App. Nº EP19823676), not yet granted.

PARTNERING OPPORTUNITIES

CSIC and FIRHSCSP are seeking for out-licensing the technology to pharmaceutical companies interested in the development and commercialization of the product for treatment of aortic aneurysms. We are open to analyze different forms of collaboration

PROFILE

Protein Alternatives ('**PROALT**') is a Spanish biotechnology company founded in 2006 by researchers of the Spanish Research Council (CSIC) and the Cancer Research Center (CNIO) focused on the development of biomarker-based assays for early diagnosis of cancer and the development of therapeutic monoclonal antibodies for the treatment of metastatic cancers. The company also offers Contract Research (CRO) and Manufacturing (CMO) services and owns a broad catalogue of research-use-only products..

SPEAKER

Dr. Juan Ignacio Imbaud, is a Biochemist (UM), Ph.D. in Molecular Biology (UAM) and PADIIT2 degree (Senior Management Program of Research, Innovation and Technology Transfer Institutions) by IESE Business School. Leads Protein Alternatives spin-off company since its creation in 2006, building up the Therapeutics, Diagnostics and CRO/CMO business units. More than 16 years of experience in biotechnology industry combining scientific with management skills.

jimbaud@proteinalternatives.com

PRODUCT

PA-0661 monoclonal antibody for the treatment of metastatic colorectal cancer

MECHANISM OF ACTION

The candidate hPA-0661 inhibited cell adhesion, cell migration and cell proliferation in in vitro studies. In in vivo efficacy studies, hPA-661 significantly improved survival rates of all treated animals and avoided metastasis formation in 50% of the treated individuals in the metastatic CRC tumor model.

Blockade of the CDH17-$\alpha 2\beta 1$ (ligand-receptor) interaction. PROALT's founder Dr Ignacio Casal (Centro de Investigaciones Biológicas - CSIC) has discovered and demonstrated that RGD motifs in some cadherins (CDH17, VEcadherin, CDH6) are ligands capable of activating a2β1 integrin, a cell surface protein receptor. This discovery also demonstrated the critical role of a2β1 integrin in cancer metastasis and its capacity to be considered an RGD receptor, which was previously unknown. hPA-0661 antibody inhibits the activation of $\beta 1$ integrin, thus diminishing the activation FAK, JNK, and ERK kinases, which correlate with a decrease in cell adhesion and proliferation.

TARGET INDICATIONS

Oncology. Main therapeutic indication: liver metastasis of colorectal cancer (mCRC). Additional potential indications: lung metastasis of melanoma or breast cancer.

CURRENT STATUS

- Completion of in vitro and in vivo efficacy studies generated with the murine monoclonal antibody (mPA-0661) in metastatic colorectal and melanoma models.
- PA-0661 antibody humanization completed in collaboration with Fusion Antibodies Plc (UK) and development candidate selected for pre-clinical studies.

- Non-regulatory in vitro and in vivo efficacy results generated with the humanized selected candidate hPA-0661 in metastatic colorectal cancer (mCRC) murine models.
- Non-clinical safety studies and pre-clinical development strategy for enabling first-in-man study designed.

INNOVATIVE ASPECTS

- Data about the target and in vitro and in vivo results obtained with the humanized monoclonal antibody hPA-0661 (the selected candidate for development), demonstrating the efficacy of this biological drug in inhibiting beta-1 integrin activation, a critical cell-signaling pathway associated to metastasis.
- Different therapeutic target and mechanism of action (MOA) compared to Avastin®, Erbitux® and Vectibix®, the three monoclonal antibodies on market currently used alone, or in combination with chemotherapy, for the treatment of CRC.
- No active developments of anti-CDH17 compounds.
- Proven interest of big pharma companies in cadherin targets: CDH3 and CDH6 therapeutic mAbs developed by Pfizer, Novartis and Fujifilm are in Phase I clinical studies.
- No anti cadherins RGD specific drugs under development.

IPR

International Application No. PCT/EP2015/058527 (Filed 22 April 2015) extended to Europe (EP3286218; Intention to Grant Feb 2021), Canada (2,980,495; Filed), Australia (2015392603; Filed) and EEUU (10,829,560, Granted 10 November 2020).

Complementarity-Determining Regions (CDRs) in the heavy (VH) and light chains (VL) from the monoclonal antibody clone 6.6.1 protected. Patent of product and use.

Opportunity to create new additional IP around the humanized sequences: under evaluation.

PARTNERING OPPORTUNITIES

The completion of the regulatory preclinical stage of the therapeutic antibody hPA-0661 requires 6 M € of private capital within 2 years. The company is willing to create a new company (Joint venture) to separate hPA-0661 from the rest of its business units.

PROFILE

The Research Group, at **Centro Nacional de Biotecnología,** is focused in generating novel immunotherapies using the ability of bacteria to modify the immune responses. It has been discovered that conventional CD4+ T cells can be trained by bacteria engineered to express tumor antigens. Bacteria-trained CD4+ T cells (bacT) became potent antigen presenting cells activating naïve CD8+ T cells that became effective anti-tumor cytotoxic cells and generating central memory (resistant to tumor induced exhaustion). Antitumor activity of BacT cells was tested in proof-of-concept models.

SPEAKER

Dr Esteban Veiga is a PhD in Molecular Biology by Universidad Autónoma de Madrid, 2003. Postdoctoral at Institute Pasteur (Paris, France. 2003-2007). Research Visitor at University of California at Berkeley (Ca, USA: 1999 and 2000), Harvard Medical School (Boston, Ma, USA, 2005). Ramón y Cajal Researcher at Hospital de la Princesa (Madrid, 2008-2010). Senior Scientist CSIC at CNB (Madrid) from 2010.

eveiga@cnb.csic.es

PRODUCT

Bacteria-trained lymphocytes as novel anti-cancer immunotherapy

MECHANISM OF ACTION

Bacteria-trained CD4+ T (BacT) cells are conventional Cd4+ T cells (extracted from the patient) and later "trained" by bacteria engineered to express tumor antigens. BacT cells are able to activate naïve CD8+ T cells that recognize these tumor antigens. BacT-activated CD8+ T cells migrate to the tumor locations and are able to trigger a potent cytotoxic response against the tumor cells. In addition, BacT-activated CD8+ T cells differentiate into central memory CD8+ T cells, the population more resistant to tumor induced exhaustion, which in addition expressed very low levels of PD1, the major check point inhibitor molecule.

BacT became potent antigen presenting cells able to (1) activate naïve CD8+ T cells that became effective tumor cytotoxic cells and (2) generating central memory; activities involved in the removal of tumors. Note that actually there exist huge efforts to generate central memory CD8+ T cells from tumor infiltrating lymphocytes. These effects, together with (3) the localized secretion of inflammatory cytokines by bacT cells, which could block the immunosuppressive environment generated by solid tumors, prompted us to hypothesized that bacT cells could be useful in antitumor therapies. This hypothesis was tested, mice treated with bacT cells were protected against tumor development.

TARGET INDICATIONS

The present product is a novel cancer immunotherapy that could act against immunogenic tumors (the vast majority). It could be use against any tumor (solid or liquid) with identified tumor-associated antigens.

CURRENT STATUS

- Proof of concept experiments have been performed, demonstrating that BacT cells impeded the implantation of the tumor as well as tumor growth.

- Mice vaccination with bacT cells impeded the implantation of aggressive melanoma.
- BacT cells were useful not only at preventive but also at therapeutic level, we tested BacT against already established tumors using B16 melanoma and MC38 (colon cancer; non orthotopic). In both models a clear reduction of tumor growth was observed.
- In order to achieve this task, we engineered bacteria expressing tumor-associate antigens. In these preliminary experiments, we used 100x less cells than the equivalent (taking into account the weight differences between species) used in TILs therapies in humans, and we used only 3 doses when other experiments use up to seven inoculations of the treatment.

INNOVATIVE ASPECTS

- The closest technology is the use of dendritic cells as anti-cancer vaccines. DC-based cancer vaccines unfortunately show very low responses, underlining the need for novel therapies.
- Note that BacT cells is superior in generating effective antitumor CD8+ T cells which in addition are more resistant to exhaustion.
- Other cellular technologies are TILS (tumor infiltrating lymphocytes) or CAR-T. Here also, BacT technology generate improved anti-tumor responses against solid tumors, and more resistance to exhaustion.

IPR

The use of bacT cells in cancer immunotherapies has been protected by patent, and this has been extended to USA, Canada, EU and Australia.

PARTNERING OPPORTUNITIES

We would like to strengthen the possibility to transfer these discoveries to the society. Ideally be by founding a Spin-Off company or by licensing the patent.