MEDICAMENTOS INNOVADORES
Plataforma Tecnológica Española

farmaindustria

XXIV Encuentro de Cooperación Farma-Biotech

Miércoles, 23 de octubre de 2024

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 24 desde que se inició el programa en el año 2011, está enfocada a la presentación de proyectos de medicamentos innovadores desarrollados en distintos centros de investigación y pequeñas empresas *spin-offs*, que han sido seleccionados por su potencial y prometedor estado de desarrollo, dentro del ámbito de la investigación preclínica.

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

Esta jornada tendrá lugar de forma presencial en la sede de Farmaindustria en Madrid. Para cualquier duda o aclaración adicional por favor contactar con:

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Agenda

El programa Farma-Biotech, patrocinado por FARMAINDUSTRIA, pretende dar énfasis tanto a las presentaciones como a la interacción personal entre los asistentes, de acuerdo con la siguiente agenda:

Hora	Presentación	Ámbito terapéutico	Ponente
09:00	Recepción, contactos informales, café		
09:25 09:45	*Bienvenida y presentación de la jornada*		***Amelia Martín*** FARMAINDUSTRIA
09:45 10:15	*Péptidos TAT-CX43 para el tratamiento de tumores cerebrales*	Oncología	***Arantxa Tabernero*** UNIV. DE SALAMANCA
10:15 10:45	*Modulador de neuroplasticidad "first-in-class" para enfermedades del neurodesarrollo*	SNC	***Jordi Fábrega*** CONNECTA THERAPEUTICS
10:45 11:15	*Terapia basada en el bloqueo de BAMBI (proteína antagonista de TGFβ)*	Enfermedades autoinmunes	***Ramón Merino*** INHIBITECH ANTICUERPOS
11:15 11:45	*Vectorización selectiva hacia las células diana de los principios encapsulados*	Oncología	***Cristina Fornaguera*** INST. QUÍMICA DE SARRIÁ
	DESCANSO. Café y refrescos. Contactos informales		
12:00 12:30	*ApoE-EA complejos aberrantes de Apolipoproteina E como biomarcador*	SNC	***Javier Sáez*** UNIV. MIGUEL HERNÁNDEZ
12:30 13:00	*Terapia STAb-TCD19. Linfocitos T autólogos modificados genéticamente*	Oncología	***Carolina Pola*** STAb THERAPEUTICS
13:00 13:30	*Nueva modalidad terapéutica basada en ARN para el tratamiento del cáncer*	Oncología	***Gisela Lorente*** APTADEL THERAPEUTICS
13:30 14:00	*Nuevos compuestos para tratar tumores resistentes a ciclos previos de quimioterapia*	Oncología	***Fernando Cossio Mora*** UNIV. PAÍS VASCO
	FINAL. Aperitivos y refrescos. Contactos informales		

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: **miércoles día 23 de octubre de 2024**

MINISTERIO DE CIENCIA, INNOVACIÓN Y UNIVERSIDADES
AGENCIA ESTATAL DE INVESTIGACIÓN

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PRESENTACIONES QUE TENDRÁN LUGAR EN ESTA JORNADA

PROFILE

VNiVERSiDAD D SALAMANCA

The Research Group focuses on the study of glioblastomas, brain tumors and the role played by glial cells within the central nervous system in health and disease. Their basic research has resulted in the design of the cell-penetrating peptide (TAT-Cx43) with the ability to inhibit the activity of Src, an important oncoprotein involved in several signaling pathways related to cancer and specifically glioblastoma.

SPEAKER

Arantxa Tabernero is a Full Professor of Biochemistry and Molecular Biology at the University of Salamanca. She leads the consolidated research group "Neurobiochemistry" at the Institute of Neuroscience Castilla y León (INCyL), where she is Vice-director. She has obtained the excellence scientific award "María de Maeztu" by the University of Salamanca.

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PRODUCT

TAT-Cx43, a Src inhibitor peptide for glioblastoma therapy

MECHANISM OF ACTION

Glioblastoma, the most common and aggressive primary brain tumor with an average survival rate of 14 months, remains one of the most difficult to treat cancers and an unmet clinical need. The oncoprotein Src is a key target in glioblastoma.

Our research has demonstrated that the Src inhibitor peptide TAT-Cx43 exerts important antitumor effects in preclinical models of glioblastoma in vitro, including fresh patient-derived samples, improving the survival of glioblastoma-bearing mice.

TAT-Cx43 is a specific inhibitor of Src with a novel mechanism of action. This cell-penetrating peptide recruits intracellularly the active form of Src together with its endogenous inhibitor, CSK, promoting Src inhibition. Therefore, TAT-Cx43 is a targeted therapy that acts specifically on cells with high Src activity, such as glioblastoma cells, without toxic effects in non-tumor cells.

Src is activated by EGFR, frequently amplified or mutated in Glioblastomas resulting in high activity of Src, which correlates with poor prognosis. TAT-Cx43 targets specifically glioblastoma with EGFR alterations.

TARGET INDICATIONS

Oncology. Because Src is an oncogene involved in many tumors we do not exclude anti-tumor effects in other cancers and other pathologies in which Src activity is involved, apart from glioblastoma.

CURRENT STATUS

- TAT-Cx43 exerts antitumor effects in various in vitro and in vivo models of intracranial glioblastoma in immunocompetent and immunosuppressed mice after IP and/or intracerebral administration, as well as in samples obtained from patients immediately after surgery (control and TAT-Cx43 treated samples).
- No toxicity was detected in brain, heart, liver, kidney, lung, spleen or thymus in TAT-Cx43 treated mice.
- Unbiased proteomic results confirm TAT-Cx43 mechanism of action and support its clinical relevance.
- We have recently discovered that EGFR-alterations (EGFRamp and EGFRvIII) are biomarkers of response of TAT-Cx43. These are frequent alterations in glioblastoma, indicating that this treatment can benefit an important number of patients (more than 50%).
- In addition, EGFR alterations are commonly assessed in the clinical diagnose, providing an important advantage for patient stratification in a future clinical trial.

INNOVATIVE ASPECTS

- TAT-Cx43 mechanism of action ensures high specificity and low toxicity, confirmed in comparison with the classical Src inhibitor, dasatinib.
- In contrast to other peptide-based drugs, TAT-Cx43 exhibits high plasma stability due to albumin binding, which also increases tumor tropism.
- Good blood brain barrier penetrance after IP administration due to TAT sequence.
- TAT-Cx43 targets glioblastoma cells resistant to conventional treatments, such as temozolomide.
- High solubility in water and low production cost compared to other biological treatments.
- The frequent EGFR alterations are biomarkers of TAT-Cx43 response.

IPR

International patent, PCTEP2023051210, WO2023139156A1 with positive International Preliminary Report on Patentability (IPRP), meeting the requirements of novelty, inventive step and industrial applicability. The patent application is currently being processed in the USA, PCT-Europe, Canada, Australia, Japan, China and Mexico.

PARTNERING OPPORTUNITIES

A company willing to license the international patent PCTEP2023051210, WO2023139156A1. We are open to explore other collaborative approaches.

PROFILE

CONNECTA Therapeutics is a clinical stage biotech company, based in Barcelona, developing new treatments for CNS diseases with a strong commitment to orphan and paediatric indications. CONNECTA's leading program, CTH120, is focused on the clinical development of a first-in-class neuroplasticity modulator, orally bioavailable, with a clinically validated safety profile and broad therapeutic application.

SPEAKER

Jordi Fabrega, M.Sc., MBA, is Co-Founder and CEO of CONNECTA Therapeutics and serves on its Board of Directors. He has held various positions in the pharmaceutical industry and has several years of consultancy experience in the healthcare sector. Jordi has broad experience in strategy, business development, market access and regulatory.

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PRODUCT

CTH120, first-in-class neuroplasticity modulator for neurodevelopmental disorders.

MECHANISM OF ACTION

CTH120 is a small molecule (NCE) that has shown excellent preclinical efficacy results in adult and juvenile FXS KO animal models after acute and chronic administration. CTH120 rescues the dendritic pathology of FXS, improves cognitive ability and completely restores the social abnormalities linked to the disorder.

The mechanism of action of CTH120 is based on a dual effect on neurotransmitters and neurotrophic factors pathways, which are essential for brain function and neuronal development. On the one hand, CTH120 inhibits in a balanced manner the reuptake of serotonin (5-HT) and norepinephrine (NE), and slightly the reuptake of dopamine (DA), and, additionally, activates neurotrophic factor cascades by increasing p-Erk and p-Akt, leading to the downstream phosphorylation of CREB (cAMP Response Element-Binding), a key mediator of neural functions and neuroplasticity.

TARGET INDICATIONS

Fragile X syndrome (FXS). The asset has also potential for other neurodevelopmental disorders with dysregulation of protein networks involved in synaptic and structural plasticity like Rett syndrome, Down syndrome, autism spectrum disorder or DiGeorge syndrome, among others.

CURRENT STATUS

- As of July 2024, CONNECTA is completing Phase I clinical trials of CTH120 in healthy adult volunteers. 48 out of the 60 volunteers, males and females, have already been administered with CTH120 at different doses and regimens, wherein CTH120 has demonstrated to be safe and well tolerated by all the participants, without any treatment-related adverse events reported so far.
- Likewise, CONNECTA is performing the preclinical evaluation of CTH120 and other molecules in different animal models of neurodevelopmental disorders with favourable results, resulting in new intellectual property (patent filed).

INNOVATIVE ASPECTS

- At present there are no approved treatments for FXS. Other active molecules under development have been designed to act selectively on specific targets. This strategy can effectively block the functions of their main targets, but the activation of compensatory cellular processes limits their efficacy in the medium and long term.
- On the contrary, the innovative pharmacological approach of CTH120 addresses different targets and levels, overcoming these compensatory mechanisms, as well as reducing unwanted off-target effects that often limit the clinical utility of conventional drug treatments.

IPR

CTH120 is protected by an international patent (WO2014/096377 A1), granted in EU, US, Canada, Australia and Japan, and is exclusively licensed to CONNECTA by Prous Institute for Biomedical Research, co-founder and current shareholder of the company.

PARTNERING OPPORTUNITIES

CONNECTA is exploring different modalities of collaboration with pharma companies. Co-development or Licensing-out formulas (upfront + milestones) are the ones that are being most actively considered at this stage.

PROFILE

Inhibitec

The goal of **Inhibitec Anticuerpos** is the development of a new therapy against chronic autoimmune/inflammatory diseases. To this end, we have generated a monoclonal antibody (mAb) that blocks BAMBI, a protein that antagonizes TGFβ cellular signaling. The deficiency or pharmacological inhibition of BAMBI has preventive and therapeutic effects in various experimental models of pathologies such as psoriasis (PsO), psoriatic arthritis (PsA), and rheumatoid arthritis (RA).

SPEAKER

Dr. Ramón Merino holds an MD degree from the University of Cantabria (Spain) and a PhD in Immunology from the University of Geneva (Switzerland). After completing his PhD, he conducted postdoctoral studies at the University of Michigan (USA) and the University of Cantabria. He has been awarded Principal Investigator (PI) positions in the FIS and Ramón y Cajal programs. Since 2006, he has been a PI scientist at the CSIC. He is the author of 108 publications, most of them original or review articles in top-quartile journals in his field. He is the inventor of two international patents and a founding partner of Inhibitec-Anticuerpos S.L..

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PRODUCT

Anti-BAMBI mAb

MECHANISM OF ACTION

Inhibitec's monoclonal antibody targets BAMBI, a transmembrane protein that blocks TGFβ cellular signaling by preventing active receptor/ligand complexes. Our studies show that inhibiting BAMBI with our antibody increases both the number and functional activity of protective Treg lymphocytes while reducing inflammatory Th17 cells. This novel and disruptive mechanism of action has preventive and therapeutic effects in autoimmune pathologies like psoriasis, psoriatic arthritis and rheumatoid arthritis. Anti-BAMBI dual therapeutic effect differs from existing treatments, which mainly target the Th17 axis, providing a broader therapeutic approach, as seen in comparative studies.

Most of PSA patients exhibit increased numbers of Th17 cells, an enhanced Th17/Treg ratio and a compromised Treg activity. Accordingly, current therapies targeting only defined proinflammatory mediators, but not Treg number and activity, are unable to be effective in around 40% of PsA patients. Inhibitec provides a novel therapeutic option that restore the mentioned immunological abnormalities of these patients.

TARGET INDICATIONS

Chronic autoimmune/inflammatory diseases with indications such as psoriasis, psoriatic arthritis, rheumatoid arthritis, lupus, and IBDs are among those protected by our intellectual property.

CURRENT STATUS

- Identification of BAMBI as a key molecule in the control of CD4 lymphocytes differentiation,

- Development of B101.37 mAb that blocks BAMBI specifically with therapeutic activity for psoriasis, PsA and rheumatoid arthritis (RA).
- Recent humanization of B101.37 mAb to be used in patients.
- Pre-clinical murine models shown improved therapeutic effect for anti-BAMBI therapy compared to current biologics at the clinic.
- 90% of pre-clinical phase has been completed including pilot toxicity studies without compromising safety.

INNOVATIVE ASPECTS

- Anti-BAMBI mAb offers an innovative therapy with a dual mechanism of action, which offers broader protection as it increases the activity of Treg cells while reducing pro-inflammatory Th17 cells, expanding the biological spectrum and improving efficacy compared to current treatments.
- Our therapy provides a disruptive approach not explored before that positions Inhibitec therapy as a leading therapeutic alternative in the future.

IPR

International Patent filed in 11/2015 'Anticuerpos monoclonales frente a BAMBI y uso para tratamiento de enfermedades inflamatorias'. This patent has been extended to the EU (02/07/2019) and USA (16/07/2019) and finally approved in 2022 (EU ref number EP3385282; US patent ref 11,518,802).

PARTNERING OPPORTUNITIES

Our primary interest in collaborating with the big pharma is co-development. Our roadmap to the clinic includes several tasks that we will need to outsource, such as GMP production and regulatory toxicity testing. Therefore, we are seeking a partnership to facilitate these processes.

PROFILE

The activity of the **Research Group** includes 1) Synthesis of smart cationic polymers for the encapsulation of nucleic acids through electrostatic interactions, including targeting moieties and functional groups (i.e. zwitterionics); 2) Formulation of nanoparticles with synergistic therapeutic nucleic acids; 3) Isolation and engineering of extracellular vesicles as natural therapeutic delivery systems; 4) Validation of the safety and functionality of engineered nanosystems in vitro and in vivo; and 5) Use of the precision nanosystems for cancer immunotherapy, gene and targeted therapies.

SPEAKER

Dr. Fornaguera is an expert on formulation of nanomedicines, namely focused on the design of actively targeted polymeric nanoparticles, loaded with active nucleic acids for cancer immunotherapies. With a strong background and demonstrated expertise in developing transdisciplinary projects, she leads a multidisciplinary team able to synthesize the polymers, formulate at the nanoscale and in vitro and in vivo validate the designed nanotherapies.

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PRODUCT

NanoTarget, a technological proprietary polymeric library for the encapsulation of nucleic acids through electrostatic interactions.

MECHANISM OF ACTION

Through the combination of different polymeric variants, nanoparticles with different functionalities and directed to different cells can be obtained. Likewise, the encapsulation of different nucleic acids allows the design of combination synergistic therapeutic moieties to tackle different molecular pathological targets.

The mechanism of action is the typical one from vaccines: the transfection and expression of the encapsulated antigenic mRNA on the surface of dendritic cells, to achieve the further interaction with T helper cells, thus boosting an adaptive humoral and cellular response that will generate an immune attack to the tumor cells presenting the same tumoral antigens.

TARGET INDICATIONS

Tumor therapeutics: targeted therapies for oncogenes silencing (i.e. mTOR pathway); or immunotherapy through personalized antigenic mRNA vaccination. Gene therapy of rare diseases: through delivery of mRNA as supplementary therapies of neurodegenerative diseases or viral vectors coating for the treatment of muscular dystrophies. Other targeted therapies: delivery of therapeutic RNAs for depressive disorder, aortic aneurism or Marfan disease, among others

CURRENT STATUS

- NanoTarget polymeric platform is present through its champion product: a mRNA vaccine, based on the so-called ZION nanoparticles, to treat lung cancer.
- It consists on a combination of three polymers: 1) zwitterionic modified one, to achieve stealth effect while avoiding immune recognition and unspecific cell interaction; 2) WH-targeted polymer, adding this peptide targeting the Clec9A receptor, overexpressed

on the surface of dendritic cells; 3) cationic polymer for the electrostatic interaction with the mRNA. The mRNA will be personalized depending on the antigens presented by the cohort of patients analysed.

- We have already validated, at preclinical level, the safety and functionality of the champion product, the mRNA antitumor vaccine.
- We have validated the lyophilization methodology.
- We produced big batches of the polymer (up to 1g) and of the nanoparticles (up to 50mL), suing an automatized, GMP-like microfluidics system maintaining critical quality control attributes.

INNOVATIVE ASPECTS

- Robust and versatile polymeric platform that allows facile adaptation to different nucleic acid loadings and to different targeted cells, thus allowing the therapy of different unmet needs.
- Targeted particles that broaden the therapeutic window.
- Polymeric mRNA vaccine, without PEG, which avoid PEG-related eventual immune rejection.
- Possibility to encapsulate more than one antigenic mRNA, thus making the formulation not necessarily personalized at a single patient level.
- Possibility to lyophilize the formulation, thus enhancing the storage stability and avoiding the requirements of costly extreme cold freezers.

IPR

Polymeric library protected under an international patent, with a priority date from 2021, that is currently under national phases.

PARTNERING OPPORTUNITIES

We would like to license out specific uses of the polymeric platform. Previously, with international companies, we have tested the application of the polymers for biomedicine / pharmaceutical applications.

PROFILE

STAb Therapeutics is a biotechnology spin-off from the Research Institute of Hospital 12 de Octubre, launched to develop next-generation immune system redirection strategies for solid and hematological tumors, based on groundbreaking discoveries from the laboratories of Dr. Luis Alvarez-Vallina and Dr. Belén Blanco. The company specializes in genetic engineering for the development of an innovative type of cell therapy called STAb-T cell therapy, aimed at efficiently redirecting the immune system to different cancers.

SPEAKER

Carolina is an innovation professional with more than 15 years of experience in the biotechnology sector and an international perspective after one decade in the US. She has a doctorate in molecular biology from NYU and ample experience in technology transfer and business development from research centers, such as the CNIO in Madrid, and tech companies, such as PharmaMar and Arquimea. She is also an associate at the business angels association, WA4STEAM.

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PRODUCT

STAb-T19, a novel autologous T cell immunotherapy for the treatment of CD19 positive B-cell Acute Lymphoblastic Leukemia and B-cell Non-Hodgkin Lymphoma.

MECHANISM OF ACTION

The product consists of genetically-modified autologous T lymphocytes secreting anti-CD19xanti-CD3 bsAbs for the treatment of B-cell malignancies. STAb-T19 lymphocytes reinfused into the patient in situ secrete an anti-CD19xanti-CD3 bsAb that redirects T cells to CD19-positive tumor cells. The bsAb triggers tumor-specific T cell activation and cytotoxic activity by crosslinking the T-cell activating molecule CD3 with the tumor associated antigen CD19. STAb-T cell activation leads to the generation of memory STAb-T19 cells that keep on secreting the bsAb and protect the patient from potential relapses, which bsAbs do not do once their administration has been discontinued. Importantly, since all the T cells express CD3, the soluble anti-CD3xanti-CD19 bsAb recruits not only genetically-modified STAb-T19 cells, but the entire T cell repertoire to attack the tumor. This greatly amplifies the immune response compared to CAR-T cells.

TARGET INDICATIONS

Our pipeline consists of 4 therapeutic programs: 2 therapies in IND enabling phase to treat blood tumors and 2 therapies in preclinical development for hard-to-treat solid tumors.

CURRENT STATUS

- We have developed STAb-T19 therapy from concept to clinical trial stages. We have conducted exhaustive preclinical studies in which we have shown that human primary T cells can be transduced with a lentiviral vector that encodes an anti-CD3xCD19 bsAb in tandem-scFv format to efficiently secrete functional bsAb.
- The secreted molecule binds its two targets (CD3 and CD19) and redirect modified and unmodified bystander T cells to kill B-ALL cells, both in vitro an in relevant in vivo models using patient tumor cells.

- Finally, we have performed three STAb-T19 productions under GMP conditions using the CliniMacs Prodigy system, in which we have generated STAb-T19 cells with demonstrated anti-tumor efficacy.
- We have received public funding totaling 1.2 Mill € to perform a phase I clinical trial after authorization approval from the AEMPS, which is expected in Q4 2024.

INNOVATIVE ASPECTS

- Our STAb-T therapies represent an innovative approach that provides the main advantages of current T cell redirecting strategies, e.g. CAR-Ts and systemically administered bsAbs, and addresses some of their major limitations. The product STAb-T19 is engineered to redirect both STAb-T19 T cells and the patient's unmodified T cells to the antigen CD19, which is expressed by tumor cells in B-cell malignancies.
- There are 4 CAR T-19 products: Kymriah, Yescarta, Tecartus and Breyanzi, and 1 CD3xCD19 bsAb: Blincyto, that are currently approved. Other products in development are focused on strategies for dual targeting CAR T and in vivo CAR T. Compared to conventional CART cells, STAb-T cells have a significant advantage in that they promote the "polyclonal recruitment" of both modified STAb-T and unmodified T cells present in the tumor microenvironment. This results in enhanced antitumor efficacy.
- This polyclonal recruitment is associated with an additional benefit, in that the exhaustion suffered by CAR-T cells that leads to their lack of efficacy, does not preclude STAb-T cells from secreting the bsAb, which can activate circulating T cells.
- In addition, the downregulation of the target antigen CD19 and the Modified from Blanco B, Trends Immunol 2019 internalization of the CAR in CAR-T cells that occur during CAR-T19 treatment leads to tumor escape. This phenomenon is not observed with STAb-T19. Compared to bsAb, STAb-T cells are a "fully-human cell factory" thus producing a constant release of bsAb compared to the short half-life of administered bsAb and circumventing any technical problems and high costs associated to mass production of bsAb in industrial systems. Finally, STAb-T cells can actively traffic to tumors and generate a pool of memory T cells compared to bsAbs.

IPR

STAb Therapeutics holds the exclusive rights for the exploitation and commercialization of the know-how for the STAb technology and the patent family EP4107183 that is protecting the product STAb-T19 through a licensing agreement with the academic co-owners of the IP. This family of patents is currently in national phases in Europe and the US. The first claim covers the T cells characterized by secreting a bsAb comprising a large set of sequences encompassing combinations for a bispecific antibody with an anti-CD19 and an anti-CD3. In subsequent claims, the patent includes the use of the modified T cells as a drug.

PARTNERING OPPORTUNITIES

Our business model is based on an out-licensing strategy for our STAb-T cell products and technology with biopharmaceutical companies seeking novel immunotherapeutic assets for their oncology pipelines and that have the capacity and expertise to carry out the late-stage phases of clinical development. We envision establishing both co-development agreements and/or licensing agreements with established market terms. In this regard, our goal to maximize the value of our products and the company's technology and know-how is to develop the candidates up to a phase I to provide clinical proof of concept and validation in the clinical setting. Given our expertise and the innovative capacity of the scientific team, we aim to develop the technology into cell immunotherapeutic products for hard-to-treat tumors in both blood and solid cancers.

PROFILE

The research group aims to clarify the pathological molecular mechanisms behind Alzheimer's disease (AD) and lately, to translate our research into diagnostic tools and processes with therapeutic relevance. Among our goals, we aim to identify biomarkers that serve as a read-out of impaired brain function. We validate these potential biomarkers in cellular models modeling the disease condition. We are interested in particular glycoforms of proteins that can improve the sensitivity and specificity of the diagnostic biomarkers.

SPEAKER

Javier Saez-Valero is a PhD in Biology at the University of Murcia (Spain); Postdoctoral stay at the Dep of Pathology, University of Melbourne (Australia) and at the Institute Mario Negri in Milan (Italy). PI of national and international projects since 2002 at the Institute of Neuroscience, Alicante. Member of the "Society for CSF analysis and clinical neurochemistry" and of the "Tear Research Network".

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PRODUCT

Detection of aberrant apolipoprotein E (apoE) complexes as an Alzheimer's biomarker

MECHANISM OF ACTION

In cellular cultures, treatment with amyloid peptide Aβ42, the pathological effector of Alzheimer's disease (AD), affects the secretion of mature glycoforms of apoE. In an in vitro assay, using Aβ42 and recombinant apoE, we have demonstrated the generation of aberrantly resistant apoE aggregates, both features in which detection is based our biomarker kit. Thus, amyloid will be the triggering effector responsible of altered apoE in AD.

Humans have three versions of the APOE gene, allele ε2 (apoE2), ε3 (apoE3) and ε4 (apoE4). APOE ε4 is the most important risk factor for sporadic AD, and many labs develop kits to determine APOE genotype. We have demonstrated alterations in the apoE protein in AD cerebrospinal fluid (CSF), leading to a compromise in biological function, and that served to develop a kit for AD diagnosis. We are developing a kit, based in the determination of apoE aberrant complex, with anti-apoE antibodies (preferably with conformational antibodies), and immature glycoforms with lectins; a unique qualitative kit on the market in a plastic support, and a further quantitative ELISA kit.

TARGET INDICATIONS

Early diagnosis of AD. Our biomarker allows the development of both qualitative and quantitative approaches to detect AD and monitoring the evolution of the patients. The biomarker could be very useful in choosing patients to participate in clinical trials and in their follow-up.

CURRENT STATUS

- We have described the occurrence of two abnormalities in the CSF of AD patients. The first is an imbalance in the ratio of mature/immature glycoforms of apoE, and the second is the existence of aberrantly resistant apoE aggregates almost exclusively in AD.
- In brain extracts from AD patients, we have corroborated that the shift in the ratio of mature/immature glycoforms of apoE progresses with the disease.

- Lectin-binding analysis revealed in AD brain an abnormal glycosylation of apoE, and currently we are carrying out a glycoproteomic analysis of apoE. All these abnormalities are present independently of the APOE genotype, but more profound changes occur in APOE3 carriers (more common genotype).
- In tears we demonstrated that both mature and immature apoE glycoforms are also present. We are currently collecting tear samples from AD subjects (with CSF also available from the same individuals).

INNOVATIVE ASPECTS

- The biomarker allows the development of both qualitative and quantitative approaches to detect AD, and will allow patient monitoring/evolution, both are characteristics that current fluid biomarkers lack.
- Double labeling with antibody/lectin would imply a refinement of the biomarker specificity.
- The possibility of developing a qualitative test on fluids such as tears increases the interest on it.
- Our preliminary data indicate that apoE is present in tears with a pattern of molecular forms similar to that of CSF.

IPR

National Patent (method and diagnostic kit of Alzheimer's disease based on the detection of Apolipoprotein E), with application date 03/17/2022. Extended internationally with reference PCT/ES2023/070162. Currently preparing the documentation for entry into national phases.

PARTNERING OPPORTUNITIES

The biomarker would be useful in the selection and monitoring of participants in clinical trials for therapies against Alzheimer's. For the applicability in a clinical laboratory, further development of the diagnostic kit is required. We can lead or assess in such development.

PROFILE

Aptadel is a biotech company incorporated in December 2020 in Barcelona, Spain. Aptadel is developing an RNA aptamer-based platform for the targeted treatment of cancer. The technology is currently in preclinical stage. The lead candidate will be taken into clinical stage while further developing other company's programs.

SPEAKER

Dr. Gisela Lorente holds a Ph.D. in Biomedicine. She specializes in innovation and technology transfer. She started her career in the United Kingdom and was thereafter head of the Innovation portfolio and Tech Transfer of IDIBELL for 5 years. Her activities at IDIBELL included the creation of Aptadel, leading the seed financing round and the company as a CEO. She is also actively involved in the entrepreneurial ecosystem, serving as a public funding evaluator for competitive calls and holds the Academy for Woman Entrepreneur (AWE) award 2024.

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PRODUCT

An RNA aptamer-based platform technology for the targeted treatment of Cancer

MECHANISM OF ACTION

Aptadel has developed a novel platform technology based on aptamer-drug conjugates for generating new personalized candidates for different types of tumors expressing the EphA2 cell membrane receptor. EphA2 overexpression has been reported in several solid tumors. The core aptamer has anti-metastatic properties.

Aptadel's lead product, ADEL-101, is an RNA aptamer against the EphA2 receptor, linked to a siRNA that specifically inhibits EWS/FLI1, a transcription factor fusion, the key driver of Ewing Sarcoma (ES).

Aptadel's Aptamer Drug Conjugates (ApDC) can be personalized for the treatment of different cancer types overexpressing EphA2 cell receptor with a high specificity and low toxicity. The Aptamer selectively targets the cancer cell, and upon binding to EphA2, inhibits its metastatic potential and delivers the cytotoxic cargo inside the tumoral cell.

TARGET INDICATIONS

All those cancer types overexpressing EphA2 receptor (sarcomas, pancreatic cancer, colorectal cancer, ovarian cancer, breast cancer, melanoma, prostate cancer, bladder cancer, glioblastoma, among others). PoC in Ewing Sarcoma.

CURRENT STATUS

- Aptadel's lead program, ADEL-101, has already demonstrated efficacy and security both in vitro and in vivo (xenograft mice models).

- We are currently working on dosage optimization and route of administration selection. After completion of this milestone, ADEL-101 will be ready to enter in regulatory pre-clinical stage (regulatory tox studies and CMC production).
- Within its pipeline Aptadels is developing new candidates to treat other childhood and adult tumors.

INNOVATIVE ASPECTS

- Aptamers can be compared to Antibodies in terms of binding affinity and specificity, but present higher tissue penetration (specifically in tumors), higher stability, lower toxicity and improved cost-effectiveness in manufacturing. Different antibodies targeting EphA2 have failed in clinical trials due to toxicity or lack of efficacy.
- Moreover, delivery of siRNAs only has been possible in the liver with the current technologies, Aptadel's technology has the potential to be a first-in-class delivering siRNAs into tumoral cells.

IPR

Aptadel's technology is protected by 2 patent applications. One is already granted in China and under examination in other countries (EU, US, Ca, Ja, Au). The other one is entering in PCT, with a positive EESR. Both have positive FTO reports.

PARTNERING OPPORTUNITIES

Aptadel is interested in co-development with pharmaceutical industry for both developing its lead candidate and exploring new indications for its proprietary platform technology. Also, the business model of the company will be licensing out its technology or an M&A to a big Pharma.

PROFILE

The Research Group work has been focused on the design and chemical synthesis of bioactive molecules, with a special interest in the discovery and synthesis of novel small molecules for the treatment of cancer (inhibition of metastasis via integrins and of epigenetic targets such as HDACs). The collaboration between Biogipuzkoa and UPV/EHU groups led to the design, synthesis, and patenting of Aurkines, novel molecules that possess a marked polyelectrophilic character.

SPEAKER

Fernando Cossío holds a Chemical Sciences degree from the University of Zaragoza (1982) and a Ph.D. in Chemistry from UPV/EHU (1986). After research in France (CNRS, Bordeaux) and the U.S. (UCLA), he joined UPV/EHU in 1988 and became a professor in 2002. He served as Vice-Rector for Research (2001-2003) of the UPV/EHU. Since 2009, he is the Scientific Director of Ikerbasque, the Basque Foundation for Science. He co-founded the biotechnology company Ikerchem S.L., now Quimatryx Ltd., which develops novel chemical entities, including one HDAC inhibitor (QTX125) currently in Phase I clinical trials.

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PRODUCT

Aurkines: novel chemical entities with marked polyelectrophilic properties, specifically designed to induce double-strand DNA breaks

MECHANISM OF ACTION

Unlike conventional dielectrophilic chemotherapeutic agents like Cisplatin, which have only two electrophilic moieties, Aurkines introduce an additional electrophilic position to significantly increase the rate of double-strand DNA breaks. Each molecule contains one Pt(II) electrophilic center that can replace two leaving groups with G or A units, as well as one C(sp3) center that facilitates a third nucleophilic substitution reaction. This design enhances the molecule's ability to distort and damage DNA in cancer cells.

All Pt(II)-derived chemotherapeutic agents developed to date, like Cisplatin, Oxaliplatin, and Carboplatin, predominantly induce single-strand DNA breaks, with double-strand breaks occurring infrequently (less than 5% of cases). This allows cancer cells to activate DNA repair mechanisms, contributing to treatment resistance.

TARGET INDICATIONS

This new product can be used to treat a wide range of cancers, including those currently treated with platinum (Pt)-based drugs (e.g. Cisplatin). It is also effective against cancers that are resistant to Cisplatin or other analogues used in clinical practice. Moreover, it has the potential to be combined with immune checkpoint inhibitors (ICIs) to enhance tumor antigenicity and promote the immune response.

CURRENT STATUS

- We have designed, chemically synthesized, and therapeutically evaluated two novel chemotherapeutic agents, Aurkine 16 and Aurkine 18, which exhibit marked poly-electrophilic properties and potent antitumor effects.
- Unlike Cisplatin, these compounds induce double-strand DNA breaks, resulting in increased cytotoxicity in both naïve and Cisplatin-resistant cancer cells (including biliary, breast, and ovarian cancers) as well as in cancer-associated fibroblasts.
- Importantly, Aurkines show minimal toxicity to healthy cells, demonstrating selective targeting of malignant cells due to differences in chromatin remodelling.
- In vivo studies reveal that Aurkines effectively halt cancer growth without causing adverse effects. These findings position Aurkines as promising therapeutic candidates for treating both naïve and Cisplatin-resistant cancers.

INNOVATIVE ASPECTS

- Aurkines induce high rates of double-strand DNA breaks, a form of damage that cancer cells struggle to repair, thereby increasing cancer cell death and reducing chemoresistance.
- Aurkines are more effective than Cisplatin in treating various naïve cancer types and are also effective against Cisplatin-resistant tumors.
- Aurkines selectively target cancer cells and cancer-associated fibroblasts (CAFs), demonstrating minimal toxicity in healthy cells due to differences in chromatin remodelling.
- Overall, Aurkines represent a novel therapeutic strategy with significant potential for treating different types of naïve and Cisplatin-resistant tumors.

IPR

Priority Spanish National Patent Application (P202231032) with a priority date of 11/30/2022. The State-of-the-Art Report (IET) from the OEPM was positive on 09/29/2023.

PCT Application PCT/EP2023/083500 filed on 11/29/2023.The International Search Report (IBI) and Written Opinion from the European Patent Office (EPO) was positive on 08/04/2024. Patent published on 6/06/2024

PARTNERING OPPORTUNITIES

The team's primary interest is to advance to the next stages of development, including further clinical testing and marketing.