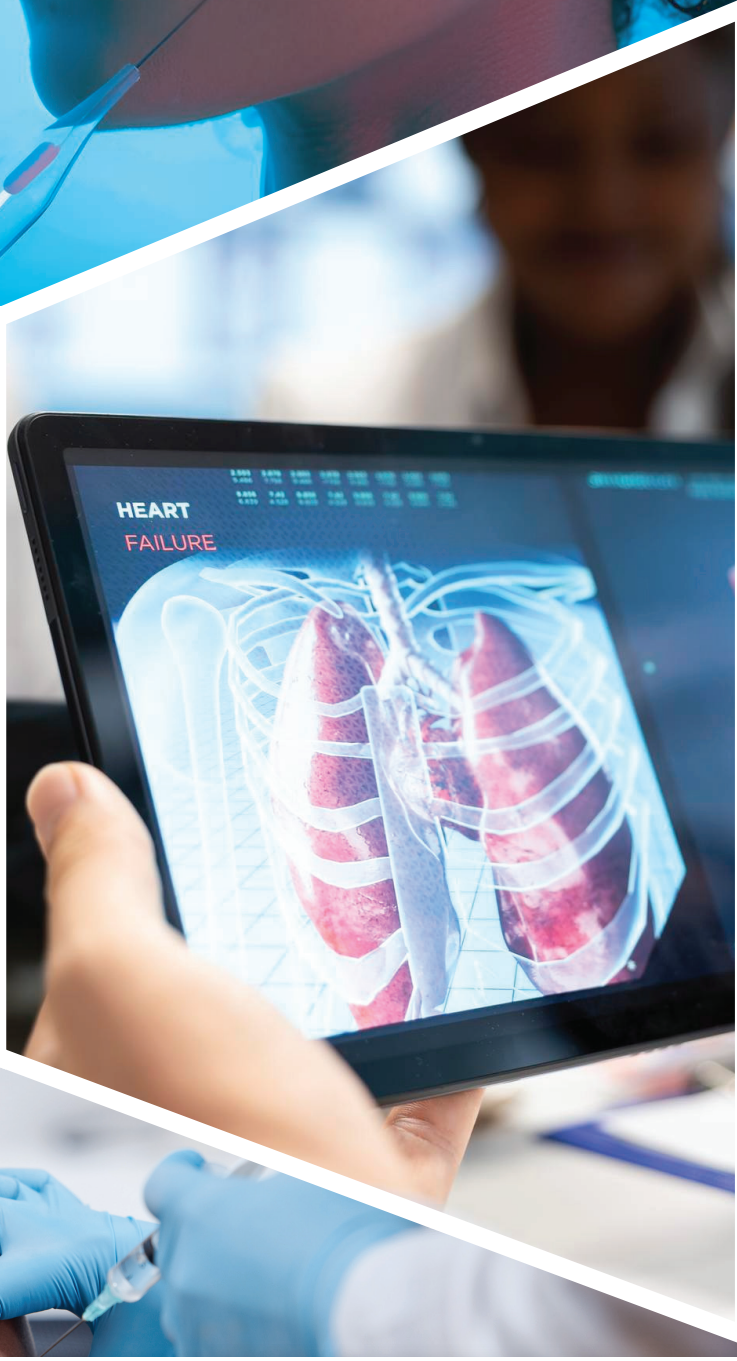
TECHNOLOGY PROFILES

SOUTH AFRICA-CUBA BIOTECHNOLOGY COLLABORATION



science, technology & innovation
Department:
Science, Technology and Innovation
REPUBLIC OF SOUTH AFRICA

BIOCUBA FARMA

15 YEARS OF SUPPORTING INNOVATION

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PROJECT TITLE: JUSVINZA, MODIFIED PEPTIDE LIGAND TYPE PEPTIDE FOR THE TREATMENT OF AUTOIMMUNE DISEASES AND ACUTE AND CHRONIC INFLAMMATORY DISEASES

Company: Center for Genetic Engineering and Biotechnology
Therapeutic or preventive area/Indications: Autoimmune diseases and acute and chronic inflammatory diseases/rheumatoid arthritis, COVID-19, and others.

PROJECT DESCRIPTION:

The active ingredient of the product is a modified peptide, of the APL (altered peptide ligand) type. This peptide is derived from the 60 kDa cellular stress protein (HSP60), which acts as a chaperone, and is involved in the pathogenesis of several autoimmune and inflammatory diseases. It was designed using bioinformatics tools, and is obtained by chemical synthesis.

Jusvinza inhibits the activity of neutrophils, monocytes and macrophages, with a consequent decrease in plasma levels of several pro-inflammatory cytokines and soluble mediators of inflammation. This peptide is biodistributed in the lymph nodes and the gastrointestinal tract, promoting the induction of apoptosis of activated peripheral and intestinal lamina propria T cells. In addition, Jusvinza induces T cells with a regulatory phenotype and exerts a protective effect on apolipoprotein A-I (Apo A-I), which favors the stability of high-density lipoproteins (HDL). Jusvinza has an anti-inflammatory effect and induces mechanisms associated with the restoration of immunological tolerance.

Main results of pre-clinical and clinical studies:
The therapeutic potential of CIGB-814 (Jusvinza) in Rheumatoid Arthritis (RA) was evaluated in two animal models: Adjuvant-induced arthritis in Lewis rats (AA) and in collagen-induced arthritis (CIA) in DBA/1 mice. Clinical and histopathological analyzes in animals demonstrated that CIGB-814 efficiently inhibited the course of RA.
In clinical trials, two indications have been addressed:

- Rheumatoid arthritis: The treatment was safe at all doses tested. The peptide reduced the disease and the MRI score in the patients. Five and 11 of the 18 patients achieved ACR 50 and ACR 70, respectively, at the end of treatment. This therapy improved the quality of life of the patients.

- COVID-19: Safety and effect studies of Jusvinza were carried out in the treatment of serious and critically ill patients positive for COVID-19. The results obtained allowed the registration to be maintained for emergency use during the pandemic.

Current stage:
- **Phase III** clinical trial in rheumatoid arthritis underway.
- **Phase II** clinical trial in community-acquired pneumonia is ongoing.
- **Phase II** clinical trial in acute respiratory distress syndrome is ongoing.

Intellectual Property:

1. Peptides and their derived type APL of the HSP60 and pharmaceutical compositions. PCT/CU2005/000008. Granted in Europe, United States, Japan, Korea, China, Russia, Australia.
2. Use of an altered peptide ligand for treatment type 1 diabetes and bowel intestinal disease. CU 2008-0254. Granted in Europa, USA, Japón, Corea, China, Rusia, Australia
3. Pharmaceutical composition comprising peptide type APL. PCT/CU2018/050007, WO/2019/129315.
4. Peptide for the treatment of cytokine storm syndrome. CU 2020-0026.
5. Peptide for the treatment of diseases related to affectations in apolipoprotein AI or transtyretine: CU 2022-0040.

Competitive advantages:

- Jusvinza is safe, a crucial advantage over current treatments for Rheumatoid Arthritis.
- Jusvinza induces regulatory T cells, an element that reinforces the therapeutic action of the product, especially the reduction of the inflammatory response.
- It can be used in combination with current treatments for target diseases.

Business or cooperation opportunities:

- Patent license for the development of clinical trials, registration and marketing of the product.
- Academic collaboration for the evaluation of Jusvinza in new reference animal models that allow expanding its therapeutic potential.

Main publications:

- Baldomero J, et al. Early Treatment with a Peptide Derived from the Human Heat-Shock 60 Protein Avoids Progression to Severe Stages of COVID-19. Journal of Biotechnology and Biomedicine. 2021;4:196-210.
- Dominguez MC, et al. An altered peptide ligand corresponding to a novel epitope from heat-shock protein 60 induces regulatory T cells and suppresses pathogenic response in an animal model of adjuvant-induced arthritis. Autoimmunity.2011;44(6):471-82.doi: 10.3109/08916934.2010.550590.
- Corrales O, et al. CIGB-814, an altered peptide ligand derived from human heat-shock protein 60, decreases anti-cyclic citrullinated peptides antibodies in patients with rheumatoid arthritis. Clin Rheumatol. 2019 Mar;38(3):955-960. doi: 10.1007/s10067-018-4360-
- Prada D, et al. Phase I Clinical Trial with a Novel Altered Peptide Ligand Derived from Human Heat-Shock Protein 60 for Treatment of Rheumatoid Arthritis: Safety, Pharmacokinetics and Preliminary Therapeutic Effects. J Clin Trials. 2018;8:339. doi:10.4172/2167-0870.1000339
- Barberá A, et al. APL1, an altered peptide ligand derived from human heat-shock protein 60, increases the frequency of Tregs and its suppressive capacity against antigen responding effector CD4 + T cells from rheumatoid arthritis patients. Cell Stress Chaperones. 2016;21(4):735-44. doi: 10.1007/s12192-016-0698-0

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PROJECT TITLE: HEBERPROT-P, INJECTABLE FORMULATION BASED ON RECOMBINANT HUMAN EPIDERMAL GROWTH FACTOR, FOR THE TREATMENT OF DIABETIC FOOT ULCER (DFU) IN ADVANCED STAGE

Company: Center for Genetic Engineering and Biotechnology

Therapeutic or preventive area/Indications: Healing therapy/treatment by local infiltration of diabetic foot ulcers of grades 3 and 4 in the Wagner classification, with neuropathic or ischemic components, and high risk of amputation.

PROJECT DESCRIPTION:

Heberprot-P is an injectable lyophilized formulation, based on recombinant human epidermal growth factor (hrEGF), indicated for infiltration into the bed and contours of diabetic foot ulcer (DFU) and lower extremity wounds, including ulcers and the residual bases of amputation, to reverse the chronicity phenotype, as an adjuvant therapy to trigger and maintain the healing process and eventual re-epithelialization.

The product is indicated for high-grade wounds, recalcitrant to healing, classified as grades III and IV on the Wagner scale. For formulation, the growth factor is presented as a preparation of 75 µg hrEGF per vial.
The efficacy and safety of the intervention has been tested in five exploratory and one confirmatory, randomized, double-blind, placebo-controlled clinical trials.

Subsequently, other post-marketing pharmacovigilance studies have also been developed. The clinical development has addressed a type of patient not typically included in DFU clinical trials. The characteristics of the patients included have been quite homogeneous between the trials, mainly due to (i) long-term diabetes mellitus, mostly type 2; (ii) average age > 60 years; (iii) chronic ulcers (more than one month of evolution); (iv) deep ulcers (exposing subcutaneous cellular tissue or tendons, or joint capsule); (v) advanced basal infection, given its large size (average area always > 20 cm2, which had to be treated before the use of hrEGF), necrotic tissue (which had to be surgically removed); (vi) approximately half of the patients with poor irrigation of the corresponding leg (ischemia).

The last three characteristics are often exclusion criteria in DFU clinical trials. These ulcers correspond to grades 3 or 4 of the Wagner classification. Overall, these patients represent 50% of the entire DFU population, and result in the majority of amputations.

Main results of pre-clinical and clinical studies:
Preclinical studies show that hrEGF binds to EGFR in laboratory animals and triggers a host of biological and pharmacological actions. Topical administration of hrEGF in injured animal models has been shown to improve the healing process and stimulate cell proliferation to a limited extent. Systemic administration of hrEGF has been shown to improve cell turnover and homeostasis of epithelial cells in the gastrointestinal tract. Systemic administration of hrEGF has been shown to stimulate cell survival, contributing to a sustained cytoprotective effect.

The entire program of clinical studies in patients with advanced DFU (Wagner grade 3 or 4, mean size > 20 cm2, ischemic not excluded) has shown that hrEGF injected intralesionally, adjuvant to good standard wound care, has the potential to promote granulation, complete wound healing, even in subjects who do not respond to other treatments, faster than subjects treated with good standard wound care alone. The relapse rate is also reduced. The procedure has the potential to reduce amputation rates, particularly in neuropathic or mildly ischemic patients, with considerable improvement in personal and public health. No serious adverse events related to the particular treatment were observed.

Everything can be explained by the underlying disease. No increase in cardiovascular, respiratory, or renal complications was reported. Adverse events attributed to treatment have generally been limited to tremors, chills, and pain at the injection site. These have been mild and self-limiting. No increase in the development of cancer has been observed in treated patients. In conclusion, the data confirmed the clinical usefulness of this route of administration to trigger and maintain the healing process. Infiltrated EGF was shown to result in a 75% complete granulation response, 61% wound closure, and a 71% reduction in the relative risk of amputation, as well as a positive risk-benefit balance. Of utmost clinical and social relevance is that recurrences were reported as an exceptional event (approximately 5%) in a 12-month follow-up period.

Current stage:
- Product registered in Cuba and 26 other countries, including Turkey, Mexico and Colombia.

Intellectual Property:
- Patent applied

Competitive advantages:
- Heberprot-P stimulates granulation tissue, angiogenesis, contraction and re-epithelialization.
- Reduces inflammation, systemic toxicity due to reactive oxygen species (ROS) and does not recruit inflammatory cells.
- It is useful for urgent coverage of bone, cartilage, vessels, nerves and capsules by local peripheral infiltration. It is a unique medicine in its class.
- Induces paracrine expression of other healing growth factors.
- Reduces the number of debridements and surgical interventions due to its cytoprotective effects.

- Molecular changes in situ support the notion that EGF somehow modifies the “way of life” of cells and the extracellular matrix, so that local recurrences are low.

Business or cooperation opportunities:
Co-development agreements for the introduction of Heberprot-P in new markets for UPD indication.

Purchase and distribution contracts.
Joint development agreement for new indications.
Joint development agreement for new EGF formulations.
Some of these alternatives could include technology transfer of the final steps to obtain the finished product.

Main publications:

- Montequin JF, et al.Intralesional and perilesional application of an epidermal growth factor (Heberprot-P) in diabetic foot ulcers. Part one. Angiol Sosud Khir. 2018;24(4):33-42. English, Russian. PMID: 30531767.
- Berlanga-Acosta JA, et al.Cellular Senescence as the Pathogenic Hub of Diabetes-Related Wound Chronicity. Front Endocrinol (Lausanne). 2020;11:573032. doi: 10.3389/fendo.2020.573032. PMID: 33042026; PMCID: PMC7525211.
- González-Bravo M, et al.Applying Quantitative Immunogold Labeling Distributions of Cellular Compartments in Immunoelectron Microscopy Images to the Study of EGFR Intracellular Signaling. Biomed J Sci & Tech Res 26(3)-2020. BJSTR. MS.ID.004352.
- Ferrer-Tasies L, et al.Recombinant Human Epidermal Growth Factor/Quatsome Nanoconjugates: A Robust Topical Delivery System for Complex Wound Healing. Adv. Therap.2021,4, 2000260. DOI: https://doi.org/10.1002/adtp.202000260.
- Berlanga-Acosta J, et al.Intralesional Infiltrations of Cell-Free Filtrates Derived from Human Diabetic Tissues Delay the Healing Process and Recreate Diabetes Histopathological Changes in Healthy Rats. Frontiers in Clinical Diabetes and Healthcare. 2021;2. DOI: 10.3389/fcdhc.2021.617741.

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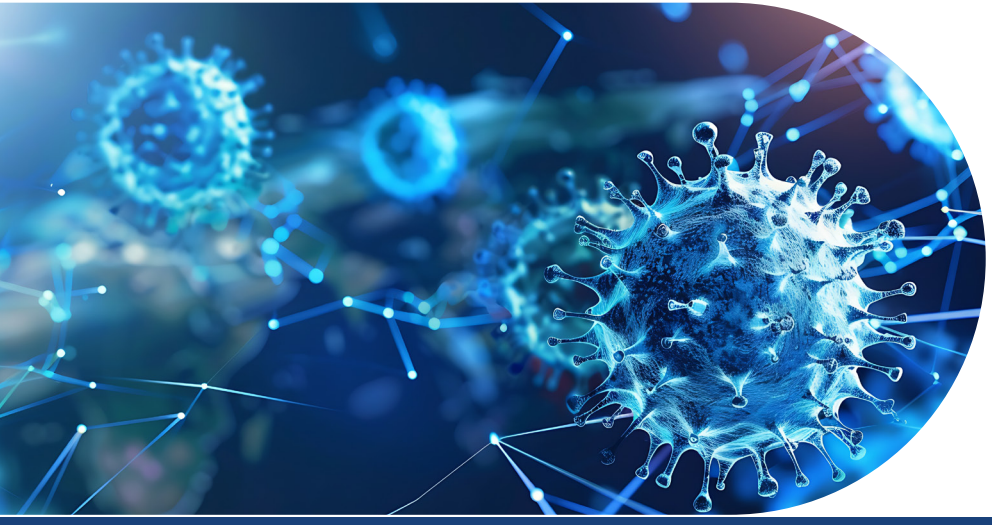

PROJECT TITLE: NIMOTUZUMAB. CANCER IMMUNOTHERAPY

Company: Center for Molecular Immunology
Therapeutic or preventive area/Indications: Oncology

PROJECT DESCRIPTION:

Nimotuzumab is the first monoclonal antibody approved by CECMED for the treatment of head and neck tumors, in 2002. Its mechanism of action is based on blocking the binding of ligands to the epidermal growth factor receptor EGF- R, which inhibits the tyrosine kinase activity of the receptor, interfering with the cell signaling pathway involved in cell proliferation. Nimotuzumab has anti-angiogenic, anti-proliferative and pro-apoptotic effects in those tumors that overexpress the EGF-R, therefore, it inhibits the growth of tumor cells of epithelial origin in vitro and in vivo. There is evidence that suggests that Nimotuzumab can be combined with other therapies such as anti-check point antibodies and enhance the antitumor response.
In COVID-19, EGF-R is overexpressed in type II alveolar epithelial cells due to reduced STAT-1 and acute lung damage. Overexpression of EGF-R further activates STAT-3 and increases lung pathology and hypo-fibrinolytic state. The EGF-R pathway is also one of the main nodes of pulmonary fibrosis, controlling several cascades of cell proliferation, mucus secretion, inflammatory response and tissue repair.

Main results of pre-clinical and clinical studies:
- Product registered in Cuba and 24 countries, for the treatment of head and neck tumors. It also has registration in esophagus, high-grade gliomas, pancreas, lung and more recently in COVID-19.
- Positive results in pancreatic cancer, which allowed registration for this indication in 2023 in China.

Current Stage:
- Three clinical trials are being carried out in Cuba, two in the area of Oncology and one in severe and moderate high-risk patients with SARS-CoV-2 pneumonia.
- Five clinical trials are ongoing abroad.

Intellectual property:
Information in preparation.
Use of anti-EGFR monoclonal antibody in the treatment of patients with hypoxemic acute respiratory failure (2021). Patent filed.

Competitive advantages:
This monoclonal antibody can be considered a best in class product.
Business or cooperation opportunities:
Agreements for the execution of clinical trials in various indications, registration and commercialization

Main publications:

- Yuan Y, Chen J, Fang M, Guo Y, Sun X, Yu D, Guo Y, Xin Y. Nimotuzumab combined with chemoradiotherapy for the treatment of cervical cancer: A meta-analysis of randomized controlled trials. Front Oncol. 2022 Oct 3;12:994726. doi: 10.3389/fonc.2022.994726. PMID: 36263226; PMCID: PMC9573994.
- Lu, Y., Chen, D., Liang, J. et al. Administration of nimotuzumab combined with cisplatin plus 5-fluorouracil as induction therapy improves treatment response and tolerance in patients with locally advanced nasopharyngeal carcinoma receiving concurrent radiochemotherapy: a multicenter randomized controlled study. BMC Cancer 19, 1262 (2019). https://doi.org/10.1186/s12885-019-6459-6

- Bartels, U., J. Wolff, L. Gore, I. Dunkel, S. Gilheeney, J.Allen, et al. 2014. Phase 2 study of safety and efficacy of nimotuzumab in pediatric patients with progressive diffuse intrinsic pontine glioma. Neuro. Oncol.16:1554–1559.
- Bode, U., M. Massimino, F. Bach, M. Zimmermann, E.Khuhlaeva, M. Westphal, et al. 2012. Nimotuzumab treatment of malignant gliomas. Expert. Opin. Biol. Ther. 12:1649–1659.
- Solomon, M. T., J. C. Selva, J. Figueredo, J. Vaquer, C.Toledo, N. Quintanal, et al. 2013. Radiotherapy plus nimotuzumab or placebo in the treatment of high grade glioma patients: results from a randomized, double blind trial. BMC Cancer 13:299.

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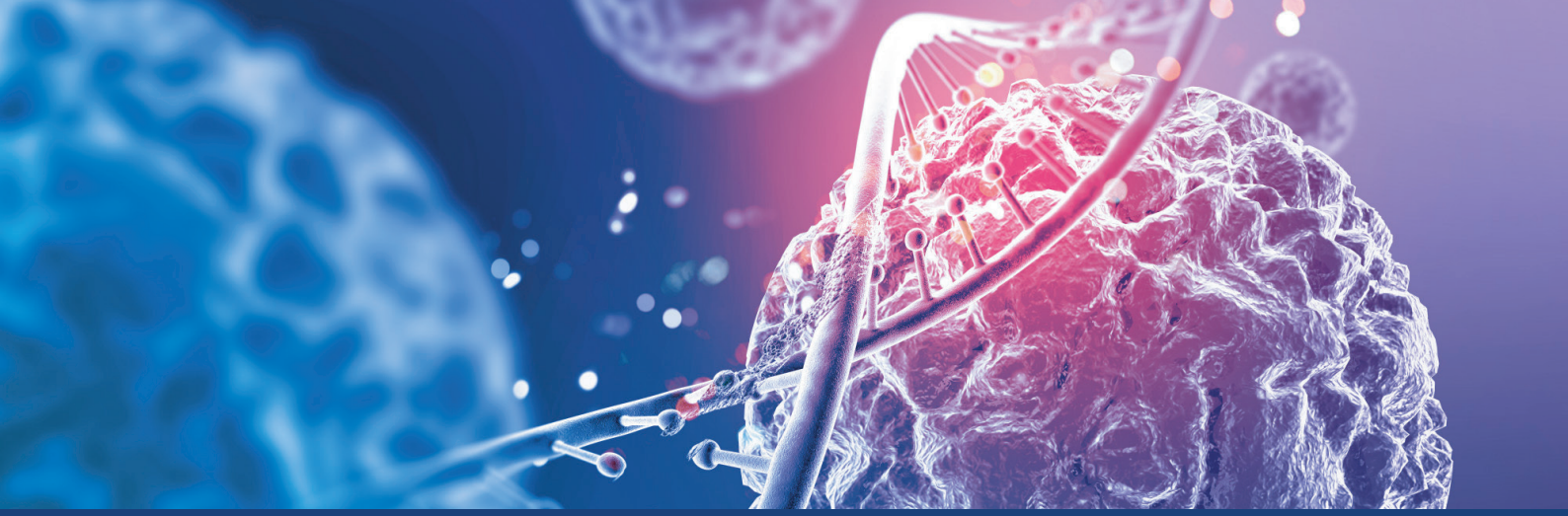

PROJECT TITLE: HEBERSAVAX, IMMUNOTHERAPY BASED ON VASCULAR ENDOTHELIAL GROWTH FACTOR FOR CANCER TREATMENT

Company: Center for Genetic Engineering and Biotechnology
Therapeutic or preventive area/Indications: Oncology / Treatment of solid tumors concomitant with standard chemotherapy, radiotherapy or biological drugs previously approved for a specific condition.

PROJECT DESCRIPTION:

HeberSaVax is a novel immunotherapy for the treatment of cancer, also known by the code CIGB-247. It is designed to induce an immune response directed at vascular endothelial growth factor (VEGF), by generating specific antibodies that block the interaction of VEGF with its receptors, reduce the availability of this growth factor and, therefore, inhibit the effects proangiogenic and immunosuppressive of this molecule. This active immunotherapy produces cytotoxic T lymphocytes that directly eliminate tumor cells that secrete VEGF, through the recognition of VEGF peptides associated with the major histocompatibility complex (MHC) type I that is expressed on the surface of these cells.

Specific active immunotherapy uses a modified human VEGF as an antigen, which is obtained by recombinant means, and has been tested with two adjuvants: very small particles derived from the outer membrane protein (OMP) of the bacteria Neisseria meningitidis (VSSP) and aluminum phosphate.

Main results of pre-clinical and clinical studies:
The available clinical data of HeberSaVax not only demonstrate its safety, immunogenicity and potential clinical benefits, but also provide important elements for the design of more advanced clinical trials, focusing on its therapeutic potential.

Two sequential phase Ia and phase Ib clinical trials were conducted, demonstrating an excellent safety profile and evidence of clinical benefit in patients.

In summary, HeberSaVax meets the immunogenicity requirements as an active immunotherapeutic treatment against cancer.

Current stage:
Two clinical trials are ongoing:
a) focused on ovarian and fallopian tube tumors (phase II/III) and
b) aimed at hepatocellular carcinoma (phase I/II).
Other phase II/III clinical studies in cancer patients are under discussion or in advanced planning.

Intellectual Property:
- The use of mutated VEGF for antiangiogenic therapy; EP1502599. Granted in Europe, Pacific and Oceania. Active antiangiogenic therapy; US7556809B2. Granted in the United States. Active antiangiogenic therapy; Application of new patent filed in Cuba dated December/2019. International application December/2020. PCT/CU2020/050011.

- Application of new patent filed in Cuba dated December/2019. International application December/2020. PCT/CU2020/050011.

Competitive advantages:

- HeberSavax is a novel VEGF-specific active immunotherapy with an excellent safety profile.
- Combination of HeberSavax with other anticancer or antiangiogenic agents could be due to the absence of overlapping toxicities.
- HeberSavax is the only VEGF-based vaccine in the world that has demonstrated evidence of specific immunogenicity in cancer patients.
- HeberSavax exerts a dual mechanism of action: it induces neutralizing anti-VEGF antibodies and generates cytotoxic T cells.
- HeberSavax is administered subcutaneously, offering cost reduction in healthcare institutions.
- HeberSavax targets several oncology indications such as advanced ovarian cancer, hepatocellular carcinoma and metastatic colorectal cancer.

Business or cooperation opportunities:

- Future clinical trials with HeberSaVax.
- Phase III clinical trial of HeberSaVax combined with chemotherapy in ovarian carcinoma.
- Phase II/III clinical trial of HeberSaVax in hepatocellular carcinoma.
- Phase II/III clinical trial of HeberSaVax combined with chemotherapy in non-small cell lung cancer.
- Phase II/III clinical study of HeberSaVax combined with chemotherapy and Avastin in metastatic colorectal cancer.
- Phase II/III clinical study of HeberSaVax combined with sunitinib in renal cell carcinoma.

Main publications:

- Morera, Y et al. Immunogenicity and some safety features of a VEGF-based cancer therapeutic vaccine in rats, rabbits and non-human primates. Vaccine. 2010;28(19):3453-61. doi: 10.1016/j.vaccine.2010.02.069.
- Bequet-Romero M, et al. CIGB-247: a VEGF-based therapeutic vaccine that reduces experimental and spontaneous lung metastasis of C57Bl/6 and BALB/c mouse tumors. Vaccine. 2012;30(10):1790-9. doi: 10.1016/j.vaccine.2012.01.006.
- Pérez L, et al. Experimental studies of a vaccine formulation of recombinant human VEGF antigen with aluminum phosphate. Hum Vaccin Immunother. 2015;11(8):2030-7. doi: 10.1080/21645515.2015.1029213.
- Gavilondo JV, et al. Specific active immunotherapy with a VEGF vaccine in patients with advanced solid tumors. results of the CENTAURO antigen dose escalation phase I clinical trial. Vaccine. 2014;32(19):2241-50. doi: 10.1016/j.vaccine.2013.11.102.
- Sánchez-Ramírez J, et al. Characteristics of the specific humoral response in patients with advanced solid tumors after active immunotherapy with a VEGF vaccine, at different antigen doses and using two distinct adjuvants. BMC Immunol. 2017;18(1):39. doi: 10.1186/s12865-017-0222-z.

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Web site: www.cigb.edu.cu

PROJECT TITLE: CIMAVAX-EGF®, IMMUNOTHERAPY FOR LUNG CANCER

Company: Center of Molecular Immunology
Therapeutic or preventive area/Indications: Oncology / Lung cancer

PROJECT DESCRIPTION:

CIMAvax-EGF® is the first product in its class for the treatment of non-small cell lung cancer (NSCLC), which targets epidermal growth factor (EGF). It is made up of the conjugated antigen of the rhEGF and rP64k proteins and the adjuvant Montanide ISA51.

The purpose of immunization with CIMAvax-EGF® is to induce the generation of neutralizing antibodies against EGF. This prevents its binding to the epidermal growth factor receptor (EGF-R), which is overexpressed in tumor cells of epithelial origin. These antibodies inhibit the signal that promotes cell growth, causing the death of cancer cells, with an antiangiogenic effect and negative regulation of tumor-induced immunosuppression.

Main results of pre-clinical and clinical studies:
CIMAvax-EGF® is a registered product for patients with NSCLC, in advanced stages. In 2018, CECMED modified the indication of the product, restricting it to patients with serum EGF levels greater than 870 pg/mL, for which the use of an accompanying biomarker was incorporated.

Current Stage:
A phase IV clinical trial is being carried out in Cuba. A clinical trial is also underway for the treatment of patients with premalignant lesions (chronic obstructive pulmonary disease: COPD) and another for the selection of new biomarkers of clinical efficacy.
A Phase I/II clinical trial is underway in the US for the treatment of lung cancer in combination with the anti-checkpoint monoclonal antibody Nivolumab. The first phase of the study concluded satisfactorily, observing a substantial increase in the survival of patients with tumors that express the unmutated KRAS oncogene.

Intellectual Property:
- CU 0154-2007: Homogeneous vaccine composition for the treatment of cancer and its method of obtaining. Granted in Cuba, the US, Europe and 25 other countries.
- Vaccine compositions based on inorganic nanoparticles for the treatment of cancer (2020). Patent applied.
- Use of epidermal growth factor depleting agents in the treatment of chronic obstructive pulmonary disease (2020). Patent applied.
- Use of therapeutic compositions for the treatment of patients with tumors of epithelial origin (2021). Patent applied.

Competitive advantages:
Based on the concept of vaccination for the treatment of lung cancer.

Business or cooperation opportunities:
Agreements for the conduct of clinical trials until commercialization.

Main publications:

- Survival of NSCLC Patients Treated with Cimavax-EGF as Switch Maintenance in the Real-World Scenario. Yoanna I. Flores Vega et al. 2023. J Cancer 2023; 14(5):874-879. doi:10.7150/jca.67189.
- Augmenting antibody response to EGF-depleting immunotherapy: Findings from a phase I trial of CIMAvax-EGF in combination with nivolumab in advanced stage NSCLC. Evans R. et al. Front Oncol. 2022; 12: 958043. doi: 10.3389/fonc.2022.958043
- A Phase III Clinical Trial of the Epidermal Growth Factor Vaccine CIMAvax-EGF as Switch Maintenance Therapy in Advanced Non-Small-Cell Lung Cancer Patients. Rodriguez PC et al. Clin Cancer Res. 2016 Feb 29.
- Effect of blockade of the EGF system on wound healing in patients vaccinated with CIMAvax®EGF. Fernández Lorente A et al. World J Surg Oncol. 2013.
- CIMAvax EGF vaccine for stage IIIb/IV non-small cell lung carcinoma. Cheng JY et al. HumVaccin Immunother. 2012 Dec 1;8(12):1799-801

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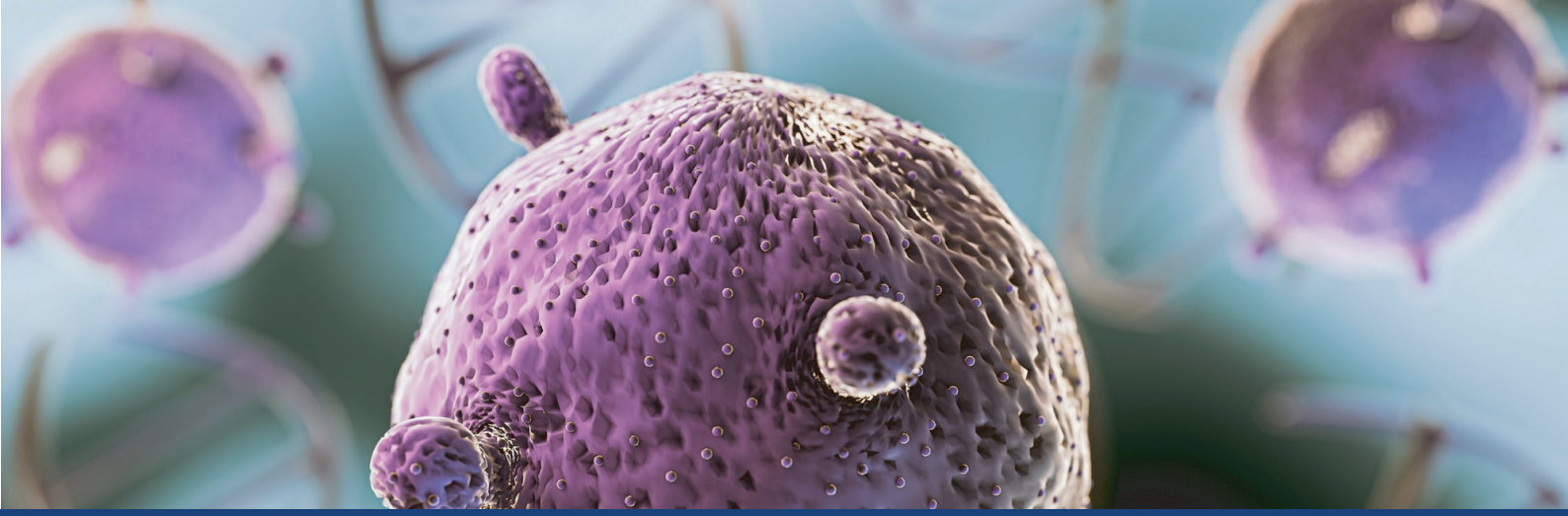

PROJECT TITLE: AGONIST IL2 MUTEINS: A PLATFORM FOR DEVELOPING NOVEL CANCER IMMUNOTHERAPIES.

NEED PARTNER, FOR DEVELOPING EITHER:

- Platform of bispecific immuno-cytokines, based on the fusion of a monoclonal antibody and two copies of a mutant variant of IL2;
- Novel IL2 muteins for the treatment of solid tumors and/or for the combination with adoptive cells therapies (CART or TILS).

Background

Interleukin-2 (IL2) has pleiotropic effects over immune cells. driven by their differential expression of the IL2R subunits (CD25), (CD122) and (CD132). The IL2R subunits dynamically assemble on cells membrane forming two classes of signaling receptors, the high affinity IL2Rαßγ (10-12 M) and the intermediate affinity IL2Rßγ (10-9 M). IL2 stimulate proliferation/differentiation of NK and CD8+ T cells, which express mostly the IL2Rßγ, and mediate destruction of tumor cells. The latter properties lead to the successful development of IL2 as an anticancer drug back in the nighties. Today, high-dose IL2 (HD-IL2, e.g. with Aldesleukin) remains as a second line or subsequent therapy for metastatic or unresectable cutaneous melanoma (NCCN Guidelines 2023) and also remain as a useful choice in certain circumstances in relapse or stage IV kidney cancer with clear cell histology. In clinical trials (Clark, J. I, et al, 2021), HD-IL2 induced objective responses in 15-16% of metastatic Renal Cell Carcinoma patients and metastatic Melanoma patients (with 6-7% long lasting Complete Responses).

However, several problems limit the efficacy and use of HD-IL2 in clinical practice: a) severe life threatening toxicities, mostly the vascular leak syndrome (VLS), likely related to the expression of α subunit of IL2 receptor in endothelial cells (Kim, D. W, et al, 2014); b) the constitutive over-expression of high affinity IL2Rαßγ in CD4+FOXP3+ regulatory T cells (TRegs), whose preferential expansion inhibit antitumoral response (Ohue, Y., et al., 2019); c) induction of activation-induced cell death (AICD), which prevents extensive effector cell expansion (Holder, P. G , et al, 2022); and d) induction of terminal differentiation in CD8++ T cells, towards an exhaustion phenotypes, driven by sustained high intensity IL2 signal (Chin, S. S. et al, 2022).

Our technology platform.

Center of Molecular Immunology (CIM), founded in 1994, is a leader biotechnology organization in Cuba, devoted to research, develop and manufacture biopharmaceutical products. CIM has developed a platform, based on combining mathematical modelling, bioinformatics tools and phage display technology to design, select and obtain innovative IL2 muteins (Leon K et al, 2018).

In our platform, huge libraries of IL2 variants designed rationally, semi-rationally or randomly around a desired theoretical concept are displayed on filamentous phage's PIII protein (Rojas G et al, 2015, 2018, 2019 & 2023). High expression of IL2 variants on phages predict good developability properties as recombinant proteins, e.g. good expression level, appropriate folding and low aggregation propensity. IL2 variants over the phages are selected primarily by its binding properties against different components of the IL2R (either for reducing or increasing affinity). But more relevantly, they are also directly tested on biological assays in vitro, e.g cell proliferation and differentiation assays. This platform has been used to generate several products candidates, which exploit the well-known biological functions of the IL2 and overcome its limitations.

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In our platform, huge libraries of IL2 variants designed rationally, semi-rationally or randomly around a desired theoretical concept are displayed on filamentous phage's PIII protein (Rojas G et al, 2015, 2018, 2019 & 2023). High expression of IL2 variants on phages predict good developability properties as recombinant proteins, e.g. good expression level, appropriate folding and low aggregation propensity. IL2 variants over the phages are selected primarily by its binding properties against different components of the IL2R (either for reducing or increasing affinity). But more relevantly, they are also directly tested on biological assays in vitro, e.g cell proliferation and differentiation assays. This platform has been used to generate several products candidates, which exploit the well-known biological functions of the IL2 and overcome its limitations.

Basic no-alpha IL2 mutein (mIL2no)

The mIL2no has 4-point mutations which abrogate binding to the subunit of the IL2R (CD25). As consequence, it preferentially binds and signal through the intermediate affinity IL2Rßγ, highly expressed in effector NK and CD8++ T cells. The mutein is currently expressed as a recombinant protein in E.coli and purified using a his-tag. The mutein, as others in our platform, could be complemented with an extra mutation K35E, to improve developability, by increasing productivity and reducing aggregation propensity.

The mIL2no is a weak IL2 agonist, which triggers a qualitatively different signal through the IL2Rßγ receptor as compared to the signals triggered by wildtype IL2 and other cytokines (IL15) (Ortiz-Miranda Y, 2023). As consequence, the mutein induces a strong CD8+ T cell proliferation, as native IL2 does, but without inducing terminal differentiation/exhaustion, or AICD. Moreover, the mutein leads to a preferential differentiation towards a central memory phenotype, as IL15 also does, but without pushing the cells towards a rather quiescence state.

In mice, in vivo treatment with mIL2no preferentially stimulates the cytotoxic CD8+ T cells and the NK cells, without significantly activating the TRegs. Indeed, the mIL2no shows a higher antitumor effect than IL2 in several transplantable tumor models (Carmenate T et al., 2013 & 2022). Moreover, this mutein shows much less toxicity than IL2 even when administered at doses substantially higher than those necessary to induce the antitumor effect. Such better toxicity profile is likely explained by mutein reduced capacity to interact with the α subunit of the IL2R (CD25) expressed on the endothelial cells of the lung and other organs. Further preclinical data support potentiation of mIL2no antitumoral effect by its combination with immune checkpoint inhibitors (anti PD1-anti-PDL1 MAbs)

A phase I/II clinical trial, currently ongoing in Cuba (RPCEC00000234), have already recruited 9 patients with solid tumors and no other therapeutic alternative. Treatment scheme, as monotherapy, resembles that typically used in HD-IL2 therapy on humans. Our mIL2noα has a short half live (9-12 minutes), similarly to native IL2, which might be the right design when a large and relatively short bolus of drug is needed. So far, application dose has been scaled up to 2400 IU/kg, with no sign of VLS or CRS or any other dose limiting toxicities. Evaluation of T cells expansion in the PBMC confirms preferential stimulation of NK and CD8+ T cells after treatment, whith no significant expansion of TRegs. Interestingly, some suggestion of positive clinical response has been observed (60% stable diseased achieved after treatment, unexpected long survival in patients with PDAC, TNBC, OC) (Caballero Aguirrechu et al, 2025).

The mIL2noα works by expanding the CD8+ T cells, which mediates direct antitumor cytotoxicity and by expanding also the NK cells that kill the tumor cells downloading MHC-I to escape from CD8+ T cells attack. Therefore, the mutein would be useful to treat "cold tumors", where little infiltration of effector immune cells is primarily observed; especially those tumors where TRegs accumulation inhibits the naturally induced anti-tumor immune response (e.g. Ovary, pancreas, gastric, hepatobiliary, melanoma, kidney, lung and bladder).

The use of the mIL2no in combinations with adoptive cells therapies.

Preclinical data highly support the use of mIL2no in combination with adoptive T cell treatments (likely with TILs or CART cells). The mutein could substitute IL2, IL5 and IL7 in protocols for in vitro expansion of T cells from PBMC, enriching the population of cells with a central memory phenotype, which persist better and mediate a higher antitumoral effect upon transfer in vivo. Mutein encoding gene has been also transfected into the T cells causing an autocrine production and signaling in the cells, which further increases their persistence and their antitumoral effect upon transfer in vivo (Corria-Osorio J et al 2023, Ortiz-Miranda Y, 2023). The rather unique effect of our mIL2no on T cells differentiation is key for this alternative avenue of application.

Immunocytokines to direct the activity mIL2no

The reduced affinity of mIL2no for IL2R (10-9 M) allows its fusion to monoclonal antibodies, which then guide/target its function in vivo. We have successfully fused the mutein to several antibodies, which bind to tumors associated or specific antigens (e.g CD20, HER1, NGcGM3). We have genetically fused two copies of the mIL2no to a fully functional IgG MAb. Muteins were fused by their N terminal to the C-terminus of Ig heavy chains. The Fc receptor binding capacity of the MAbs was kept intact.

Different to other immunocytokines based on IL2-muteins available in literature (Tichet, M, et al 2023), we chose MAbs known to mediate significant antibody dependent cell cytotoxicity (ADCC). We found that our immunocytokines are highly functionals.

They retain the basic immunomodulatory properties of the mIL2no and more significantly, they could increase/potentiate the effector functions of the Mabs (Casadesús et al. 2020 & 2022). Our immunocytokines, work as special NK and T cells engagers, they enhance specific attachment to the tumor cells targeted by the MAb, but also provide a local activation signal through the IL2R. The unique signaling properties of the mIL2no might be instrumental to the immune cytokines by reducing the potential negative impact of AICD.

Other types/classes of immune cytokines could be envisioned to be fused to MAbs targeting markers overexpressed on a given immune cell population.

Increasing signaling strength of mIL2no: the mIL2 no
Introduction of 5 additional point mutations to the mIL2 noincreases its binding affinity for the intermediate affinity IL2Rßγ receptor. The new mutant, referred as mIL2 no is a quite strong IL2 agonist, which retains the preferential tropism for effector NK and CD8+ T cells. This mutein is produced as a recombinant protein fused to a LALA-Fc IgG domain in mammalian cell lines.

Preclinical data shows that mIL2 no induces a much potent preferential expansion of NK and CD8+ T cells in vivo than the mIL2 no Furthermore, the new mutant also exhibits higher antitumoral effect at much lower molar dose and with less frequent administrations. However, increasing dosing can result in toxicity, although a wide therapeutic window is observed. Currently, the effect of this new mutant in T cell differentiation is being evaluated. At first, we envisioned this mutein as more appropriate design for therapeutics applications based on local, intratumoral or peritumoral administration.

Positioning of our IL2 muteins in current cancer immunotherapy landscape.
According to the current worldwide biotech pipeline, there are several IL2 and IL15 variants under development (Hernandez R et al 2022; Holder, P. G., et al 2022). Most of them exploit a theoretical design towards a preferential signaling through the intermediate affinity IL2Rβγ. Some of them have reached clinical stage, with a notorious recent failure of NKTR214 lead candidate.

Our mIL2no have the following features, which might position it as a best in class solution:

- It is the only mutein using treatments schemes similar to that of clinically validated HD-IL2 therapy. Indeed, we have already seen some evidence of clinical responses as a monotherapy; and initial attempts to increase IL2 live span, by PEGylation, failed due to a worsening of activity vs. toxicity balance (Yang JC, 1995).
- It is the only mutein documenting the induction of a qualitatively different signal, from the one induced by either IL2 or IL15. This leads to relevant properties regarding CD8+ T cell differentiation, which provide especially unique possibilities for application in the context of adoptive cell therapies.
- Combination in the format of immunocytokines, helps targeting the mutein effect, providing the means for rational patient selection, with further reduction of toxicity risk and additional differentiation by the specific target of the MAb selected.
- Business strategy of competitor's relies on the exclusive association with other drug companies for the co-development of particular drug combinations. This, naturally positions mIL2no as an attractive partner for potential competitors of the second drug in the combination, for instance the competitors of the anti-checkpoint MAbs (Nivolumab and Pembrolizumab).

Furthermore, the strong agonist (mIL2 no) face much less competition. To our knowledge only MEDICENNA have muteins with similar design concept (MDNA11), but our technology platform allowed us finding of better structural solutions (e.g. less aggregation tendency and better developability properties Merchant, R, et al 2022). Overall, including several mutant variants, enlarge the potential pipeline of the program, increasing the overall possibilities of success.

Patent status:
- WO2012/062228. : Covers IL2 muteins sequence. It has been granted in 30 countries so far, including Russia, USA, Japan, China and other countries from South East Asia.
- WO2018/091003 24. Covers additional mutation K35E inserted on IL2 muteins to enhance developability. Granted in 25 countries
- WO 2020/187340. Protect application of mIL2no in adoptive cells therapies. Granted in 6 countries, under examination in other 10 countries
- CU2022/050012. Protects the building of immune-cytokines with our mIL2noα. Granted in Cuba, under examination in 15 countries
- CU-2022-0020. Protects mIL2noαβ+ sequence. Granted in Cuba, under examination in 15 countries, including China.

Business opportunities
Commercial and development exclusive rights of mIL2 for the US territory have been granted to Innovative Immunotherapy Alliance (IIA), a JV company, derived from the collaboration between CIM and the Roswell Park Cancer Institute in Buffalo, New York.

An option agreement has been signed with ALFANIL a Russian company resident on the Skolkovo Technological Park. This agreement is conditioned to the initiation of clinical trial within a one-year period, for the territory of the EEAU, and for the therapeutic application (via direct iv injections) of the mIL2no in the treatment of melanoma. Other potential/independent applications of interest, like the combination with Adoptive Cells Therapies (CART cells or TILS) or the generation of novel immune-cytokines have no commercial commitments in Russia or the EEAU territories.

CIM/CIMAB are looking to incorporate new partners for the co-development and commercialization of the no-alpha IL2 mutein in different territories. We are especially interested in building business alliances with companies, having the capacity to conduct/finance clinical trials and/or having immune-therapies on their pipeline, which could be combined with our IL2 mutein. Business model could be flexible, it could include the whole technology platform or just some selected products or product applications.

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PROJECT TITLE: PANHER VACCINE: THERAPEUTIC CANCER VACCINE PLATFORM BASED ON THE HER ONCOGENE FAMILY FOR THE TREATMENT OF EPITHELIAL TUMORS (PANHER VACCINE)

Company: Center of Molecular Immunology.
Therapeutic or preventive area/Indications: Oncology / Solid tumors.

PROJECT DESCRIPTION:

Develop therapeutic vaccines with the capacity to simultaneously activate the humoral and cellular immune response directed at the HER family of oncogenes. The vaccines could be used, alone or in combination with immunomodulators, for the treatment of epithelial tumors that express low or intermediate levels of HER1/HER2, or have activating HER1/RAS mutations, which escape the action of drugs targeting HER1/HER2 and Their possible tumor targets would be HRPC, head and neck, colon, pancreas, breast and NSCLC. Oncogenes of the HER (Human Epidermal growth factor Receptor) family are considered tumor-associated antigens due to their aberrant expression in tumors of epithelial origin and their role in sustained tumor proliferation, metastasis, inflammation, and tumor escape. tumor to the immune system. Furthermore, activating mutations in these receptors and in the intracellular signaling cascades that they activate, lead to resistance of tumors to passive drugs directed at HER1 and HER2, such as already registered Monoclonal Antibodies and Tyrosine Kinase Inhibitors (TKIVaccine candidates based on HER receptors contain as antigen the recombinant extracellular domain of the receptor(s) (HER-ECD), produced in mammalian cells. The vaccine adjuvant/immunomodulator are nanoparticles based on proteins from the outer membrane of Neisseria meningitidis, called VSSP, which simultaneously activate the humoral and cellular immune response, while modulating the myeloid compartment.

Main results of pre-clinical and clinical studies:
The HER1 vaccine candidate is a project in the clinical stage. It has been evaluated in a first phase I clinical trial in patients with hormone-resistant prostate carcinoma (HRPC). The vaccine simultaneously induced HER1-specific polyclonal antibodies (PAbs) neutralizing receptor activation and CD8+ T cell (CTL) response.
The HER1+HER2 vaccine candidate is a project in the preclinical stage. This candidate has demonstrated the ability to induce specific polyclonal antibodies (PAb) for HER1 and HER2, which degrade these receptors in the treated tumors. Furthermore, these polyclonal antibodies reduce the viability of tumor cells to a greater extent compared to registered monoclonal antibodies, even in the presence of activating mutations that confer resistance to drugs targeting HER1/HER2

- The HER1 vaccine candidate induces high titers of polyclonal IgG antibodies in patients with HRPC with different doses of antigen.
- The bivalent HER1+HER2 vaccine candidate induces polyclonal IgG antibodies that reduce the viability of tumor cells more than mAbs, in tumors (such as PC9ER) that contain activating mutations.

Current Stage:
Phase I/II Clinical Trials.

Intellectual Property:

- Bivalent vaccine compositions and the use thereof for treating tumors. International presentation date: 08/01/2014. Granted in Europe, Indonesia, Japan, Ukraine, Canada, Colombia, Mexico, Australia and New Zealand. Pending in Malaysia, Algeria, Thailand, Brazil and Vietnam.
- Method for the treatment of patients with carcinomas. International presentation date: 03/08/2018. Filed in Europe, USA and Australia.
- Nano-particles that contain synthetic variants of GM3 ganglioside as adjuvants in vaccines. International presentation date: 10/24/2018. Granted in Taiwan, Cuba, Russia, Colombia and South Africa. Pending in China, Hong Kong, Malaysia, Japan, Singapore, Thailand, USA, Vietnam, Korea, Europe, New Zealand, Brazil, Canada, Indonesia, Mexico and Argentina.

Competitive advantages:
The HER1 vaccine candidate simultaneously induces TCD8+ and polyclonal antibody (PAb) lymphocyte responses in cancer patients. The in vitro effect of AcP on tumor cells is greater than that of AcMs as a consequence of the strong degradation of the receptor. Furthermore, due to its clinically demonstrated tolerability, and the connection of HER1 not only with tumor proliferation but also with tumor immune escape and inflammation, the HER1 vaccine could be combined with immunomodulatory (anti-checkpoint) antibodies for treatment. of cold tumors.
The HER1+HER2 vaccine candidate simultaneously generates specific mAbs for HER1 and HER2 that cause a strong degradation of the receptors and decrease cell viability, with advantages over the registered mAbs of tumor cells that express low/intermediate levels of HER1/HER2, or tumor cells that contain activating mutations in the HER1/RAS intracellular signaling axis, which confer resistance to mAbs and TKIs.

Business and cooperation opportunities:
Commercial alliances with companies that have the capacity to conduct/finance clinical trials and/or that have immunotherapies in development, which could be combined with HER-based vaccines. The business model could be flexible, it could include the entire technology platform or only some selected products or product applications.

Main publications:

- Sánchez-Ramírez B et al., Active antimetastatic immunotherapy in Lewis lung carcinoma with self EGFR extracellular domain protein in VSSP adjuvant. Int J Cancer. 2006 Nov 1;119(9):2190-9.
- Caballero I et al., Safety and Immunogenicity of a Human Epidermal Growth Factor Receptor 1 (HER1)-Based Vaccine in Prostate Castration-Resistant Carcinoma Patients: A Dose-Escalation Phase I Study Trial. Front Pharmacol. 2017 May 10;8:263.
- Bergado-Baez Gretchen et al., Polyclonal antibody-induced downregulation of HER1/EGFR and HER2 surpasses the effect of combinations of specific registered antibodies. Front.Oncol.2022 Nov2;12:951267.

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PROJECT TITLE: NEUROEPO, INTRANASAL FORMULATION OF RECOMBINANT HUMAN ERYTHROPOIETIN FOR THE TREATMENT OF ALZHEIMER'S AND OTHER DISEASES

Company: Center of Molecular Immunology

Therapeutic or preventive area/Indications: Neurodegenerative disease therapy: Alzheimer's disease, Ataxia, Stroke, Parkinson's disease

PROJECT DESCRIPTION:

NeuroEPO is an intranasal formulation of recombinant human erythropoietin with low sialic acid content. Due to its specific composition and its innovative route of administration, NeuroEPO is capable of reaching pharmacological concentrations within the brain and inducing a biological activity similar to erythropoietin produced in the brain; without inducing systemic erythropoiesis and minimizing potential adverse side effects. The drug candidate is being clinically evaluated in Cuba for the treatment of several neurodegenerative diseases, such as Alzheimer's, Parkinson's and Ataxia.

Erythropoietin (EPO) plays an important role in brain homeostasis. Both neurons and astrocytes express EPO receptors on the cell membrane, and some glycoforms of EPO are produced locally in the brain. It has been suggested that in some brain pathological processes, EPO could have neuroprotective and/or neuroregenerative therapeutic effects. However, clinical evaluation of recombinant human erythropoietin (rhEPO) as a neuroprotective agent has been limited due to its hematological side effects. Intravenous administration of rhEPO has a very narrow therapeutic window due to the risk of thrombotic events. Clinical trials with rhEPO have been conducted in several inflammatory brain diseases with encouraging results, but registration approval for medical use has not been obtained so far.

In this project, two important technological improvements have been carried out to address the drawback of the current Pharmacopoeia-approved formulation of rhEPO. Firstly, the identification of rhEPO glycoforms (with low sialic acid content) obtained from a fermentation process, with a glycosylation profile similar to that of natural human EPO produced in the brain (rhEPOb). Secondly, the development of a pharmaceutical formulation for nasal administration of rhEPOb, which takes advantage of the unique physiological and anatomical attributes of the olfactory region, provides extracellular and intracellular routes to the Central Nervous System (CNS) evading the Blood-Brain Barrier (BBB).). This pharmaceutical formulation of rhEPOb (NeuroEPO) could have pharmacological effects on the brain without erythropoietic activity.

Extensive preclinical evaluation of NeuroEPO has been carried out in various experimental models of stroke and neurodegenerative disorders (including dementia), showing neuroprotective and neuro-regenerative effects. Some preliminary data suggest that astrocytes could be involved in the neuro-regenerative effect of NeuroEPO in several inflammatory brain diseases. In addition, clinical data have been collected in patients with Alzheimer's, spinocerebellar ataxia type 2, stroke and Parkinson's disease, with positive results, which open up new therapeutic possibilities to stimulate tissue regeneration and recovery of brain areas through the use of a Safe and non-invasive therapy.

Main results of clinical studies:

- A phase I clinical trial was completed in 25 healthy people with positive results. Tolerance to local administration was good. No serious AEs were reported. Vital signs and hematological and biochemical values, including Hb, remained within normal levels.
- Alzheimer's disease (AD): A phase II/III, double-blind, randomized clinical trial has been completed in 174 patients with AD. After 18th months of treatment, more than 80% of treated patients stabilized or improved their baseline ADAScog13 scores, compared to the placebo group, in which 86% of patients worsened. There was also evidence of significant improvement in other cognitive tests, as well as in functional parameters such as cerebral blood perfusion. The encouraging results of this trial led the Cuban regulatory agency (CECMED) to grant conditional marketing approval to NeuroEPO (NeuralCIM®) in 2022.

- Parkinson's disease: A phase II clinical trial in Parkinson's disease is underway.
- Spinocerebellar ataxia type 2: A phase II clinical trial has been completed with positive results and demonstration of effects as a neuroprotective agent. An additional trial is underway for the treatment of a broader range of ataxias, with a view to approval of its marketing in Cuba, as an orphan treatment for this rare indication.

Intellectual Property:
Patents and patent applications:
- Nasal Rh-EPO formulations with low concentration of sialic acid for the treatment of diseases of the central nervous system (WO 2007/009404). Granted in: Mexico, MX/a/2008/000997; Cuba, CU 2758/2008; Europe, Ep 1997483, and Canada, 2,616,156.
- Use of the basic form of recombinant human erythropoietin in the treatment of patients with spinocerebellar ataxia with cag repeat type mutations. (WO/2017/220053; EP 3473264) Granted in Europe.
- Recombinant hyposialylated human erythropoietin, purification methods and therapeutic uses thereof. (WO 2021/043345 A1). Granted in China.

Competitive advantages:
Intranasal administration of NeuroEPO has demonstrated its therapeutic potential to treat neurodegenerative diseases in which brain homeostasis is imbalanced due to chronic inflammations, metabolic dysfunctions, etc. As a homeostatic regulator, NeuroEPO has demonstrated its effectiveness in the treatment of Alzheimer's patients in a phase III clinical trial, not only delaying cognitive decline, as other anti-amyloid B drugs can do, but also recovering the patient's cognitive and functional parameters. .
Similar approaches have been published about modified variants of rhEPO for the treatment of AD. However, none of these candidates have completed clinical trials. Therefore, NeuroEPO could be considered a “first-in class” product for the treatment of AD.

Business or cooperation opportunities:
IncuBIO S.A., a subsidiary of CIMAB S.A., has been incorporated in Cuba and holds the exclusive commercial rights to the Intellectual Properties of NeuroEPO in the main markets.
Depending on the development phase, IncuBIO seeks to receive financial investment through any of the following sources:
- Non-dilutive funds (non-refundable grants)
- Capital investment* (venture capital funds willing to acquire IncuBIO shares)
- Granting of licenses to large pharmaceutical companies.

IncuBIO would also consider creating a subsidiary located in any of the major markets as the Joint Company in which the VC investors would invest, in case the potential VC would be more comfortable with any specific Companyrial environment.

Main publications

- A unique erythropoietin dosage induces the recovery of long-term synaptic potentiation in fimbria-fornix lesioned rats. Brain Res. 2023 Jan15;1799:148178. doi: 10.1016/j.brainres.2022.148178. Epub 2022 Nov 26. PMID: 36442648
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- El efecto de Neuroeposobre la cognición en pacientes con enfermedad de Parkinson está mediado por la actividad de la fuente del electroencefalograma.Front Neurosci. 2022 Jun 30;16:841428. doi: 10.3389/fnins.2022.841428. eCollection 2022. PMID: 35844232
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- Tolerancia a corto plazo de NeuroEPOadministrada por vía nasal en pacientes con enfermedad de Parkinson.MEDICC Rev. 2021 Jan;23(1):49-54. doi: 10.37757/MR2021.V23.N1.10. Epub 2021 Ene 30. PMID: 33780423. Ensayo clínico.

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PROJECT TITLE: CNEURO-201, NEW BIOACTIVE MOLECULE FOR THE TREATMENT OF ALZHEIMER'S DISEASE (AD) IN THE EARLY STAGES

Company: Cuban Neuroscience Center

Therapeutic or preventive area/Indications: Treatment of Alzheimer's disease.

PROJECT DESCRIPTION:

CNEURO-201 (Amylovis-201) is a small chemical molecule, considered the first-in-class, which constitutes a new bioactive molecule. It is designed to interact with amyloid proteins in conformational diseases. It was initially characterized as a chaperone molecule capable of inhibiting the aggregation of human islet amyloid protein (hIAPP1–37), which is associated with diabetes mellitus. CNEURO-201 has demonstrated in silico and In vitro studies have shown that it has a high affinity for Aβ1–42 monomers and fibrils, inhibiting their aggregation and destabilizing the fibrillar structure. Preclinical studies in 3xTg-AD mouse models and streptozotocin-induced AD rats have shown that CNEURO-201 significantly reduces Aβ burden in hippocampal regions, improving spatial memory and memory consolidation. It also exerts neuroprotective effects against neuronal loss. More recently, CNEURO-201 was reported to be a potent agonist of the σ1 receptor (σ1R) with anti-amyloidogenic action, capable of preventing cognitive deficits. in murine models at low doses, highlighting its potential as a multitarget agent for the treatment of AD. for the treatment of Alzheimer's disease (AD).

Main results of pre-clinical tests:

In addition to inhibiting and disassembling the fibrillogenesis process of β-amyloid proteins by interacting with native and fibrillar structures and breaking them down, CNEURO 201 is a potent sigma-1 receptor agonist. CNEURO 201 has been shown to improve memory in an in vivo model of chronic cholinergic dysfunction obtained from scopolamine administration. In a transgenic model of Alzheimer's disease (AD) (3xTg), oral administration of CNEURO-201 (1 mg/kg for eight weeks) improves cognitive function and significantly reduces the amyloidogenic burden in the hippocampus by more than 50%. It also reduces the activation of glial cells associated with the inflammatory response in AD. This glial modulation suggests that CNEURO-201 may alleviate neuroinflammation related to amyloid pathology, which could limit expansion and facilitate the clearance of Aβ plaques. This supports its multifunctional therapeutic potential in AD. CNEURO-201 has also been shown to protect mitochondria from Ca^{2} -induced deterioration, preserve cellular energy balance, and reverse apoptosis in neuronal cells exposed to a low-potassium environment.

CNEURO-201 is a sigma-1 receptor (S1R) agonist that dissociates BiP from S1R, with an IC_{50} of 362nM. This is a higher affinity than that of the prototype S1R agonist, PRE-084 (IC_{50} of 426nM). Its effect was blocked by the autoinhibitory S1R antagonist, NE-100. This confirms its agonist character. In other assays confirming its agonist action, CNEURO-201 attenuated the increased visual hyperlocomotor response of wolframin mutant (Wfs1ab KO) zebrafish larvae, an in vivo model of Wolfram syndrome. In a mouse model with cognitive deficits induced by dizocilpine (an NMDA antagonist), CNEURO-201 improved working and long-term contextual memory without affecting locomotion.

The effective doses of CNEURO-201 were low, ranging from 0.03 to 0.1 mg/kg. In models of Aβ25-35 neurotoxicity, CNEURO-201 prevented cognitive deficits, impairment in spatial memory, and impairment in passive avoidance at low therapeutic doses. It also protected SH-SY5Y cells from Aβ-induced cytotoxicity.

Treatment with CNEURO-201 was found to prevent memory impairment in male C57BL/6 mice that were chronically exposed (33 days) to rotanone (ROT, 3.0 mg/kg). Thus, it is suggested that the neurotoxic effects of ROT, which are mediated by the inhibition of mitochondrial complex I, could be counteracted by CNEURO-201's ability to act as an agonist of σ1R. Acute toxicity results obtained in mice by i.p. administration showed no toxicity (death) and/or anatomopathological lesions (in major organs such as liver, lung, brain) with CNEURO-201 administered at doses up to 300 mg/kg, much higher than the doses with protective effects in animal models of AD (0.1 to 1 mg/kg body weight).

In a sub-chronic toxicity study female and male Sprague-Dawley rats CNEURO-201 was administered by oral gavage once daily for three months (25, 75 and 200 mg/kg). Results showed that CNEURO-201 administered by oral route at 200 mg/kg did not produce significant changes in body weight, food consumption or adverse clinical effects. In addition, no obvious pathologic changes were observed based on histology, hematology, serum biochemistry, or necropsy compared to placebo-treated controls. Thus, CNEURO-201 has a maximum tolerated doses (MTD) of 200 mg/kg per day, far higher than the maximum effective doses (0.1 and 1 mg/kg) observed in experimental in vivo models of AD. In special toxicology, CNEURO-201 does not induce chromosomal aberrations or chromosome migration disorders (micronucleus test).

Current stage: Advanced preclinical phase.

Intellectual Property:

- "Procedures for obtaining novel naphthalene derivatives for in vivo diagnosis of Alzheimer disease". Granted: CU 24012B1 Cuba, 10155053B2, United States; US9764047B2, United States; SMT201400118B, San Marino; HRP20140628T1, Croatia; MX338943B, Mexico; MX2011013405A, México; HUE042030T2, Hungary; MY162719A, Malaysia; EP2860169B1, European Patent Office; EP2436666B1, European Patent Office; PL2436666T3, Poland; PT2436666E, Portugal; SI2436666T1, Slovenia; ES2478442T3, Spain; ES2692072T3, Spain; DK2436666T3, Denmark; CA2789869C, Canadá y P58243ZA00, Sudáfrica.
- "Chemical chaperones as novel molecular modulators of beta aggregation in proteins, characteristic in conformational disease" Filed: 2013 Granted CA2904762, Canadá; JP2016510007, Japón; US20160106691, United States; P71686ZA00, Sudáfrica.
- Patent application: ¨Pharmaceutical composition of naphthalene derivatives as multi-targeted therapeutic agents for the treatment of Alzheimer's disease. PCT published/CU2021/050012 (granted). Application in Switzerland, Germany, Spain, France, United Kingdom, Italy, Turkiye, China (including HK), USA, Canada, Malaysia, Mexico, Brazil, Japan, Russia, South Africa, Rep. of Korea, India, Vietnam, Indonesia, Iran, Thailand and Australia. Granted Cuba

Competitive advantages:
Multitarget small molecule drug against a multifactorial disease that affects more than 50 million patients in all countries of the world and continues to grow.

Business or cooperation opportunities: Association for joint development, production and marketing.

Main publications:

- Drug Development in Conformational Diseases: A Novel Family of Chemical Chaperones that Bind and Stabilise Several Polymorphic Amyloid Structures. Marquiza Sablón-Carrazana. PLOS ONE, 2015. DOI: 10.1371/journal.pone.0135292.
- Diabetes Drug Discovery: hIAPP1–37 Polymorphic Amyloid Structures as Novel Therapeutic Targets. Isaac Fernández-Gómez. Molecules, 2018. DOI: 10.3390/molecules23030686.
- [18F]Amylovis as a Potential PET Probe for β-Amyloid Plaque: Synthesis, In Silico, In vitro and In vivo Evaluations. Suchitil Rivera-Marrero. Current Radiopharmaceuticals, 2019. DOI: 10.2174/1874471012666190102165053
- A new naphthalene derivative with anti-amyloidogenic activity as potential therapeutic agent for Alzheimer's disease. Rivera-Marrero S. Bioorganic & Medicinal Chemistry, 2020. DOI: 10.1016/j.bmc.2020.115700
- Amylovis-201 enhances physiological memory formation and rescues memory and hippocampal cell loss in a streptozotocin-induced Alzheimer's disease animal model. Mercerón-Martínez D. Brain Research, 2024. DOI 10.1016/j.brainres.2024.148848.
- Amylovis-201 is a new dual-target ligand, acting as an anti-amyloidogenic compound and a potent agonist of the σ1 chaperone protein. García-Pupo L. Acta Pharmaceutica Sinica B, 2024. DOI: 10.1016/j.apsb.2024.06.013.
- CNEURO-201, an Anti-amyloidogenic Agent and σ1-Receptor Agonist, Improves Cognition in the 3xTg Mouse Model of Alzheimer's Disease by Multiple Actions in the Pathology. Martínez-Orozco H. International Journal of Molecular Sciences, 2025. DOI: 10.3390/ijms26031301.

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PROJECT TITLE: CNEURO-211, A PROMISING CANDIDATE FOR THE TREATMENT OF PARKINSON'S DISEASE (PD)

Company: Cuban Neuroscience Center

Therapeutic or preventive area/Indications: Treatment of Parkinson's disease.

PROJECT DESCRIPTION:

CNEURO-211 (Amylovis-211) is a small chemical molecule, considered the first-in-class, which constitutes a new bioactive molecule. It is designed to interact with amyloid proteins in conformational diseases. It was initially characterized as a chaperone molecule capable of inhibiting the aggregation of human islet amyloid protein (hIAPP1–37). More recently, CNEURO-211 was reported to be a potent agonist of the σ1 receptor (σ1R), capable of preventing cognitive deficits in murine models at low doses. Treatment with CNEURO-211 was found to prevent memory impairment in male C57BL/6 mice that were chronically exposed (33 days) to rotanone (ROT, 3.0 mg/kg). Thus, it is suggested that the neurotoxic effects of ROT, which are mediated by the inhibition of mitochondrial complex I, could be counteracted by CNEURO-211's ability to act as an agonist of σ1R. Rescue of hippocampal-dependent memory in a model of Parkinson's disease (ROT-induced model) suggests neuroprotective effects of CNEURO-211 at very low doses (0.1 mg/kg).

Main results of pre-clinical tests:

In addition to inhibiting and disassembling the fibrillogenesis of β-amyloid proteins by interacting with both native and fibrillar forms, CNEURO-211 is a potent sigma-1 receptor agonist. It has demonstrated memory improvement in an in vivo model of chronic cholinergic dysfunction induced by scopolamine. Additionally, CNEURO-211 reduces glial cell activation associated with inflammatory responses in Alzheimer's disease models, which may also impact Parkinson's disease pathogenesis due to shared inflammatory mechanisms in both disorders

CNEURO-211 has also been shown to protect mitochondria from Ca^{2}-induced deterioration, preserve cellular energy balance, and reverse apoptosis in neuronal cells exposed to a low-potassium environment. CNEURO-211 is a sigma-1 receptor (S1R) agonist that dissociates BiP from S1R, with an IC_{50} of 362nM. This is a higher affinity than that of the prototype S1R agonist, PRE-084 (IC_{50} of 426nM). Its effect was blocked by the autoinhibitory S1R antagonist, NE-100. This confirms its agonist character. In other assays confirming its agonist action, CNEURO-211 attenuated the increased visual hyperlocomotor response of wolframin mutant (Wfs1ab KO) zebrafish larvae, an in vivo model of Wolfram syndrome.

Treatment with CNEURO-211 prevented memory impairment in male C57BL/6 mice chronically exposed to rotenone (ROT, 3.0 mg/kg) for 33 days. This suggests that CNEURO-211's agonist activity at the σ1 receptor may counteract ROT-induced neurotoxicity, which is mediated by mitochondrial complex I inhibition. The rescue of hippocampal-dependent memory in this ROT-induced Parkinson's disease model indicates that CNEURO-211 exerts neuroprotective effects at very low doses (0.1 mg/kg). Acute toxicity studies in mice via intraperitoneal administration of CNEURO-211 revealed no mortality or anatomopathological lesions in major organs such as the liver, lung, and brain, even at doses up to 300 mg/kg—significantly higher than the protective doses observed in Alzheimer's disease (AD) animal models (0.1 to 1 mg/kg body weight). In a sub-chronic toxicity study, both female and male Sprague-Dawley rats received daily oral gavage of CNEURO-211 at doses of 25, 75, and 200 mg/kg for three months. At the highest dose of 200 mg/kg, there were no significant changes in body weight, food intake, or adverse clinical signs. Histological, hematological, serum biochemical, and necropsy analyses showed no pathological alterations compared to placebo controls. Therefore, the maximum tolerated dose (MTD) of CNEURO-211 is established at 200 mg/kg/day, which is considerably higher than the maximum effective dose range (0.1 to 1 mg/kg) shown in in vivo AD models. Additionally, specialized toxicological assessments indicate that CNEURO-211 does not induce chromosomal aberrations or mitotic spindle disruptions, as confirmed by micronucleus testing

Current stage: Advanced preclinical phase.

Intellectual Property:
- “Chemical chaperones as novel molecular modulators of beta aggregation in proteins, characteristic in conformational disease” Filed: 2013 Granted CA2904762, Canadá; JP2016510007, Japón; US20160106691, United States; P71686ZA00, Sudáfrica.
- Patent application: ¨Pharmaceutical composition of naphthalene derivatives as multi-targeted therapeutic agents for the treatment of Alzheimer's disease. PCT published/CU2021/050012 (granted). Application in Switzerland, Germany, Spain, France, United Kingdom, Italy, Turkiye, China (including HK), USA, Canada, Malaysia, Mexico, Brazil, Japan, Russia, South Africa, Rep. of Korea, India, Vietnam, Indonesia, Iran, Thailand and Australia. Granted Cuba

Competitive advantages:
Multitarget small molecule drug against a multifactorial disease that affects more than 10 million patients in all countries of the world and continues to grow.

Business or cooperation opportunities: Association for joint development, production and marketing.

Main publications:

- Drug Development in Conformational Diseases: A Novel Family of Chemical Chaperones that Bind and Stabilise Several Polymorphic Amyloid Structures. Marquiza Sablón-Carrazana. PLOS ONE, 2015. DOI: 10.1371/journal.pone.0135292.
- Diabetes Drug Discovery: hIAPP1–37 Polymorphic Amyloid Structures as Novel Therapeutic Targets. Isaac Fernández-Gómez. Molecules, 2018. DOI: 10.3390/molecules23030686.
- [18F]Amylovis as a Potential PET Probe for β-Amyloid Plaque: Synthesis, In Silico, In vitro and In vivo Evaluations. Suchitil Rivera-Marrero. Current Radiopharmaceuticals, 2019. DOI: 10.2174/1874471012666190102165053
- A new naphthalene derivative with anti-amyloidogenic activity as potential therapeutic agent for Alzheimer's disease. Rivera-Marrero S. Bioorganic & Medicinal Chemistry, 2020. DOI: 10.1016/j.bmc.2020.115700
- Amylovis-201 enhances physiological memory formation and rescues memory and hippocampal cell loss in a streptozotocin-induced Alzheimer's disease animal model. Mercerón-Martínez D. Brain Research, 2024. DOI 10.1016/j.brainres.2024.148848.
- Amylovis-201 is a new dual-target ligand, acting as an anti-amyloidogenic compound and a potent agonist of the σ1 chaperone protein. García-Pupo L. Acta Pharmaceutica Sinica B, 2024. DOI: 10.1016/j.apsb.2024.06.013.
- CNEURO-201, an Anti-amyloidogenic Agent and σ1-Receptor Agonist, Improves Cognition in the 3xTg Mouse Model of Alzheimer’s Disease by Multiple Actions in the Pathology. Martínez-Orozco H. International Journal of Molecular Sciences, 2025. DOI: 10.3390/ijms26031301.

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PROJECT TITLE: PCIGB-845, COMBINED THERAPY BASED ON EGF AND GHRP6 FOR THE TREATMENT OF NEURODEGENERATIVE PROCESSES AND ACUTE CEREBROVASCULAR DISEASE

Company: Center for Genetic Engineering and Biotechnology

Therapeutic or preventive area/Indications: Therapy neurodegenerative diseases/Neurodegenerative disorders and acute stroke.

PROJECT DESCRIPTION:

CIGB-845 is the combination of EGF and GHRP6, with which a large amount of pre-clinical evidence in vitro and in vivo has been accumulated on the neuroprotective effect of EGF+GHRP6 co-administration (CIGB 845). Its conception responds to health needs in fields of clinical neurology not covered in Cuba and on a global scale.

Its mechanism of action is based on the fact that EGF and GHRP6 have common and exclusive effects aimed at complex phenomena related to cell death, such as apoptosis, inflammation, proteinopathies, mitochondrial dysfunction, glutamate-mediated toxicity, among others, and also it have a systemic effect on the cardiovascular, renal and digestive systems.

Main results of pre-clinical and clinical studies:

Abundant preclinical evidence in vitro and in vivo on the neuroprotective effect of CIGB 845. Safety and preliminary evidence of effect in clinical studies have been demonstrated.

Current stage:

Phase III clinical study in Cuba ongoing.

Intellectual Property:

- Combination of EGF/GHRP-6 for neuroregeneration of central nervous system. European Patent EP1870106. Publication Date: 08.09.2006. Accepted in PCT countries, Japan, South Africa, Canada, Russia, Korea Europe, Australia, Mexico, China.
- Pharmaceutical combination for the restoration of brain damage. (08/21/2018). This patent is granted in Cuba, and filed in the countries of the A-Persian Gulf and through the PCT, in February 2021, in Europe, USA, Canada, Brazil, Japan, Malaysia, Mexico and Russia.

Competitive advantages:

Demonstrated safety profile. It can be administered together with recanalization therapies.

Its therapeutic effects can transcend beyond the acute and subacute stage of cerebral infarction.

Pre-clinical demonstration that the effect of EGF + GHRP6 in models of global and focal cerebral ischemia is similar to that of therapeutic hypothermia, without the adverse effects of the latter.

Business or cooperation opportunities:

Patent license for clinical development.

Scientific collaboration agreements to argue the mechanism of action.

Main publications:

- García-del-Barco D, Subirós N, Pérez-Saad H. Epidermal growth factor and growth hormone-releasing peptide-6: Combined therapeutic approach in experimental stroke. International Journal of Stroke. World Stroke Organization 2015;10(Suppl. 2):437.
- Subirós N, Pérez-Saad H, Berlanga J, Aldana L, Garcia Illera G, Gibson C, Garcia del Barco Herrera D. Assessment of dose-effect and therapeutic time window in preclinical studies of rh-EGF and GHRP6 coadministration for stroke therapy. Neurological Research. 2015;38(3):187-95.

- ubirós N, Pérez-Saad H, Aldana L, Gibson CL, Borgnakke WS, Garcia-del-Barco D: Neuroprotective effect of epidermal growth factor plus growth hormone-releasing peptide-6 resembles hypothermia in experimental stroke, Neurological Research, Neurol Res. 2016;38(11):950-8.
- Perez-Saad H, Subiros N, Berlanga J, Aldana L, Garcia del Barco D. Neuroprotective effect of epidermal growth factor in experimental acrylamide neuropathy: an electrophysiological approach. J Peripher Nerv Syst. 2017 Apr 1; n/a. Disponible en http://dx.doi.org/10.1111/jns.12214.
- Báez SC, García del Barco D, Hardy-Sosa A, Guillen Nieto G, Bringas-Vega ML, Llibre-Guerra JJ, Valdes-Sosa P. Scalable Bio Marker Combinations for Early Stroke Diagnosis: A Systematic Review Front Neurology. 2021;12(638693). Disponible en doi: 10.3389/fneur.2021.638693.

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Web site: www.cigb.edu.cu

PROJECT TITLE: CIDEM-112, HYBRID MOLECULAR CHEMICAL ENTITY FOR THE TREATMENT OF ALZHEIMER'S DISEASE AND OTHER TYPES OF DEMENTIA

Company: Drug Research and Development Center (CIDEM)
Therapeutic or preventive area/Indications: Therapy of neurodegenerative diseases / Treatment of Alzheimer's disease (AD) and other types of dementia.

PROJECT DESCRIPTION:

According to the World Health Organization, 50 million people suffer from dementia worldwide and 82 million are expected to suffer from it by 2030. Currently, there is no treatment that can stop this disease. CIDEM-112, also known as JM-20, is a small hybrid molecular chemical entity with multiple cellular and subcellular targets, designed and developed to address the treatment of Alzheimer's disease (AD) and other types of dementia.

Main results of pre-clinical and clinical studies:
CIDEM-112 was evaluated in different animal models of dementia and Alzheimer's disease, showing the following results:

- In the scopolamine-induced cholinergic dysfunction model, it improved cognitive impairment and showed antioxidant and mitoprotective properties.
- In the aluminum trichloride-induced memory impairment model, it prevented and reversed the impairment of different types of memory. Mitochondrial protection and modulation of the antiapoptotic cell signaling pathway were observed.
- Showed cognitive protection on memory after the administration of Aβ (1-42) oligomers.
- In the animal model of streptozotocin-induced dementia, it prevented cognitive decline in mice, improved mitochondrial functionality, and decreased oxidative stress.
- It interacts with the enzyme acetylcholinesterase, another important molecular target for the treatment of Alzheimer's disease, and inhibits V-ATPase, showing antiexcitotoxic properties.
- It was safe in genotoxicity, acute toxicity and repeated dose toxicity studies in rats.

Current stage:
Pre-clinical phase in preparation of request for clinical studies.

Intellectual Property:
Benzodiazepine derivative with activity in the central nervous and vascular systems. CU 2016/0058. PCT/CU2017/050002; WO/2017/190713.

Competitive advantages:
Ability to inhibit acetylcholinesterase activity, glutamate-mediated excitotoxicity, mitochondrial dysfunction, different pro-apoptotic pathways, the production of reactive oxygen species and calcium fluence. All of these properties qualify CIDEM-112 as a first-in-class compound.

Business or cooperation opportunities:
- License and/or co-development agreements.
- International Economic Association, Mixed Companies or variants.

Main publications:

- Nuñez-Figueredo Y, Pardo-Andreu GL, Ramírez-Sánchez J, Delgado-Hernández R, Ochoa-Rodríguez E, Verdecia-Reyes Y, Naal Z, Muller AP, Portela LV, Souza DO. Antioxidant effects of JM-20 on rat brain mitochondria and synaptosomes: mitoprotection against Ca^{2} -induced mitochondrial impairment. Brain Res Bull. 2014;109:68-76.
- Nuñez-Figueredo Y, Ramírez-Sánchez J, Delgado-Hernández R, Porto-Verdecia M, Ochoa-Rodríguez E, Verdecia-Reyes Y, Marin-Prida J, González-Durruthy M, Uyemura SA, Rodrigues FP, Curti C, Souza DO, Pardo-Andreu GL. JM-20, a novel benzodiazepine–dihydropyridine hybrid molecule, protects mitochondria and prevents ischemic insult-mediated neural cell death in vitro. Eur J Pharmacol. 2014;726:57-65.
- Figueredo YN, Rodríguez EO, Reyes YV, Domínguez CC, Parra AL, Sánchez JR, Hernández RD, Verdecia MP, Pardo Andreu GL. Characterization of the anxiolytic and sedative profile of JM-20: a novel benzodiazepine-dihydropyridine hybrid molecule. Neurol Res. 2013;35(8):804-12.
- Furtado, A.B.V., et al., JM-20 Treatment After Mild Traumatic Brain Injury Reduces Glial Cell Pro-inflammatory Signaling and Behavioral and Cognitive Deficits by Increasing Neurotrophin Expression. 2021. 58(9): p. 4615-4627.
- Wong-Guerra, M., et al., JM-20 treatment prevents neuronal damage and memory impairment induced by aluminum chloride in rats. Mol Neurobiol, 2021. 87: p. 70-85.

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Web site: www.cidem.cu

PROJECT TITLE: CIDEM-113, HYBRID CHEMICAL ENTITY FOR THE TREATMENT OF PARKINSON'S DISEASE

Company: Drug Research and Development Center (CIDEM)
Therapeutic or preventive area/Indications: Therapy neurodegenerative diseases/treatment of Parkinson's disease (PD)

PROJECT DESCRIPTION:

The prevalence of PD is estimated at 0.3% in the general population and approximately 1% in those over 60 years of age, reaching 2% after 65 years of age. In the coming years, it is expected that the upward trend in prevalence will continue and that by 2030, the number of people living with the disease will increase considerably, reaching values of up to 12 million people. Currently, there is no treatment that can stop this disease. CIDEM-113, also known as JM-20, is a small hybrid molecular chemical entity with multiple cellular and subcellular targets, designed and developed to address the treatment of PD disease.

Main results of pre-clinical and clinical studies:
CIDEM-113 was evaluated in two animal models of PD, showing the following results:

- CIDEM-113 has been shown to inhibit glutamate-mediated excitotoxicity, increased calcium influx, mitochondrial dysfunction, different pro-apoptotic pathways and the production of reactive oxygen species; may have therapeutic advantages over current treatments for PD.
- In the in vitro model of PD induced by 6-OHDA and rotenone, the cytoprotective and protective effect on mitochondrial functionality was demonstrated.
- In the in vivo damage model, induced by 6-OHDA and rotenone, elCIDEM-113 prevented the behavioral alteration of the animals, the loss of dopaminergic neurons, neuroinflammation, oxidative stress at the level of the substantianigrapars compacta and the striatum, as well as mortality.
- In addition, CIDEM-113 was shown to inhibit the formation of toxic α-synuclein aggregates and cytotoxicity induced by the aminochrome.
- It was safe in genotoxicity, acute toxicity and repeated dose toxicity studies in rats.

Current stage:
Pre-clinical phase in preparation of request for clinical studies.

Intellectual Property:
Benzodiazepine derivative with activity in the central nervous and vascular systems. CU 2016/0058. PCT/CU2017/050002; WO/2017/190713.

Competitive advantages:
Ability to inhibit the formation of toxic α-synuclein aggregates, glutamate-mediated excitotoxicity, mitochondrial dysfunction, neuroinflammation and apoptosis, the death of dopaminergic neurons, the production of reactive oxygen species. All of these properties qualify CIDEM-113 as a first-in-class compound.

Business or cooperation opportunities:
- License and/or co-development agreements.
- International Economic Association, Mixed Companies or variants.

Main publications:

- Figueredo YN, Rodríguez EO, Reyes YV, Domínguez CC, Parra AL, Sánchez JR, Hernández RD, Verdecia MP, Pardo Andreu GL. Characterization of the anxiolytic and sedative profile of JM-20: a novel benzodiazepine-dihydropyridine hybrid molecule. Neurol Res. 2013;35(8):804-12.
- Furtado, A.B.V., et al., JM-20 Treatment After Mild Traumatic Brain Injury Reduces Glial Cell Pro-inflammatory Signaling and Behavioral and Cognitive Deficits by Increasing Neurotrophin Expression. 2021. 58(9): p. 4615-4627.
- Santos, C. C. et al. JM-20, a Benzodiazepine-Dihydropyridine Hybrid Molecule, Inhibits the Formation of Alpha-Synuclein-Aggregated Species. Neurotoxicity research 2022; 40, 2135-2147.
- Fonseca-Fonseca, L. A. et al. JM-20, a novel hybrid molecule, protects against rotenone-induced neurotoxicity in experimental model of Parkinson's disease. Neuroscience letters 2019; 690, 29-35.
- Fonseca-Fonseca, L. A. et al. JM-20 protects against 6-hydroxydopamine-induced neurotoxicity in models of Parkinson's disease: Mitochondrial protection and antioxidant properties. Neurotoxicology 2021; 82, 89-98.

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Web site: www.cidem.cu

PROJECT TITLE: ESTEP: TRANSCUTANEOUS ELECTRICAL VAGUS NERVE STIMULATOR FOR THE TREATMENT OF REFRACTORY EPILEPSY

Company: Cuban Center for Neuroscience

Therapeutic or preventive area/Indications: Therapy of drug-resistant epilepsy by transcutaneous electrical stimulation of the left atrial branch of the vagus nerve. Significant potentialities for the treatment of other brain disorders such as depression.

PROJECT DESCRIPTION:

The ESTEP device is a battery-powered, personalized stimulator designed for individual patient use. Internationally, the effectiveness of transcutaneous electrical stimulation of the left auricular branch of the vagus nerve for therapeutic purposes in the treatment of Drug-Resistant Epilepsy is well recognized. The ESTEP device specifically implements this therapy in a manner that is safe for patients, user-friendly for both medical personnel and patients, and has demonstrated satisfactory results in clinical trials conducted for regulatory approval.

The operation of the ESTEP device is based on the placement of electrodes that automatically adjust to the patient's ear, and therapy sessions are initiated by simply pressing a button. As a result, the device does not impose an additional burden on the patient. All patients and their caregivers were able to learn how to use the device within 15–20 minutes.
The ESTEP device is supplied with a stimulation cable and an external battery charger, eliminating the need for patients to remove and replace batteries. Healthcare professionals can program individualized therapy parameters for each patient, including the number of sessions per day, session duration, type of stimulus, stimulus duration and intensity, and stimulation frequency. This information cannot be modified by the patient or any unauthorized person.

Main results of pre-clinical and clinical studies:
A pilot trial was conducted in Cuba in conjunction with the Institute of Neurology and Neurosurgery. Over 80% of patients participating in the trial achieved a reduction of more than 50% in their monthly seizure frequency (MSF) compared to baseline, and no patient experienced worsening symptoms or adverse effects. Additional patients experienced a reduction in MSF below the threshold required to be classified as "treatment responders."

Current stage:
The product has achieved Technology Readiness Level 9. It is registered with health authorities in Cuba, Venezuela and Colombia, and applications for regulatory approval are currently underway in Mexico. A clinical trial in children with refractory epilepsy is ongoing at the National Institute of Neurology and Neurosurgery in Cuba, while another trial in adults with depression is being prepared. In addition, a closed-loop strategy for seizure detection and subsequent preventive stimulation is under development.

Intellectual Property:
No patent applied

Competitive advantages:
The ESTEP device stands out for its ease of use and low cost, making it suitable as the foundation for therapeutic protocols in public healthcare, while also being valuable in private medical practice. Notably, the ESTEP device enables much less invasive vagus nerve stimulation procedures compared to commercially available implants, which require surgical intervention under general anesthesia and frequent generator replacements. It is important to highlight that the supplier of the ESTEP device is committed to providing comprehensive after-sales service, thereby ensuring the proper functioning of the device throughout its lifecycle.

Business or cooperation opportunities:

- Co-development agreements for the introduction of ESTEP in new markets
- Purchase and distribution contracts.
- Joint development agreement for new indications such as depression or headache
- Joint development agreement for new generation based on closed-loop strategy.
- Some of these alternatives could include technology transfer of the final steps to obtain the finished product.

Main publications:

- González-Fernández RI, Río-Vázquez V, García-Giró A, Fernández-Rodríguez A, Pérez-Blanco JG, Velarde-Reyes E, Portela-Hernández L, Gutiérrez-Gil J, Santos-Santos A, Hernández-Cáceres JL. Development and Evaluation of a Transcutaneous Stimulator for the Treatment of Refractory Epilepsy. World Congress of the International Federation of Clinical Neurophysiology. Geneva, Switzerland. September, 2022.
- González-Fernández RI, Río-Vazquez V, Pérez-Blanco JG, Velarde-Reyes E, Portela-Hernández L, Gutierrez-Gil J, Santos-Santos A, Sanchez-Moya A, Hernández-Cáceres JL. A standardization proposal for the refractory epilepsy therapy based on transcutaneous electrical vagus nerve stimulation. First outcomes. IX Congress of the Latin American Chapter of the International Federation of Clinical Neurophysiology. Mexico City. November 2023.
- Anabel Sánchez Moya, René González Fernández, Ernesto Velarde Reyes, Jaime González Albiza, René Jerez, José L. Hernández Cáceres. Desarrollo de un nuevo neuroestimulador para el tratamiento de la Epilepsia Refractaria. BioHabana 2024 - Tecnología Médica e Industria 4.0. Varadero. Abril, 2024
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PROJECT TITLE: NEURONIC INFANTIX: NEONATAL SCREENING SYSTEM

Company: Cuban Center for Neuroscience

Therapeutic or preventive area/Indications: Objective detection of hearing and vision disorders in newborns by recording Otoacoustic Emissions (OAE), Auditory Evoked Potentials (AEP) and Visual Evoked Potentials (VEP). Ideal for use in neonatal screening programs.

PROJECT DESCRIPTION:

INFANTIX/NEURONIC A6.2 is a modular system, with an ergonomic and user-friendly design, which has a main module called the Control Module that allows the coupling of various modules:

- Otoacoustic Emissions: to generate the required stimulus and record the OAE using a transducer called OAE Probe attached.
- AEP and VEP Recording and Stimulation: to record the evoked potentials and generate the different types of auditory stimuli, as well as the flash visual stimulus. Different transducers are coupled, in correspondence with the test to be carried out: Air – Bone with headband (3 sizes) or Binaural Air, for AEP, and the monocular goggle stimulator for VEP.

The Control Module has an LCD touch screen where the medical application is displayed, which allows to carry out all system operations through an intuitive and easy-to-use graphical interface. It is a portable system, powered by a rechargeable battery with autonomy for more than 50 tests and with a robust mechanical support for easy transportation. All the tests are executed automatically, with results presented as PASS/FAIL along with diagnostic suggestions. It is an intelligent system that incorporates automatic methods of analysis and processing of evoked potentials. INFANTIX/NEURONIC A6.2 is clinically validated.

Main results of pre-clinical and clinical studies:

A clinical trial was conducted to evaluate the system's performance at a maternal hospital from September 2022 to April 2024. The trial took place at the González Coro Maternal Hospital in Havana and involved 400 newborns. The satisfactory results obtained are summarized in the following table:

	TOAE	AEPa	Mixed	VEP
Specificity (%)	81.35 (79.4*-83.3**)	94.11	94.11	---
Sensibility (%)	85.71	100	100	100
Test time (s)	27.7	50.9	-	42.0

Current stage:

The product has achieved Technology Readiness Level 9. It is registered with health authorities in Cuba, Venezuela and Colombia, and application for regulatory approval are currently underway in Mexico.

Intellectual Property:

No patent applied

Competitive advantages:

- Novel simultaneous air and bone stimulation methodology for distinguishing between sensorineural and conductive hearing losses.
- Capability to explore bone conduction using Auditory Steady-State Evoked Potentials in children with ear malformations.
- Unique system in the market for automatic integrity testing of visual pathways in newborns using VEP.
- Availability of Technical Support in the market.
- Business or cooperation opportunities:
- Co-development agreements for the introduction of INFANTIX in new markets:
- Purchase and distribution contracts.
- Joint development agreement for new indications such as cardiovascular screening

Some of these alternatives could include technology transfer of the final steps to obtain the finished product.
This system can be integrated with the AUDIX 5 electroaudiometer and the hearing prostheses produced by CNEURO to launch a comprehensive program for auditory disability care.

Main publications:

- Pantoja-Gómez, Y., Martín-González, F., Torres-Fortuny, A., & Eimil-Suarez, E. (2019, September). Implementation of the NEURONIC INFANTIX Newborn Hearing Screening System. In VIII Latin American Conference on Biomedical Engineering and XLII National Conference on Biomedical Engineering: Proceedings of CLAIB-CNIB 2019, October 2-5, 2019, Cancún, México (Vol. 75, p. 453). Springer Nature.
- Velarde-Reyes, E., Santos-Ceballos, J. C., Pérez-Blanco, J. G., Pantoja-Gómez, Y., Torres-Fortuny, A., Cabal-Rodríguez, R., ... & Regueiro-Gómez, Á. Implementación de Sistema de Cribado para la Audición y la Visión de Neonatos. Conference: XL Congreso Anual de la Sociedad Española de Ingeniería Biomédica (CASEIB 2022) at: Valladolid, Spain.
- Márquez, I. A., Fortuny, A. T., Reyes, E. V., & Montes, E. M. (2021). Implementación en el sistema INFANTIX de una nueva estrategia para la detección automática de la respuesta evocada auditiva de estado estable. Revista Científica de Ingeniería Electrónica, Automática y Comunicaciones, 42(2), 1-16.
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PROJECT TITLE: SMART EEG REPORT: ARTIFICIAL INTELLIGENCE FOR INTERPRETING THE ELECTROENCEPHALOGRAM.

Company: Cuban Neuroscience Center, Universidad de Ciencias Informáticas

Therapeutic or preventive area/Indications: Informatics tool to aid neurophysiologists and physicians in the diagnosis of mental disorders from the analysis of the EEG.

PROJECT DESCRIPTION:

Smart EEG Report is an AI Assistant designed to help the clinical neurophysiologist, offering two powerful functionalities to enhance your daily EEG workflow.

- Smart AI Assistance for EEG Labeling: The system automatically detects and marks segments with clinically relevant events—such as artifacts, spikes and sharp waves, slow waves, generalized or lateralized epileptiform activity, eye movements, and more. This targeted event labeling enables you to visually assess the EEG more efficiently, focusing your expertise on the most important segments and expediting the overall evaluation process.
- Smart AI Assistance for EEG Reporting: Smart EEG Report also proposes automatic draft reports for each study, based on the latest international guidelines, including the 2017 American Neurophysiology Society standards and the structured SCORE report format. This ensures your reports are standardized, comprehensive, and easily accepted across clinical settings.

Smart EEG Report integrates directly into an EEG Editor software, in our case, the Neuronic EEG Editor, requiring no new training. Importantly, it is designed as a supportive tool: while it streamlines event detection and structured reporting, the final interpretation and approval remain fully under your control—always respecting the physician's judgment and responsibility.

The clinical evaluation of this tool should be performed by a group of around 20 physicians in each country, to account for the variability in handling the data, labeling and reporting. Each neurophysiologist should utilize the functions for a minimum of 20 to 30 patients (or recordings), assessing the gain in speed, the quality of the results obtained and the general usefulness of the tool to their work.

Main results of pre-clinical tests:

The Smart EEG system is currently developed in an initial version integrated with the Neuronic EEG Editor. It is based on a convolutional neural network model that achieved 94.17% accuracy during training and validation using the internationally recognized Temple University EEG database, specifically the EEG Events Corpus.

This corpus consists of over 200,000 one-second EEG segments (approximately 200 hours of EEG) with around 30,000 annotations classifying the segments into six categories: spike and slow wave, generalized periodic epileptiform discharge, periodic lateralized epileptiform discharge, eye movement, other artifacts, and background activity. The last category is also assigned when none of the other classes apply.

Preliminary generalization studies using data not involved in training, along with variations in preprocessing steps, yielded overall accuracies between 70% and 90%. Average precision and sensitivity ranged from 80% to 92%, with acceptable specificity and F1-score values. It is important to note that the class distribution was imbalanced, with an overrepresentation of the background category, which should be considered when interpreting the results. Nonetheless, on the Temple University Event Corpus test set, the model achieved a balanced accuracy between 75% and 88%.

These results indicate the feasibility of combining this approach with other methods targeting more individualized classification and suggest further improvements through alternative models. Future work will be guided by clinical trial results assessing the time-saving benefits for neurophysiologists and the model's effectiveness under realistic conditions.

Current stage: Preliminary Clinical validation phase.

Intellectual Property:
"Procedures for obtaining expert-level labeling of the EEG combining AI Foundation models with Multidimensional analysis for personalized classification". Submitted.

Competitive advantages:
Artificial intelligence has advanced rapidly across many domains, including the detection of clinically relevant EEG events. However, despite considerable research efforts toward perfect event detection—such as epileptic seizures—few user-friendly tools currently exist that effectively support neurophysiologists in clinical practice. Moreover, high detection performance demonstrated on limited datasets often does not generalize well to large, diverse external EEG databases due to variability in electrophysiological patterns across patients.

Our system's competitive advantage lies in its pragmatic design philosophy: rather than aiming for fully autonomous, infallible event detection to enable automatic diagnosis, it focuses on augmenting the neurophysiologist's workflow for EEG annotation and reporting. By leveraging simpler yet efficient computational methods, the system delivers rapid preliminary results that, while not perfectly accurate, meaningfully guide clinicians in quickly identifying potentially diagnostic EEG events. This pragmatic approach has the potential to reduce EEG review and reporting times by two orders of magnitude, significantly increasing clinical throughput and allowing specialists to devote more time to complex cases and patient care.

Additionally, the capability to bring this product to market swiftly provides a strategic advantage, enabling early adoption and establishing our tool as the default starting point for EEG analysis in clinical settings. This foundational presence will facilitate seamless integration of future iterations with enhanced functionalities, expanding gradually into specialized tasks while maintaining continuity with the core system.

This balance of usability, efficiency, and strategic market entry distinguishes our system from current research prototypes and positions it to make a meaningful impact on neurophysiology practice.

Business or cooperation opportunities:
The project offers potential for scientific cooperation and product development in future versions, including the integration of new AI models and enhancements to the user interface and physician interaction with the tool. Examples include incorporating voice-to-text conversion algorithms, interfaces for rapid physician annotations, and streamlined review interfaces for quick verification of reported findings.

Additionally, there are opportunities to customize the tools for different languages and the specific conditions of healthcare systems across various countries and regions, enabling broader distribution to potential clients in multiple markets. Opportunities also exist for partnership in product marketing efforts.

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PROJECT TITLE: PHYCOCYANOBILIN, PCB, WITH THERAPEUTIC POTENTIAL FOR THE TREATMENT OF MULTIPLE SCLEROSIS, CEREBRAL ISCHEMIA AND ALZHEIMER'S DISEASE

Company: Center for Genetic Engineering and Biotechnology

Therapeutic or preventive area/Indications: Therapy neurodegenerative diseases / Neurodegenerative disorders and acute stroke.

PROJECT DESCRIPTION:

This project is based on the therapeutic potential of phycocyanobilin, an open-chain linear tetrapyrrole molecule of C-phycocyanin, the main component of the cyanobacterium Spirulina platensis, with antioxidant, neuroprotective, remyelinating, anti-inflammatory, immunomodulatory and cytoprotective properties. Due to these characteristics, phycocyanobilin is proposed to prevent or reverse the neurodegenerative changes that occur in multiple sclerosis and Alzheimer's disease; while its effects at different stages of the ischemic cascade also make it suitable as a preventive and maintenance therapy for cerebral ischemia.

Main results of pre-clinical and clinical studies:
Phycocyanobilin acts at all stages of the ischemic cascade: it has anti-excitotoxic, anti-apoptotic, antioxidant, mitoprotective, anti-inflammatory and neurofilament stabilizing effects in models of cerebral ischemia.

The antioxidant effect of phycocyanobilin is mediated by a potent inhibition of NADPH oxidase. In addition, phycocyanobilin has anti-inflammatory, immunomodulatory and cytoprotective effects. The remyelinating effect of phycocyanobilin was also evidenced because it induces a positive regulation of remyelinating genes (MAL) and a negative regulation of demyelinating genes (LINGO). It was further shown that phycocyanobilin induces regulatory T cells (Treg) and decreases effector cytosines in the brain. It has anti-inflammatory effects, decreases the activation of microglia and decreases APP in animal models of multiple sclerosis.

Current stage:
Preclinical studies

Intellectual Property:
Pharmaceutical compounds and combinations for ischemic and neurodegenerative brain disease treatment". Awarded in the European Union, the United States, Canada, Australia, Mexico, Russia, China, Japan, South Korea and South Africa. Expiry date: 06/29/2012 – 06/29/2032.

Competitive advantages:
• Remyelinating property,
• Oral administration.
• Natural origin and GRAS category (generally recognized as safe), the highest confirmation based on background or published evidence,
• Less toxicity given its natural source,
• Potential uses for all clinical forms of multiple sclerosis.
• Effect in prophylactic regimen (oral for people with risk factors) and therapeutic regimen in acute stage (intravenous route in acute stroke),
• Effect on all stages of the ischemic cascade (excitoxicity, inflammation and neurodegeneration).

Business or cooperation opportunities:
Collaboration agreement or business models for:
- Develop oral formulations.
- Carry out preclinical and clinical studies in the indicated indications

Main publications:

- Marín-Prida J, Pavón-Fuentes N, Lagumersindez-Denis N, Camacho-Rodríguez H, García-Soca AM, Sarduy-Chávez RC, Vieira ÉLM, Carvalho-Tavares J, Falcón-Cama V, Fernández-Massó JR, Hernández-González I, Martínez- Donato G, Guillén-Nieto G, Pentón-Arias E, Teixeira MM, Pentón-Rol G. Anti-inflammatory mechanisms and pharmacological actions of phycocyanobilin in a mouse model of experimental autoinmune encephalomyelitis: A therapeutic promise for multiple sclerosis. Front Immunol. 2022;13:1036200. doi: 10.3389/fimmu.2022.1036200.
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- Piniella-Matamoros, B., Marín-Prida, J. & Pentón-Rol, G. Nutraceutical and therapeutic potential of Phycocyanobilin for treating Alzheimer's disease. J Biosci. 2021;46:42. Disponible en https://-doi.org/10.1007/s12038-021-00161-7.
- Cervantes-Llanos M, Lagumersindez-Denis N, Marín-Prida J, Pavón-Fuentes N, Falcon-Cama V, Piniella-Matamoros B, Camacho- Rodríguez H, Fernández-Massó JR, Valenzuela-Silva C, Raíces-Cruz I, Pentón-Arias E, Teixeira MM, Pentón-Rol G. Beneficial effects of oral administration of C-Phycocyanin and Phycocyanobilin in rodent models of experimental autoimmune encephalomyelitis. Life Sci. 2018;194:130-8. doi: 10.1016/j.lfs.2017.12.032.

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PROJECT TITLE: CIMEDIT. NEW ALTERNATIVE FOR THE TREATMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Company: Center for Molecular Immunology

Therapeutic or preventive area/Indications: Pulmonology/Chronic Obstructive Pulmonary Disease

PROJECT DESCRIPTION:

CIMAvax-EGF® is a Cuban biotechnology product developed for the treatment of cancer. It represents a novel approach to blocking EGFR by removing EGF, one of its most important ligands, from circulation. Its mechanism of action consists of inducing active immunity against autologous EGF in cancer patients. The formulation was designed to make the EGF molecule immunogenic by coupling it with the P64k protein from Neisseria meningitidis and emulsifying the chemical conjugate (EGFhr/P64k rec) with the oil-based adjuvant Montanide ISA 51 (Seppic, France).

CIMAvax-EGF is a registered product for patients with NSCLC, in advanced stages. In 2018, CECMED modified the indication of the product, restricting it to patients with serum EGF levels greater than 870 pg/mL, for which the use of an accompanying biomarker was incorporated.

CIMEDIT is a new formulation based on CIMAvax-EGF components. This biotechnological product was approved for use in NSCLC patients. It is currently being evaluated in patients with moderate to severe COPD.
The EGFR signaling pathway has been shown to be relevant in COPD, given the role of epithelial cells in the processes underlying bronchial obstruction associated with chronic inflammation and mucus hypersecretion.
Given CIMEDIT ability to reduce serum EGF concentrations and the role of the EGFR signaling pathway (primarily mediated by EGF) in the pathogenesis of COPD, opens a window of opportunity for treatment in COPD patients with an EGF depleting immunotherapy.

Main results of pre-clinical and clinical studies:
Experience with the use of CIMEDIT in patients with COPD comes from a Phase I study conducted in patients at high risk of lung cancer (trial code: RPCEC00000370, available at: https://rpcec.sld.cu/ensayos/RPCEC00000370-Sp. This study included a total of 33 patients with COPD.

Twenty-six patients with moderate or severe COPD were included in the trial. Participating patients had high serum EGF concentrations of 955 pg/mL.. The vaccine was well tolerated and no serious related adverse events were reported. Ninety percent of the individuals developed a protective antibody response. The specific anti-EGF antibodies had high avidity and were able to inhibit EGFR phosphorylation. At the end of vaccination, serum EGF became undetectable. After 6 months of treatment with EGF-depleting immunotherapy, the change in FEV1 from baseline was +106 mL. The percentage change in lung function at six months was 12.6%. The proportion of patients who reached a minimal clinically important difference in trough FEV1 was 46.1%.

Fourteen patients completed the physical function survey at baseline and after 6 months. At the end of vaccination, there was an improvement in the 10 physical function items, which became significant for the capacity to complete moderate activities, for lifting or carrying groceries, for climbing one flight of stairs, for bending or kneeling, and for walking one block. Overall, their physical activity significantly improved after completing vaccination. (3)

Current Stage:
A phase II/III clinical trial is ongoing in Cuba for the treatment of patients with Chronic Obstructive Pulmonary Disease (COPD). A Phase I/II clinical trial is underway in the US for the treatment of lung cancer in combination with the anti-checkpoint monoclonal antibody Nivolumab. The first phase of the study concluded satisfactorily, observing a substantial increase in the survival of patients with tumors that express the unmutated KRAS oncogene.

Intellectual Property:
Use of epidermal growth factor depleting agents in the treatment of chronic obstructive pulmonary disease (2020). Patent applied in 16 countries. Patent No. WO2022/022756. Patent granted in Australia

Competitive advantages:
Based on the concept of vaccination for the treatment of lung cancer and COPD patients
Business or cooperation opportunities:
Agreements for the conduct of clinical trials until commercialization.

Main publications:

- Survival of NSCLC Patients Treated with Cimavax-EGF as Switch Maintenance in the Real-World Scenario. Yoanna I. Flores Vega et al. 2023. J Cancer 2023; 14(5):874-879. doi:10.7150/jca.67189.
- Augmenting antibody response to EGF-depleting immunotherapy: Findings from a phase I trial of CIMAvax-EGF in combination with nivolumab in advanced stage NSCLC. Evans R. et al. Front Oncol. 2022; 12: 958043. doi: 10.3389/fonc.2022.958043
- PREVAX: A Phase I clinical trial of an EGF-based vaccine in moderate-to-severe COPD patients. Hernandez Reyes JdlC, Santos Morales O, Hernandez Moreno L, Pino Alfonso PP, et al. Vaccines. 2024;12:833. doi:10.3390/vaccines12080833.

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