BioCubaFarma: driving research and therapeutic development in brain disorders

The Cuban Center for Neurosciences (CNEURO), a core institute of the Cuban organization of Biotechnology and Pharmaceutical Industries, BioCubaFarma, has developed a portfolio of technologies and services to diagnose and treat brain disorders and promote mental health from infancy to old age.

The Cuban Center for Neurosciences (CNEURO) is one of the 34 companies and institutions in a network of resources and capabilities that constitute the backbone of BioCubaFarma, the Cuban organization of Biotechnology and Pharmaceutical Industries. CNEURO specializes in the development of products for the diagnosis and treatment of neurological diseases and the promotion of mental health. The center markets its portfolio of solutions to professionals—neurologists, neurosurgeons, neurophysiologists, intensive care physicians, psychiatrists, psychologists and educators—who need tools to evaluate the brain, sensorial impairment, learning or cognition (Fig. 1).

CNEURO brings together a multidisciplinary team of more than 200 engineers and scientists in areas such as neurophysiology, audiology, psychology, mathematics, physics, computer sciences, molecular biology, biomedicine and electronic engineering. The center’s pipeline is focused on four innovative topics in neuroscience:

•  the development of therapies for the treatment of Alzheimer’s disease and neuroimaging platforms for diagnosis of the disease;
•  technologies for early detection and treatment of cognitive and sensory problems during life;
•  the development of neuromodulators, stimulators, neurofeedback and brain–machine interfaces for therapeutic and/or rehabilitation purposes; and
•  methods for modifying neural coding in brain functional networks in specific brain disorders through the use of functional magnetic resonance imaging (fMRI)-based neurofeedback and its translation into more expandable electroencephalogram-based methodologies.

CNEURO has ongoing collaboration agreements with partners in Europe, Asia and South and North America. One of the center’s most recent collaborations has brought together scientists from China, Canada and Cuba to develop a joint brain-mapping project. The research focuses on the use of neuroinformatics methods for early detection and management of pathological aging of the brain and includes an academic exchange program to facilitate progress. The project is supported by the China National Science Foundation and Fund for Science and Technological Innovation, the Science Fund of Quebec and the Cuban Ministry of Science, Technology and Environment.

Domestically, CNEURO also leads a neuroactive molecules program that integrates the efforts of several centers and companies of BioCubaFarma searching for new treatments of diseases of the nervous system that use personalized medicine principles. CNEURO also participates in the Joint Program for Brain Dysfunctions of the Cuban Ministry of Public Health and BioCubaFarma. Here we present two of the projects from these programs.

A combined approach to ischemic stroke

As part of the neuroactive molecules program of BioCubaFarma, the Center for Genetic Engineering and Biotechnology (CIGB) is developing CIGB-845, a combination therapy of two molecules, growth hormone-releasing peptide 6 (GHRP6) and epidermal growth factor (EGF), that exhibits neuroprotective and neurorestorative properties. CIGB-845 provides protection against a broad range of pathological processes related to ischemic stroke and a range of other neurological conditions.

Acute ischemic stroke is one of the major causes of permanent disability and the third largest cause of death worldwide. The choice of treatments for ischemic stroke is limited, and the only pharmacological treatment on the market is recombinant tissue plasminogen activator (rt-TPA). Stringent inclusion criteria for reperfusion eligibility, including a limited therapeutic window of 4.5 h after symptom onset, restrict the use of rt-TPA to less than 5% of patients who have had a stroke. Alternative neuroprotective therapies have not been successful so far because the compounds under development have been directed against a single therapeutic target. However, cerebral ischemia is a multifactorial disease, in which the mechanisms responsible for damage change over time.

The combined therapy provided by CIGB-845 has the advantage of simultaneously providing antiapoptotic and antiexcitotoxic protection—EGF promotes neurogenesis and remyelination and GHRP6 induces the expression of endogenous neuroprotective factors.

CIGB-845 is being advanced as a first-in-class therapeutic approach for ischemic stroke (patents WO/2006/092106 and WO/2002/053167). Preclinical studies using models of global brain ischemia, experimental autoimmune encephalitis and in vitro or in vivo amyotrophic lateral sclerosis have further confirmed the neuroprotective effect of CIGB-845 on the central nervous system.
Visualizing β-amyloid in Alzheimer’s disease

CNEURO is developing Amylovis-Diag, a new contrast agent for imaging β-amyloid (Aβ) plaques in the human brain using MRI. Aβ plaque formation is one of the hallmarks of Alzheimer’s disease-related brain lesions and is regarded as one of the earliest, if not the first, pathological symptom of Alzheimer’s disease (Fig. 2).

Alzheimer’s disease accounts for 60–70% of all cases of dementia and is rapidly becoming one of the greatest public health challenges among aging populations worldwide. Alzheimer’s disease is characterized by the presence of Aβ plaques and neurofibrillary tangles consisting of tau protein in the brain, and recent studies have confirmed that Aβ plaques are a necessary condition for the development of Alzheimer’s disease. Although difficult to diagnose in asymptomatic individuals, these early processes are the best targets for the development of effective treatments.

Three US Food and Drug Administration-approved Aβ positron-emission tomography (PET) radiotracers have been successfully used in the diagnosis and the characterization of Alzheimer’s disease, and are playing an increasingly important role in the study of presymptomatic Alzheimer’s disease, especially in the recruitment of subjects for clinical trials. However, PET probes are expensive and require access to cyclotrons, which has restricted their use mainly to research and high-level clinical facilities. Other drawbacks of PET radiotracers include their low spatial resolution and associated radioactivity.

Cerebrospinal biomarkers obtained via lumbar puncture have emerged as an alternative to PET radiotracers, but the invasiveness of the procedure, especially when repeated measurements are required, has greatly limited the application of this approach.

CNEURO is developing high-affinity MRI probes specific for Aβ to take advantage of the higher spatial and temporal resolution, broader availability and reduced invasiveness compared with PET. The chemical probes developed by CNEURO, Amylovis (patents EP 2 436 666 A20 and US 9,764,04), have been conjugated to iron oxide and gadolinium nanoparticles for use as high-specificity MRI contrast agents for Aβ.

In silico analysis using docking and molecular dynamic techniques by saturation and competitive binding assays (dissociation constant (K_d) = 0.11 nM), have confirmed the high-specificity of the Amylovis probes for Aβ. In vivo studies have further shown that Amylovis crosses the blood–brain barrier in both healthy mice and transgenic Alzheimer’s disease mice, exhibiting high in situ affinity for Aβ in the latter.

If needed, Amylovis has the advantage of being versatile in radiolabelling, and can be labeled with different types of radionuclide, both gamma ray emitters (99mTc, 111In or 67Ga) and positron emitters (18F and 11C). Therefore, Amylovis compounds could be also used for PET and single-photon emission computed tomography.

Partnering with CNEURO

CNEURO has an open and very flexible approach to collaboration with external partners through mechanisms that range from research collaboration agreements to licensing and codevelopment agreements. In addition, CNEURO is also seeking potential partners interested in investing in the center’s neurology assets through venture funding or similar mechanisms.

In the case of Amylovis (CNEURO) and CIGB-845 (CIGB), CNEURO and CIGB are seeking corporate partnerships for the codevelopment, registration and marketing of the product in selected territories. Establishment of a joint venture in the special development zone of Mariel, Havana, Cuba, would be of particular interest to CNEURO.

Consolidating biopharma in Cuba

BioCubaFarma is a holding company that manages and coordinates national efforts in the biopharma sector to produce medicines and medical equipment that provide high-quality life science services of high economic and social impact. The biotechnology and pharmaceutical industry is one of Cuba’s strategic industries, supplying goods, technologies and services that comply with the high international quality standards in the sector.

Building on Cuba’s homegrown scientific and technical expertise and the government’s substantial support for and investment in biotechnological and pharmaceutical research and development (R&D), BioCubaFarma has brought together the many assets that make Cuba’s biotechnology and pharmaceutical industry a world-class player.

In keeping with its mission to prioritize public health and the national health system, BioCubaFarma has consolidated a deep product pipeline that includes prophylactic and therapeutic vaccines, innovative biopharmaceutical products for cancer, cardiovascular disease, neurology and other indications, biosimilar products, generic drugs, diagnostic reagents, medical equipment, agrobiotech products, and natural and traditional medicines.

BioCubaFarma manages a large portfolio of patented inventions, with 2438 patents registered outside Cuba and more than 2640 patent registration applications pending worldwide. This catalog of assets provides the basis for an open and very flexible approach to collaboration with external partners through mechanisms that range from research collaboration agreements to licensing and codevelopment agreements. BioCubaFarma is also seeking potential partners interested in investing in Cuban biopharma assets through venture funding or similar mechanisms.

BioCubaFarma centralizes the country’s efforts to open up the Cuban biotechnological and pharmaceutical industry and research infrastructure to the world. In addition to its national network, BioCubaFarma has an extensive global presence through mixed capital companies in China, Spain, Thailand and Singapore, solely Cuban-owned companies in Venezuela, Ecuador, Brazil and Mexico, a representative office in China and a branch office in Colombia.

BioCubaFarma offers many new business opportunities to potential partners, including scientific agreements, supporting the R&D of new biopharmaceutical products and broader alliances with overseas companies to clinically develop and commercialize therapeutic, diagnostic and medical technology products. BioCubaFarma is also seeking to attract foreign venture capital and to establish joint ventures to develop innovative products.

The types of partnership can include license agreements, project codevelopment agreements, incorporated joint venture companies, representation and supply agreements, incorporated subsidiaries, technology transfer agreements, contract manufacturing and foreign investments on Cuban soil.

Fig. 2 | Visualizing β-amyloid in Alzheimer’s disease. This image shows the interaction between an Amylovis and a folded Aβ17-42 fragment through a spontaneous process.