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Contents

November Editorial

The Cholinergic Theory and Acetylcholinesterase Inhibitors in the Treatment of Alzheimer's Disease: An Interesting History

The "central cholinergic system", postulated by **Feldberg** and **Vogt** in the 1940s, is composed of a network of neurons that synthesize acetylcholine (ACh). The cholinergic system has been intuitively postulated to influence higher activities of the central nervous system (CNS) since ancient times in Egypt, China, and the Arab and Roman civilizations. **Gaius Pliny the Second** (23-79 AD) (**Pliny the Elder**) anticipated the amnesic properties of *Atropa belladonna, henbane*, and *Datura stramonium*. In 1762, **Störk** reported that Jimson weed disrupted the mind, caused insanity, and erased memory; and in 1831 **Mein** showed that *Datura stramonium* contained atropine. The seeds of the Calabar bean (*Physostigma venenosum Balf.*), identified by **Hutton Balfour** in 1868, were used by the Efik tribe of Old Calabar, Nigeria, to kill criminals, according to Scottish missionaries such as **HM Wadell**. **Fraser** was the first to isolate the active ingredient, and **Jobst** and **Hesse** in Germany, and **Vee** in France, crystallized the active agent from beans (physostigmine, eserin). Physostigmine was soon used to investigate Gaskell's "involuntary system", later renamed by **John Langley** as the "autonomic nervous system." In the 1950s, **Irwin Wilson** discovered the first anticholinesterases (organophosphate agents used as pesticides and war gases; diaminoacridines used as pesticides since 1910). Four decades later, **Sam Greshom** and his co-workers demonstrated the carbamate nature of anticholinesterases. In the late 1940s and early 1950s, **Willy Lange**, **Gerhard Schrader**, and **Wolfgang Wirth** demonstrated the toxic effects of organophosphate anticholinergics.

Acetylcholine (ACh) was synthesized in 1867, and it was the first neurotransmitter discovered by **Henry Hallett Dale** in 1914, later confirmed by **Otto Loewi**. Cholinesterases, the catalytic enzymes that degrade ACh, were described in the 1920s and 1930s by **Abderhalden**, **Galehrand** and **Plattner**, **Alles** and **Hawes**, and **Glick** and **Nachmansohn** in different tissues. **Alles** and **Hawes** called these enzymes "pseudocholinesterases", but in 1944 **David Nachmansohn** called them specific cholinesterases or acetylcholinesterases. In 1961, EC numbers were assigned by the Enzyme Commission of the International Union of Biochemistry: Acetyl-choline acetyl-hydrolase for acetylcholinesterase (AChE) (ACHE; CE 3.1. 1.7) and acylcholine acyl-hydrolase for butyrylcholinesterase (BuChE) (BCHE: EC 3.1. 1.8).

ACHE and BCHE genetic variants were identified by **Werner** and **Kalow** in the late 1950s. The key authors in the early characterization of the cholinergic system were **Sir John Eccles**, **Sir Charles Sherrington**, **Sir Henry Dale**, **Sir William Feldberg**, **Martha Vogt**, **Emil Dubois-Reymond**, **Bernand Renshaw**, and many other contemporary authors. **Sir Lindor Geoffrey Brown** and **Sir William Feldberg** were the first to postulate ACh's role as a transmitter in the 1930s and 1940s. **Judah Quastel** was the first to suggest the need for an enzyme for the synthesis of ACh; and **Nachmansohn** and **Machado** identified "choline acetylase", renamed in 1961 as "choline acetyltransferase" (ChAT), and also identified acetyl-CoA as a precursor of ACh.

Based on the classic studies of **Palay** and **Palade** in the 1950s, **De Robertis** and **Whittaker** demonstrated the presence of ACh in vesicles; **William Perry** postulated that choline in the synaptic cleft was used in ACh resynthesis, and the use of hemicolinium-3, developed in the 1950s by **Fred Schueler**, served to test **Perry**'s theory. Finally, after the early work of **Emil Fisher**, **Paul Ehrlich** and **Claude Bernard**, **Sir Henry Dale** and others described the nicotinic and muscarinic receptors.

Several experimental methods have been used for decades to document the role of the cholinergic system in cognition, including nicotinic and muscarinic antagonists (scopolamine, atropine), the inactivation of cholinergic neurons (192 IgG-saponin, α-amino-3-hydroxy-5-methyl-4-isoxatol proprionate (AMPA), quiscualic acid, ibotenic acid, neurotoxin AF64A) and stimulation of brain cholinergic neurons with muscarinic agonists (arecoline, xanomelain), nicotinic agonists (nicotine), reversible (physostigmine) and irreversible cholinesterase inhibitors (methylphenidate) or newer acetylcholinesterase inhibitors (AChEIs) (donepezil, huperzine A) and acetylcholine precursors (dimethylaminoethanol, glucose, choline). **Daniel Bovet** described the effects of nicotine on memory; and the influence of the cholinergic system on memory and learning were confirmed by **David Drachman** and **Yan Bures** in the 1960s and 1970s, later popularized by **Raymond Bartus** in the 1980s.

"The cholinergic hypothesis" of Alzheimer's disease (AD) is based on the observation of the loss of neurons in the anterior lobe and the neocortex of brains extracted from patients with AD, reported by **Davies** and **Maloney** and **Bowen** *et al* in 1976, **Whitehouse** *et al* in 1982, and **DeKosky** and **Scheff** in 1990, and many other authors in successive years.

Regarding the clinical applications of cholinergic agents, **Thomas Fraser** found that Calabar bean extracts caused miosis, and **Argyl Robertson** used it to counteract belladonna (atropine) -induced mydriasis. Physostigmine was used for the treatment of glaucoma. In 1895, **Jolly** suggested the use of cholinergic drugs in myasthenia gravis, but **Mary Walker** and **Ludwig Remen** were the first to apply physostigmine in the clinic. In the 1930s, **David Click** associated ACh deficiency with psychiatric disorders; and 40 years later, **Peter Davies**, **Elaine Perry**, **Summers**, **Giacobini**, and many others began the acetylcholinesterase inhibitor (AChEI) crusade in Alzheimer's disease.

Key elements in cholinergic neurotransmission include ACh precursors (choline, acetyl-CoA), ACh synthesis (ChAT) and breakdown enzymes (AChE, BuChE), choline transporter (CHT1), vesicular ACh transporter (VAChT), and cholinergic receptors (nicotinic, muscarinic). Other players in the ACh biosynthetic pathways, in addition to choline and lecithin (phosphatidylcholine), are phospholipids such as cytidine 5'-diphosphocholine (CDP-choline) or alpha-glyceryl-phosphorylcholine (choline alfoscerate). Glucose in the brain is an important source of choline for the synthesis of ACh.

ChAT is the enzyme responsible for the synthesis of ACh from acetyl-CoA and choline in the cytoplasm where the VAChT captures ACh in vesicles that mobilize ACh to synaptic terminals. When released in the synaptic cleft, ACh interacts with nicotinic and muscarinic receptors; and the remaining ACh is hydrolyzed by the AChE which generates acetate and choline. Choline is recycled by the high affinity choline transporter (CHT1) for choline reuptake at the presynaptic level to be reused for de novo synthesis of ACh.

The cholinergic system of the brain is organized into the following pathways: (i) mesopontine-thalamic pathways, (ii) parabigeminal-tectal pathways, (iii) habenular-interpeduncular pathway, (iv) intrinsic striatal pathway, and (v) basal forebrain-cerebrocortical pathway. There is a clear deficiency of cholinergic neurotransmission in AD; however, the damage to cholinergic pathways in AD is not global, but selective. The cholinergic neurons of the basal forebrain (basocortical cholinergic pathway, septohippocampal cholinergic pathway), where the nucleus basalis of Meynert is located, and the cortical cholinergic projections are the brain territories mainly affected in AD, with a depletion of 60-80% of cholinergic markers in severe cases.

Central cholinergic neurons and the apparatus that regulates cholinergic neurotransmission are severely damaged in AD from the early stages of the disease, constituting an important pathogenic event; however, presynaptic cholinergic markers during progressive CNS amyloidogenesis in Tg2576 (hAPPswe) transgenic mice show presynaptic cholinergic integrity despite increased levels of β-amyloid protein (Aβ).

The main focus of pharmacological research in the last 50 years has been the identification of cognitive enhancers. The identification of selective cholinergic dysfunction in the basal forebrain and cortical neuronal loss in the late 1970s and early 1980s, led to the introduction of AChEIs as the first option to restore cholinergic neurotransmission, probably taking a simplistic view of AD-related neurodegeneration (i.e., acetylcholine deficiency is to AD what dopamine deficiency is to Parkinson's disease). Tacrine (9-amino-1,2,3,4-tetrahydroacridine), a product known since 1949, was the first AChEI for the treatment of AD introduced in 1993, after pioneering studies by **Summers** *et al* in 1980-1986. This drug was withdrawn from the market years later due to its hepatotoxicity and gastrointestinal problems. In successive years, a new generation of AChEIs including Donepezil, Galantamine, and Rivastigmine were approved in the United States, the EU, Japan, and in many other countries around the world. Huperzine A was approved by the Chinese authorities in 1994. Memantine, a partial inhibitor of the glutamate N-methyl-D-aspartate receptor (NMDA), was introduced as an alternative treatment for severe AD in 2003. No new FDA-approved drugs for AD have been reported in the past 18 years, until the approval of the Aducanumab antibody on June 22, 2021.

Ramón Cacabelos
Professor of Genomic Medicine

Alzheimer’s disease almost never comes alone: Concomitant diseases

Alzheimer's disease (AD) is a priority health problem in advanced societies and its prevalence and incidence are gradually increasing in many emerging and developing countries, with a high cost for public health services and for the economy of families. The cost of dementia exceeds US$ 800 billion worldwide (> 1% of GDP), with an average cost per patient/year that fluctuates between $30,000 and $60,000, depending on the country, social status, quality of the medical care and stage of the disease. Approximately 20% of direct costs are associated with drug treatment, with very low profitability. AD is the most common form of dementia (50-60%), followed by vascular dementia (30-40%), other forms of dementia (10-15%) and mixed dementia, which is the most prevalent form of dementia (> 70%) in patients older than 75 years. The disease is more frequent in females than in males. AD is the result of the premature death of neurons caused by multiple genomic, epigenomic, cerebrovascular and environmental factors, giving rise to a clinical phenotype characterized by progressive cognitive decline, behavioral changes, and functional impairment.

According to conventional criteria, AD is a continuous neurodegenerative process, which can be differentiated into early-onset AD (early AD, eAD), associated with Mendelian mutations in specific genes with familial transmission (familial AD, fAD) and late-onset AD (lAD) attributed to a more complex pathogenic profile in which multiple susceptibility genes (> 600) are involved together with various environmental factors (sporadic AD, sAD). The neuropathological features of AD are represented by extracellular deposits of β-amyloid (Aβ) protein aggregates in senile plaques and vessels (amyloid angiopathy) and intracellular neurofibrillary tangles (NFT), formed by hyperphosphorylation of the tau protein in microtubules and neurofilaments. Aβ and tau may act independently or have synergistic effects on the pathogenesis of AD. These classic neuropathological markers are accompanied by astrogliosis, activation of microglia, dendritic dystrophy, and progressive neuronal loss in critical regions of the hippocampus and cerebral neocortex, compromising the circuits involved in the higher activities of the central nervous system (CNS). This neuropathological picture is accompanied by the phenotypic expression of epigenetic aberrations, neurotrophic dysfunction, neurotransmitter deficiencies (cholinergic, monoaminergic, glutamatergic, GABAergic, neuropeptidergic), neuroinflammation, lipid peroxidation due to oxidative stress reactivity and cerebrovascular damage (hypoperfusion).

The main challenges facing the scientific community, medical services and the pharmaceutical industry today are: (i) deeper understanding of the primary causes of AD and its pathogenic

mechanisms, (ii) characterization and validation of reliable biomarkers that allow an early diagnosis, (iii) the identification and development of new drugs and therapeutic strategies capable of slowing down or stopping the course of the disease, and (iv) under optimal conditions, developing new preventive protocols capable of blocking the evolution of the disease in the population at risk in presymptomatic stages, taking into account that brain damage in AD begins several decades before the clinical manifestation of symptoms of dementia

The aging of the adult population accumulates many other concomitant pathologies with dementia that require the establishment of polypharmaceutical regimens, with the consequent increase in the risk of adverse drug reactions (*Adverse Drug Reactions, ADRs*) and dangerous drug-drug interactions (*Drug-Drug Interactions, DDIs*). In fact, more than 80% of dementia patients take more than ten different medications daily. Currently, the most efficient way to reduce ADRs and DDIs is to implement pharmacogenetic protocols for the personalization of pharmacological treatment of patients with dementia, and several studies show that the therapeutic response to conventional drugs in AD is dependent on the genomic profile of each patient.

In a cohort of more than 1,000 Spanish patients, randomly selected, with a diagnosis of neurocognitive disorder (NCD)-AD, the team of professionals led by **Dr. Ramón Cacabelos** at the International Center of Neuroscience and Genomic Medicine, investigated common related phenotypes with gender including biochemistry, hematology, metabolism, hormones, neurotransmitters, cardiovascular and cerebrovascular function, cognition, mood, behavior, genomic and pharmacogenomic profiles. Significant differences between women and men are present in many biological parameters, including biochemical, hormonal, hematological, cognitive, and behavioral markers. Cognitive markers (MMSE, ADAS) indicated that women showed worse cognitive performance than men. Depression and cognitive impairment are the first symptoms to appear in 98.5% and 99.1% of patients with lEA, and 9% and 80%, respectively, in cases of eEA. Late depression is associated with cognitive decline, and depression is associated with an increased risk of AD. Some overlapping pathogenic substrates (stress, cortisol levels, cerebral hypoperfusion, neuroinflammation, neurotrophic dysfunction, A β accumulation, tauopathic connections, epigenetic factors, gut microbiota-brain axis) can explain the comorbidity of both clinical entities. Mood disorders are more common in women than in men. More than 60% of AD patients show depressive symptoms, which are more severe in women than in men. Likewise, anxiety is also more common in women than in men. About 50% of men show no anxiety, while only 30% of women with dementia are symptom-free in the early stages of the disease. Both anxiety and depression fluctuate with the clinical course of the illness. Behavioral disorders and psychotic symptoms are also common (20-90%) in AD patients throughout the clinical course of the disease.

The electrocardiogram (EKG) is abnormal in 40% of patients (38% in women; 43% in men). A normal EKG is found more often in women (52%) than in men (43%), and a borderline EKG is found more often in men (12%) than in women (9%). No gender-related differences are found between women and men in brain abnormalities studied with structural neuroimaging (MRI) (brain atrophy, leukoaraiosis, brain microinfarcts, meningioma), which are present in more than 70% of cases.

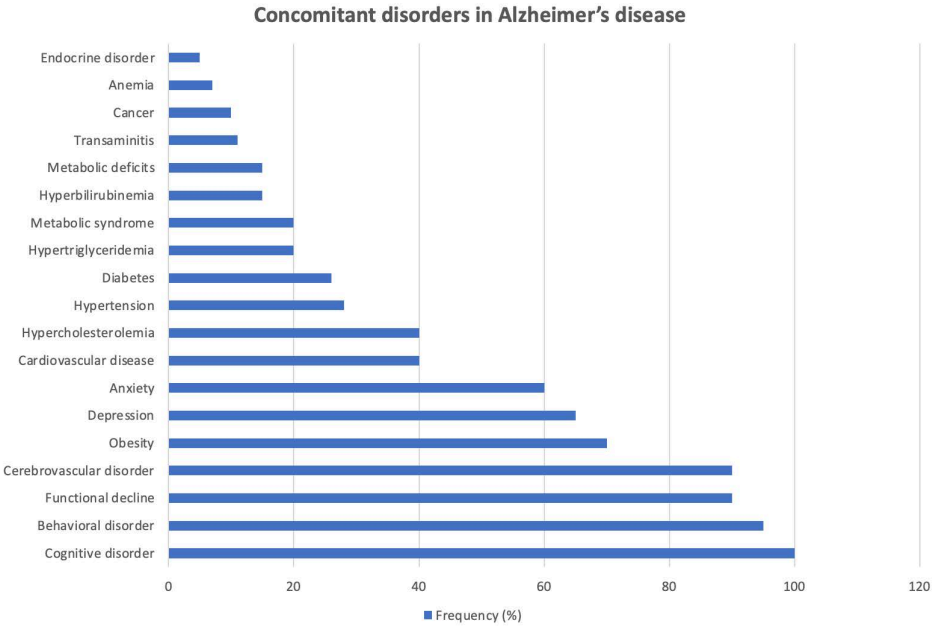
The majority of patients with dementia (> 90%) require multifactorial treatment, which implies the simultaneous administration of several pharmaceutical categories with the consequent risk of ADRs and DDIs. According to the phenotypic profile of patients with dementia, the most frequent concomitant diseases are the following: systolic hypertension (21%), diastolic hypertension (28%), obesity (> 70%), type 2 diabetes mellitus (26%), hypercholesterolemia (40%), hypertriglyceridemia (20%), hyperuricemia (6%), metabolic syndrome (20%), hypertransaminasemia (11%), hyperbilirubinemia (15%), endocrine disorders (5%), iron

deficiency anemia (7%), folate deficiency (17%), vitamin B_{12} deficiency (10%), cardiovascular disorder (40%), cerebrovascular disorder (> 90% in patients older than 80 years), anxiety (60%), depression (65%), behavioral disorders (20-90%) and cancer (10%).

Cardiovascular risk factors, such as hypertension, hypercholesterolemia and dyslipidemia, and EKG abnormalities are more common in men than in women. Hypertension is present in 21% of cases. Systolic blood pressure is similar in women and men, but diastolic blood pressure is significantly higher in men than in women. Cholesterol levels (Total, LDL) are higher in men and HDL cholesterol and triglyceride levels are higher in women. Cardiovascular disorders and changes in blood pressure, whether hypertension or hypotension, in AD are associated with an increased risk of brain damage and greater cognitive decline. Furthermore, the same APOE gene-related risk variants, which are associated with AD, also affect cardiovascular disorders, atherosclerosis, and cerebrovascular damage in dementia. The lipid metabolism disorder and the cerebrovascular component of AD have been extensively studied, and alterations in cholesterol, changes in cell membrane lipids, and arteriosclerosis lead to ischemia and cerebral hypoperfusion that contributes to accelerating the premature death of neurons in patients predisposed to AD. In contrast, the epidemiological link between diabetes and AD appears to be circumstantial, with no apparent pathogenic implications beyond the deleterious effects of hyperglycemia on brain function.

As a consequence of all these concomitant pathologies, patients with dementia consume a wide variety of drugs whose side effects contribute to accelerating the degenerative process and cognitive deterioration. Of special importance, quantitative and qualitative, are cardiovascular agents, statins, antidiabetics, antihypertensive drugs, analgesics, diuretics, bronchodilators, antirheumatics and several categories of psychotropic drugs (neuroleptics, antidepressants, anxiolytics, hypnotics, sedatives). The correct administration of these drugs requires a personalized therapeutic intervention, together with conventional anti-dementia treatments.

Combined treatments applied under pharmacogenetic guidance indicate that biochemical, hematological and metabolic differences may contribute to changes in the efficacy and safety of the drugs. Regarding cognitive function and neuropsychiatric disorders treated with multifactorial regimens, women and men respond differentially to treatment, showing a moderate improvement in cognition during the first year of treatment (with progressive cognitive decline thereafter) and significant improvements in anxiety and depression. Pharmacogenetic studies show that APOE-3 carriers are the best responders and that APOE-4 carriers tend to be the worst responders to conventional treatments. Among the CYP2D6, CYP2C19, and CYP2C9 genophenotypes, normal metabolizers (NM) and intermediate metabolizers (IM) respond significantly better than poor metabolizers (PM) and ultra-rapid metabolizers (UM) to therapeutic interventions that modify cognitive and cognitive phenotypes and mood in dementia.



References

Cacabelos R, Cacabelos P, Torrellas C, et al. Pharmacogenomics of Alzheimer's disease: novel therapeutic strategies for drug development. Methods Mol Biol. 2014;1175:323-556. DOI: 10.1007/978-1-4939-0956-8_13.

Cacabelos R, Carril JC, Cacabelos P, et al. Pharmacogenomics of Alzheimer's Disease: Genetic determinants of phenotypic variation and therapeutic outcome. J Genomic Med Pharmacogenomics. 2016;1(2):151-209.

Cacabelos R, Carril JC, Cacabelos N, et al. Sirtuins in Alzheimer's Disease: SIRT2-Related GenoPhenotypes and Implications for PharmacoEpiGenetics. Int J Mol Sci. 2019;20:E1249. DOI: 10.3390/ijms20051249.

Cacabelos R. Population-level pharmacogenomics for precision drug development in dementia. Exp Rev Precis Med Drug Develop. 2018;3(3):163-188. DOI: 10.1080/23808993.2018.1468218.

Cacabelos R. Pharmacogenomics of Cognitive Dysfunction and Neuropsychiatric Disorders in Dementia. Int J Mol Sci. 2020;21(9):3059. DOI: 10.3390/ijms21093059.

Cacabelos R, Cacabelos N, Carril JC. The role of pharmacogenomics in adverse drug reactions. Expert Rev Clin Pharmacol. 2019;12(5):407-442. doi: 10.1080/17512433.2019.1597706.

Cacabelos R, Goldgaber D, Vostrov A, et al. APOE-TOMM40 in the Pharmacogenomics of demetia. J Pharmacogen Pharmacoprot. 2014;5:135. DOI:10.4172/2153-0645.1000135.

Cacabelos R. Pharmacogenomic of drugs to treat brain disorders. Expert Review Prec Med Drug Develop. 2020;5(3):181-234. doi: 10.1080/23808992.2020.1738217.

Cacabelos R, Carril JC, Corzo L, et al. Influence of pathogenic and metabolic genes on the pharmacogenetics of mood disorders in Alzheimer's disease. Pharmaceuticals 2021;14:366.

Matej R, Tesar A, Rusina R. Alzheimer's disease and other neurodegenerative dementias in comorbidity: A clinical and neuropathological overview. Clin Biochem. 2019;73:26-31. DOI: 10.1016/j.clinbiochem.2019.08.005.

Psilocybin for the treatment of depression: hallucinogenic hope to rig emotions

The *Compass Pathways* company announced the results of a clinical trial with psilocybin, the psychedelic compound in magic mushrooms, to treat severe depression in 233 patients with depression resistant to conventional treatments. According to the developers of the study, almost 30% of the patients who received the highest dose of psilocybin (25 mg), showed remission of symptoms after 3 weeks of treatment.

The results presented by the company, which have not been published in any medical journal, did not hide important side effects, such as suicidal behavior and self-harm. These aberrant behaviors appeared after one month of treatment, especially in those patients who did not improve their depressive condition. This suicidal behavior has also been seen with other antidepressants and with esketamine, the only psychedelic currently approved for resistant depression.

The American *Food and Drug Administration* (FAD) has awarded Compass Pathways with an innovative therapy designation for this treatment, which means that the drug approval process will be sped up if studies continue to show positive results.

Basidiomycota mushrooms that contain psilocybin, known as magic mushrooms, belong to the genera *Psilocybe* (with 116 species), *Gymnopilus* (14 species), *Panaeolus* (13 species), *Copelandia* (12 species), *Pluteus* (6 species), *Inocybe* (6 species), *Pholiotina* (4 species) and *Galerina* (at least one species). The composition of magic mushrooms varies between genera and species. The main compound is psilocybin, which is converted into psilocin, responsible for the psychoactive effect. Along with psilocin there may be other derivatives (norpsilocin, baeocystin, norbaeocystin, aeruginascin) capable of modifying the effect of magic mushrooms. *Panaeolus subbalteatus* is the mushroom with the highest amount of psilocybin.

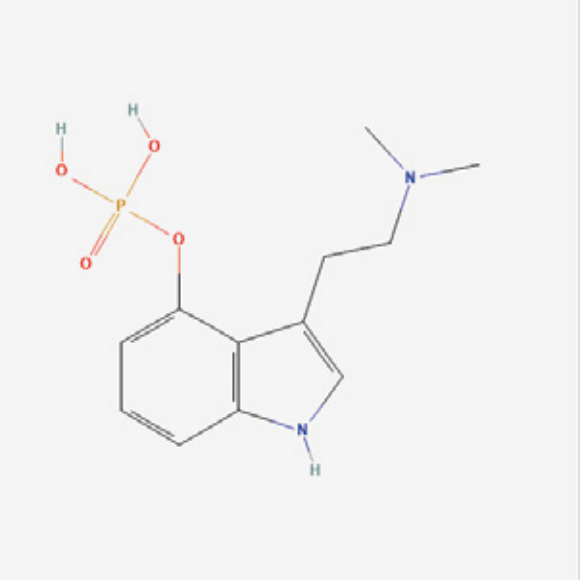
Different varieties of these mushrooms have been used in the indigenous cultures of the New World in religious, divinatory or spiritual contexts. *Psilocybe hispanica* was used in religious rituals 6,000 years ago. In contemporary Western culture, these hallucinogenic mushrooms and their derivatives are used as recreational drugs, from the experiences of **Valentina Pavlovna Wasson** and her husband **R. Gordon Wasson** in 1955 in Mexico, the identification of

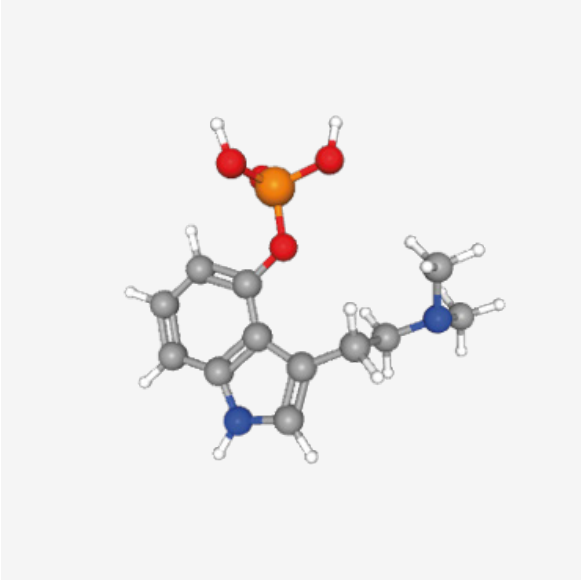
psilocybin-producing mushrooms by **Roger Heim** in 1956, the identification of psilocybin and psilocin as the bioactive compounds in magic mushrooms by **Albert Hofmann** in 1958, and the experiments of **Timothy Leary** and **Richard Alpert** at the *Harvard Psilocybin Project* in 1960 - for which they were expelled from Harvard University in 1963- and by the diffusion of the use of hallucinogenic substances in the hippie culture of the time.

Psilocybe semilanceata

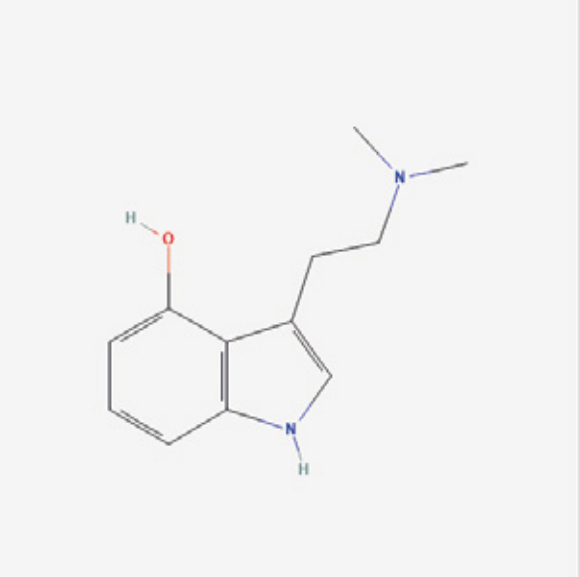
Panaeolus subbaltatus

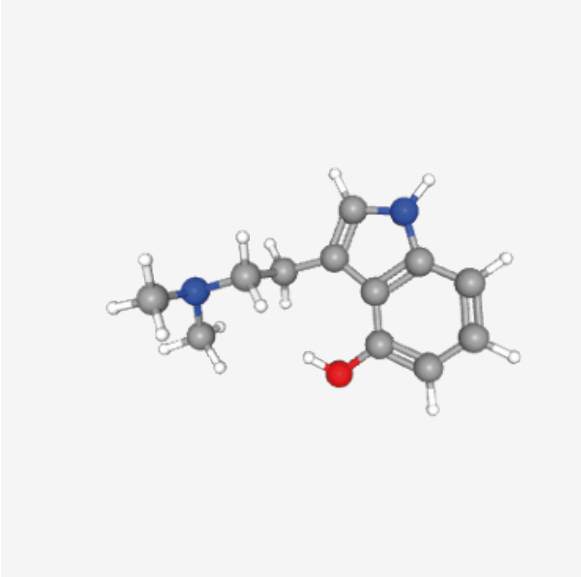
Psilocybine





Psilocin





Role of Serotonin in brain disorders and social memory

Serotonin (5-hydroxytryptamine, 5-HT) is a monoaminergic neurotransmitter. Its biological function is complex and multifactorial, modulating emotions, cognition, learning, memory and numerous physiological processes such as vomiting and vasoconstriction. Serotonin is an indolamine derived from the amino acid tryptophan. Serotonin is found primarily in the enteric nervous system located in the gastrointestinal tract and in the CNS, specifically in the raphe nuclei located in the brain stem.

About 90% of the total serotonin in the human body is found in the enterochromaffin cells of the gastrointestinal tract, where it regulates intestinal movements; 8% accumulates in platelets and 1-2% is brain serotonin. In various brain disorders, there are significant alterations in serotonergic neurotransmission mechanisms, especially in alterations in the emotional state, alert and reward mechanisms, and neurovegetative dysfunctions in the brain-intestinal axis. Many of the antidepressant treatments are based on the modulation of serotonin to increase serotonergic activity in the nerve endings that regulate emotions and mood.

Despite being a classic neurotransmitter, there are many enigmas yet to be elucidated about the functions of serotonin in the brain. In studies carried out in our Medical Center by **Dr. Ramón Cacabelos** and his team, we found important alterations in serum serotonin levels in different neuropsychiatric disorders. For example, serotonin is greatly reduced in patients with depression, anxiety, Alzheimer's disease, and amyotrophic lateral sclerosis; on the other hand, it is elevated in various ataxic syndromes, in mental retardation of organic causes and in women with xenoestrogenic syndrome in whom there is an important component of emotional dysfunction associated with estrogen toxicity.

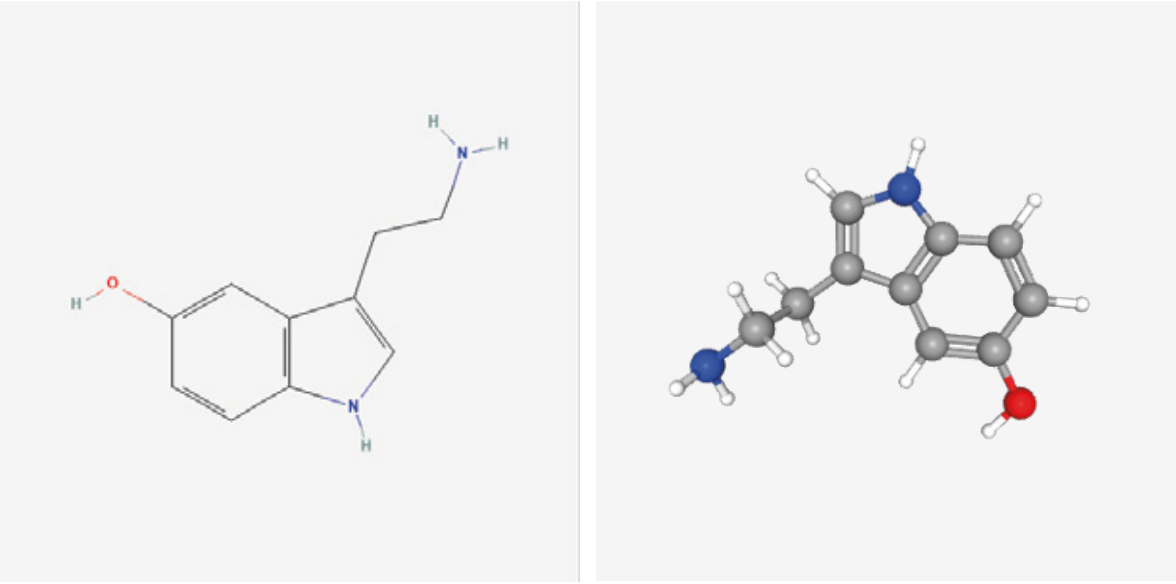
Social memory is the ability to recognize and remember family members. This mode of memory is essential for the survival of an animal in its social group. The dorsal CA2 (dCA2) and ventral CA1 (vCA1) subregions of the hippocampus and their projections to different brain regions play an important role in social memory. However, the extrahippocampal regions involved in this function are not well known.

Xiaoting Wu and his team, from **Robert C. Malenka's** group, at the Nancy Pritzker Laboratory in the Department of Psychiatry and Behavioral Sciences, Stanford University, California, identified the medial septum as the region of entry of dCA2 that is critical for social

memory, and they demonstrated that modulation of the medial septum by serotonin (5-HT) bidirectionally controls the formation of social memory, affecting memory stability. The new social interactions increase activity in septal neurons that project to dCA2 and induce plasticity at glutamatergic synapses in septal neurons and pyramidal dCA2 neurons.

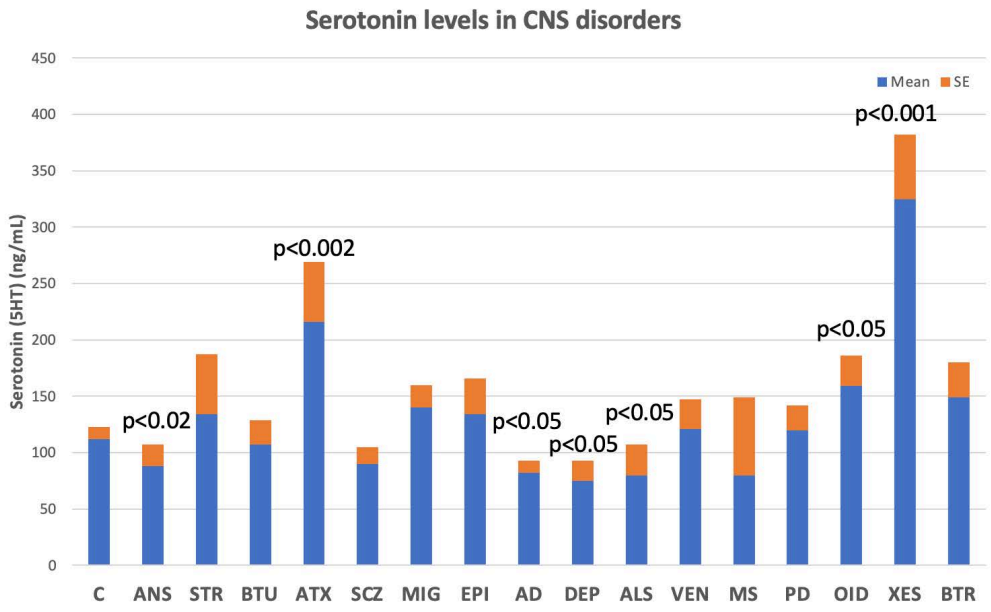
The activity of septal cells that project to dCA2 is enhanced by serotonergic neuromodulation acting on 5-HT1B receptors. Furthermore, optogenetic manipulation of the 5-HT terminals of the median raphe bi-directionally regulates the stability of social memory. These findings help to understand the neural mechanisms by which social interactions lead to social memory and provide new evidence on the critical role that 5-HT has in promoting not only prosocial behaviors but also social memory. Indirectly, these data would also justify the social disconnection and cognitive impairment that is manifested in different psychiatric disorders, such as depression or manic-depressive psychosis, when serotonergic neurotransmission mechanisms fail and peripheral serotonin levels decrease.

Serotonin (5-hydroxytryptamine, 5-HT)



References

Wu, X., Morishita, W., Beier, KT et al. 5-HT modulation of a medial septal circuit tunes social memory stability. Nature 599, 96-101 (2021). https://doi.org/10.1038/s41586-021-03956-8.



Source:

R. Cacabelos, 2021. Analysis: Lola Corzo, EuroEspes Clinical Analysis Laboratory.

C: Healthy controls; ANS: Anxiety; STR: stroke; TXA: Ataxic Syndrome; SCZ: Schizophrenia; MIG: Migraine; EPI: Epilepsy; AD: Alzheimer's disease; DEP: Depression; ALS: Amyotrophic Lateral Sclerosis; VEN: Vascular Encephalopathy; MS: Multiple Sclerosis; PD: Parkinson's disease; OID: Organic Mental Retardation; XES: Xenoestrogenic Syndrome; BTR: Brain Trauma.

Need of Bioinformatics to manage and interpret genomic information

When a new technology becomes fashionable, it is often misused, creating false expectations about its informational power. Genomics is no exception. Although the characterization of the human genome has been the most relevant scientific event in human sciences since the Renaissance, and although advances in DNA technology have revolutionized medicine, from understanding the etiopathogenesis of diseases to predictive diagnosis and personalized treatment, there are still many aspects of medical genomics that require refinement and refinement.

Interpreting the effects of genetic variants is key to understanding individual susceptibility to disease and designing personalized therapeutic approaches. Modern experimental technologies are enabling the generation of massive compendia of human genome sequence data and associated molecular and phenotypic traits, along with genome-wide expression, epigenomics, and other functional genomic data. Integrated computational models can leverage these data to understand the impact of genetic variants, elucidate the effect of deregulated genes on biological pathways in specific disease and tissue contexts, and interpret disease risk beyond what is feasible with isolated experiments.

The work of experts in medical genomics is essential to interpret the results generated by powerful computer programs that read the human genome. Such crude documentation is of little value and may even be rejected by inexperienced professionals. That is why experience is essential to interpret results, eliminate informational noise and make available to health professionals not raw gene lists but the correct selection for diagnostic and therapeutic aid. In this sense, bioinformatics has become an essential weapon to aid the interpretation of genomic information. With it we can select, from the billions of possible genomic combinations and diverse polymorphisms of doubtful value, the straw that interests us within the great haystack of structural genomics.

A team of scientists from the *Center for Computational Biology, Flatiron Institute, Simons Foundation,* New York, USA, led by **Aaron K. Wong**, has developed machine learning algorithms for genome interpretation and for comprehensive molecular-level modelling of cells, tissues, and organs relevant to different diseases. Of great importance are the existing methods and the key challenges and opportunities to identify specific genetic variants that cause disease and link them to the molecular pathways and clinical phenotypes faced in everyday medicine.

Another important aspect of genomic advances is the discipline known as macrogenetics. The emerging field of macrogenetics focuses on the analysis of publicly available genetic data sets from thousands of species to explore large-scale patterns and predictors of intraspecific genetic variation. Facilitated by advances in evolutionary biology, data infrastructure, statistics, and access to free scientific data, macrogenetics addresses core evolutionary hypotheses with a global approach. However, there are important limitations, sometimes negligently ignored, that have been analyzed by **Deborah M. Leigh** and a large group of collaborators from Switzerland, the United States, Canada and Australia; their interesting work tells the history of macrogenetics, knowledge gaps that require repair and future guidelines to be followed by this sub-discipline in the biodiversity environment.

References

Wong, A.K., Sealfon, R.S.G., Theesfeld, C.L. et al. Decoding disease: from genomes to networks to phenotypes. Nat Rev Genet 22, 774–790 (2021). https://doi.org/10.1038/s41576-021-00389-x.

Leigh, D.M., van Rees, C.B., Millette, K.L. et al. Opportunities and challenges of macrogenetic studies. Nat Rev Genet 22, 791–807 (2021). https://doi.org/10.1038/s41576-021-00394-0.

The genetic secrets of centurial fishes: New insights in marine biotechnology

80% of the nutraceutical bioproducts manufactured by Ebiotec derive from research carried out by scientists at EuroEspes in marine biotechnology. Raw materials are extracted from certain marine species that, through non-denaturing biotechnological processes, give rise to the range of biomarine nutraceuticals in our user community. For the proper selection of these marine biotechnology raw materials, it is necessary to first conduct research on the characteristics of the species to be selected, their biological properties and the chemical and organoleptic structure of those biological components that can provide benefits to human health.

Recent studies by a team of biologists from the University of California at Berkeley provide very interesting data on the genomics of centennial fish and their biological properties. This group of fish include several extreme categories in terms of longevity, from coral reef pygmies that survive less than ten weeks to Greenland sharks that can reach more than 500 years of age. The rockfish abound in coastal waters from California to Japan belong to a colorful group of more than 120 species in the genus *Sebastes*. Within this species, there are fish that live 10 years and others, such as the rough-eyed rockfish, that can live over 200 years.

The lifespan diversity of rockfish provides perfect parameters for analyzing longevity genetics, as reflected in the work of **Peter Sudmant** and his team at Berkeley, who examined the genomes of 88 species of rockfish and identified 137 specific genes related to the longevity of these fish. Size and habitat influence longevity and the adaptation of the genome to specific conditions. Larger organisms have a slower metabolism and are less susceptible to predation. Colder environments slow down metabolism and increase longevity, as might be the case with sharks that inhabit the cold waters of Greenland and survive for centuries.

When comparing the genomes of short-lived rockfish with longer-lived species, particular genes that increase longevity are distinguished, especially genes associated with the repair of damaged DNA, which makes them less vulnerable to certain types of cancer and degenerative processes that manifest in short-lived species. Long-lived fish also carry genes aimed at regulating insulin, essential in glucose metabolism. A special group of genes, which code for butyrophylins, regulate the immune system of rockfish. In humans, equivalent genes are related to inflammatory mechanisms.

These new findings suggest, consistent with other research, that longevity is the result of a clear interaction of the genome with the environment (diet, climatic conditions, stress, aggression, trauma, toxicity), under the redundant and promiscuous control of epigenetic factors.

mRNA Influenza vaccines

COVID-19 provided an opportunity for the pharmaceutical industry to demonstrate that mRNA vaccines can be useful in fighting other viral epidemics. Currently, there is fierce competition from various pharmaceutical companies to apply the same technological platform to the development of mRNA vaccines against the influenza virus.

Elie Dolgin (*Nature Reviews Drug Discovery* 20, 801-803, 2021; doi : https://doi.org/10.1038/d41573-021-00176-7) has reviewed the projects that are currently underway. At the time of the successful political-propaganda rollout of mRNA vaccines for COVID-19 prevention, at least three drug manufacturers have started the crusade for the development of seasonal flu vaccines. Proponents of mRNA technology, led by Moderna, Pfizer and Sanofi, have already started phase I trials in recent months. The new flu vaccines could be very lucrative and help sustain a global market that exceeds $10 billion in a decade. Current flu vaccines, whether manufactured from inactivated viruses or recombinant proteins, generally offer only 40-60% protection against infection. In theory, mRNA could be a better product. However, mRNA, at least when formulated into lipid nanoparticles, is prone to tolerability problems. Moderna and Pfizer/BioNTech licensed mRNA vaccines for COVID-19 often cause arm pain, headaches, fever, and fatigue. These same symptoms can also occur with flu shots.

It is believed that the potential benefits of mRNA for influenza prophylaxis could be many, depending on how the vaccines are manufactured. Because mRNA vaccines are made synthetically, encoding a sequence of target antigens on a plasmid template offers high fidelity. The coded antigens exactly match the influenza strains selected for the vaccine each year. In contrast, inactivated virus vaccines that are manufactured in egg- and cell-based systems often suffer mutations that weaken their effectiveness. Recombinant protein vaccines offer the same fidelity advantage, but the manufacturing process for these is comparatively cumbersome. The flexibility and speed in mRNA vaccine production would allow vaccine manufacturers more time to manufacture, starting in May, rather than February, for the Northern Hemisphere. This would allow them to make more informed decisions about what strains to include.

Another benefit of mRNA vaccines could be efficacy. The United States relies on quadrivalent vaccines, which contain hemagglutinin antigens (either purified from inactivated or recombinantly manufactured viruses) or live attenuated viruses that confer protection against

four strains of influenza. Other jurisdictions still use trivalent vaccines. Some researchers have argued in favor of adding protection against additional strains, but doing so is a logistical challenge with existing platforms. Some researchers also hope that mRNA vaccines will stimulate stronger or more diverse immune responses than traditional platforms. If this is true, it could be especially beneficial for older adults, who often have weak responses to flu shots.

The expectations are high, but the data on efficacy and safety are still very scarce. The propaganda apparatus is already underway, and it is to be expected that many governments will begin to embark on this new technological ship that has revolutionized the prophylaxis of COVID-19, and it is highly probable that it will do the same with other viral infections in which the mRNA platforms may be viable.

Covid-19 News

Purposes of a National Commission to review the management of the Pandemic

Many American health decisions and strategies are frequently criticized, fundamentally based on ignorance and the inability to assume that, no matter how many mistakes they make, the United States continues to be the engine of science, where the weight of opinion public and the protagonism of the population is greater than in any other country in the world. Like it or not, health is a right and an individual responsibility in which public (or political) interference should not meddle. This is the dominant premise in the United States.

A group of North American experts, composed of **Christopher F. Chyba** (cchyba@princeton.edu; *Department of Astrophysical Sciences and School of Public and International Affairs, Princeton University, Princeton*), **Christine K. Cassel** *(Department of Medicine, School of Medicine, University of California, San Francisco*), **Susan L. Graham** (*Department of Electrical Engineering and Computer Science, University of California, Berkeley*), **John P. Holdren** (*Kennedy School of Government and Department of Earth and Planetary Sciences, Harvard University, Cambridge*), **Ed Penhoet** (*Division of Biological Sciences, University of California, Berkeley*), **William H. Press** (*Department of Computer Science and Integrative Biology, The University of Texas, Austin*), **Maxine Savitz** (*National Academy of Engineering, Washington*) and **Harold Varmus** (*Meyer Cancer Center, Weill Cornell Medicine, New York*), advocate the creation of a National Commission to review the management of COVID-19 in an article published by Science on November 18 (*Science* 374 (6570): 932-935, 2021; DOI: 10.1126/science.abk0029).

The 2019 World Health Security Index concluded that while no country is fully prepared for epidemics or pandemics, the United States scored the highest of all countries in pandemic preparedness. However, in the COVID-19 outbreak beginning in October 2021, measured in deaths per 100,000 inhabitants, the United States fared worse than 30 of the 35 countries defined by the International Monetary Fund as "advanced economies," and was the worst of the first 18 countries in the ranking of the 184 countries classified, according to a study by the Johns Hopkins University (*Johns Hopkins University and Medicine Coronavirus Resource Center, "Mortality Analysis"* (October 23, 2021); https://coronavirus.jhu.edu/data/mortality). Many are now calling for a COVID-19 commission to provide a realistic historical balance of the pandemic, free from all political influence, to broaden the public's understanding of the pandemic, and to prescribe strategies that can prevent, or at least mitigate, future pandemics.

This group of experts, all former members of the Council of Advisors to the President on Science and Technology under the presidency of Barack Obama, present recommendations for the topics that will be examined by a COVID-19 commission in the United States.

For its part, Congress has created national commissions in the past to investigate events that have seriously affected life, such as the 9/11 Commission. That commission gave the country a shared, bipartisan account of what had gone wrong and why, and its recommendations led to the restructuring of the United States intelligence community and the creation of the Department of Homeland Security. Similar efforts have been undertaken in other countries to criticize national responses to COVID-19. For example, both the British House of Commons and the French Sénat have published detailed and critical accounts of their country's response to the pandemic.

So far, eight proposed bills have been presented in Congress, recommending the creation of said commission. Most include only broad requirements for the topics that will be investigated by the commission. Others outside the government have made similar proposals. A privately funded, non-governmental "COVID Commission Planning Group" has been formed. Experts acknowledge that establishing a COVID-19 commission may be challenging in the current domestic political environment of the United States, but believe that now is the appropriate time to consider the commission's plans and strategies. The design, composition, and resources of a national commission can determine the depth of its investigation and the credibility of its findings. Congressional proposals for a COVID-19 commission have been modelled after the 9/11 Commission. The key features of the 9/11 Commission - strong budget and staff, subpoena power, and access to former senior officials at all levels, as well as classified material - should be hallmarks of the COVID-19 commission.

The COVID-19 Commission is sure to run into a general problem: undervaluation and underfunding of public health capacities and practices. A prominent manifestation of this attitude has been chronic underfunding of the Centers for Disease Control and Prevention (CDC), and underfunding of state and municipal public health agencies. The COVID-19 Commission should address how to put public health agencies in the United States on a more effective and stable foundation, and should recommend means to repair budget shortfalls, expand training programs for public health professions, and improve the prestige of public health workers.

The adaptation of the public health information infrastructure and the management of public health data should be the special focus of the commission's attention. The public health methodology for data management remains often manual and outdated.

Microbiologists and epidemiologists had anticipated the pace of emerging disease outbreaks, such as the 2002-2004 SARS-CoV-1 pandemic, the 2009 H1N1 flu pandemic, and the Middle East respiratory syndrome coronavirus (MERS-CoV) epidemic of 2012. In 2004, the National Intelligence Council of the United States warned that "some experts believe that it is only a matter of time before a new pandemic appears that would be devastating and could spread rapidly around the world" (*National Intelligence Council, Mapping the Global Future: Report of the National Intelligence Council's 2020 Project, NIC 2004-13 (December 2004), p. 30;* www.dni.gov/files/documents/Global%20Trends_Mapping%20the%20Global%20Future%202020%20Project.pdf.9) A 2008 study catalogued the occurrence of 335 infectious diseases in humans between 1940 and 2004 (*KE Jones et al., Nature 451, 990, 2008*).

A COVID-19 commission must review those previous outbreaks, their causes, and state responses, and determine if there is a more prepared "panic/neglect cycle" after each episode, which then expires until the next outbreak induces another outbreak of disease. If so, the Commission should propose mechanisms to ensure more consistent attention to these threats.

It is important to understand and report on the role played by the scientific community, other governments, and international organizations in the early stages of the COVID-19 pandemic.

The commission should review the adequacy of pandemic planning prior to the COVID-19 outbreak, including the adequacy of the nation's strategic inventory and its governance strategy, preparing the supply chain to meet standards, and manufacturing demands, and the availability of research methodologies and clinical trials to respond to a new infectious agent by developing, testing and producing tests, therapies and vaccines in a coordinated and rapid manner.

The commission must consider the proper balance, synergies, and potential risk trade-offs between protection strategies against natural diseases, laboratory accidents, and biological attacks, and whether the government had these matters in place at the time of the COVID-19 outbreak.

A COVID-19 commission will need to assess the ways in which various components of the nation's medical infrastructure - public health agencies, healthcare facilities, public and private research institutions, and regulatory bodies - responded to the emergency.

The commission should examine the government's efforts to quickly establish a vaccine research initiative and provide financial incentives to private industries, in hopes of speeding up the development, testing and production of a vaccine. The commission should identify prior research underlying the capacity to develop, produce and distribute vaccines, along with production and distribution efforts (nationally and globally), and draw lessons for both future outbreaks and the production of vaccines under non-critical conditions.

Public health measures failed to prevent widespread transmission of SARS-CoV-2. At its peak, this situation created enormous strains on public and private hospitals, health centers, pharmacies, and on front-line staff and supplies. The commission should examine how the challenge of caring for so many severely affected patients by COVID-19 was managed, how the pandemic affected the fiscal status of hospitals and medical centers, and how the nation's healthcare facilities can be better prepared for future pandemics. It must also address what information should be offered to patients and families in times and places where the standard of care is compromised due to overload.

The therapeutic arsenal that could have reduced the severity of COVID-19 and its death rates remains small, despite extensive efforts to identify existing FDA-approved drugs, to find new drugs, or to develop beneficial and safe immune therapies. The commission will have to review these efforts and examine whether the FDA approval processes were properly free from political influence. An unexpected aspect of COVID-19 has been the complexity of its pathogenic process. The commission should evaluate the efforts made by the biomedical research community to assess the mechanisms of pathogenesis and identify the genetic and environmental factors that contribute to the severity and duration of the disease. The role and effects of governments and states, news programs and websites, scientists and doctors, and social media in spreading information, misinformation, and unsupported claims regarding the pandemic must be examined. The commission should produce a classified annex on the role of disinformation campaigns directed at government leaders, news programs, or the public.

The outcome of infection is known to be adversely affected by advanced age, obesity, and compromised immune systems from cancer and other conditions. Populations with a high prevalence of these conditions are at particular risk. Nearly a third of COVID-19 deaths in the United States and other countries, through June 2021, were linked to nursing homes and geriatric centers (The New York Times, "Nearly One-Third of US Coronavirus Deaths are Linked to Nursing Homes, "The New York Times, June 1, 2021; www.nytimes.com/interactive/2020/us/coronavirus-nursing-homes.html). The commission should examine how these institutions could have better protected their residents and staff. Similar questions should be asked of frontline workers in hospitals, essential workers in other professions, and prison staff and inmates. A particularly high burden of morbidity has been recorded among some ethnic minorities. Blacks, Hispanics, and Native Americans have been twice as likely to die from COVID-19 than white or Asian Americans.

The commission should investigate the nature and reasons for these disparities, investigate the extent to which they result from broader problems of health inequity, examine whether government agencies collect the type of demographic, social and public health data necessary to adequately address these problems, and make recommendations aimed at reducing these disparities.

We do not believe that any honest politician, committed professional or good citizen can object to all the proposals of the group of experts led by **Christopher F. Chyba**. The mistake would be that these national commissions, which should exist in all countries, were controlled, supervised or abducted by the governmental authority. National Commissions in the face of public danger, whatever the genre, must be multidisciplinary, highly professional and free from any political or partisan toxicity.

Children vaccination: Parental disagreement

The proposal to vaccinate children against COVID-19 is raising controversy in the scientific community and is running into opposition from many parents in the United States. In an interesting *Science* Editorial on November 18 (*Science* 374 (6570): 913, 2021), Jeffrey S. Gerber, principal investigator of the *Moderna-National Institutes of Health KidCOVE* trial at the Children's Hospital of Philadelphia, and **Paul A. Offit**, director of the Center for Vaccine Education in the Division of Infectious Diseases at Children's Hospital of Philadelphia and professor at the Department of Pediatrics at the Perelman School of Medicine at the University of Pennsylvania, Philadelphia, make an analysis, perhaps biased, of the situation based on the positions they hold.

Earlier this month, the U.S. Centers for Disease Control and Prevention (CDC) recommended Pfizer's COVID-19 messenger RNA (mRNA) vaccine for children ages 5 to 11, which would involve vaccinating 28 million American children. A parent opinion poll shows that 42% to 66% of the parents of these children are reluctant, or clearly opposed, to vaccinating their children. The authors believe that without vaccination, almost everyone, including young children, is likely to become infected with SARS-CoV-2 at some point in their lives. The question posed to parents and caregivers is: Which is worse, vaccination or natural infection? It is a bit ironic to now say that COVID-19 is a childhood disease, creating unease in families. When the pandemic broke out in early 2020, children accounted for less than 3% of cases; today, they represent more than 25%. North American statistics indicate that more than 6 million children have been infected with SARS-CoV-2 (about 2 million between the ages of 5 and 11). In October 2021, about 100,000 children were infected per week. About a third of the children hospitalized for COVID-19 were healthy. About 700 children have died from COVID-19 in the United States, where the health authority already places SARS-CoV-2 infection among the 10 leading causes of death in children. In defence of the vaccine, they claim that no child has died from vaccination.

Many parents are concerned that Pfizer's mRNA vaccine has not been adequately tested in young children. In a study with 2,400 children aged 5-11 years, the efficacy of the delta variant vaccine was 90.7% (the adult study enrolled 40,0000 people). Myocarditis occurred in 5 out of every 1,000,000 people vaccinated with the mRNA vaccines (1 in 10,000 young people).

CDC experts say that vaccine-associated myocarditis has been relatively mild compared to the cardiac effects associated with acute COVID-19 or multisystem inflammatory syndrome, which generally involve heart dysfunction and require critical care. Studies in Israel and the United States indicate that the incidence of myocarditis in children aged 12 to 15 years, who receive mRNA vaccines, is lower than in the group of 16-25 years. As the dose of Pfizer mRNA in children is one third of the dose given to adolescents, it is expected that myocarditis in children will be less common.

While it is true that most children experience mild or asymptomatic illnesses, some become ill and a small number may die. That is why they are vaccinated against influenza, meningitis, chickenpox, and hepatitis, none of which, even before vaccines were available, killed as many as SARS-CoV-2 per year. Based on short-term epidemiology, without taking into account or

making any criticism whether the methods used have been correct or not, the health authority advocates the vaccination of children. Obviously, the mortality of older adults caused by COVID with the minimum impact on the child population is not comparable. Since comparative statistics could advise against vaccination in children, it is time that rigorous risk-benefit analysis helped parents make the right decisions. This work belongs to science, not to administrations, which should also be advised by scientists rather than by those who work for the pharmaceutical industry, with the consequent conflict of interest.

Privileged immunocompetent individuals

Many of the unknowns debated deaf or blind from last year are beginning to be clarified thanks to new scientific observations. One of them is the ability of many people to resist SARS-CoV-2 infection, preventing the penetration of the virus into their body, the result of a powerful immune system.

Data from UK health workers suggests the possibility that some people can clear an early SARS-CoV-2 infection so quickly that they never test positive for the virus, without even producing antibodies against it. This resistance would be conferred by memory T cells, possibly generated after exposure to coronaviruses responsible for the common cold.

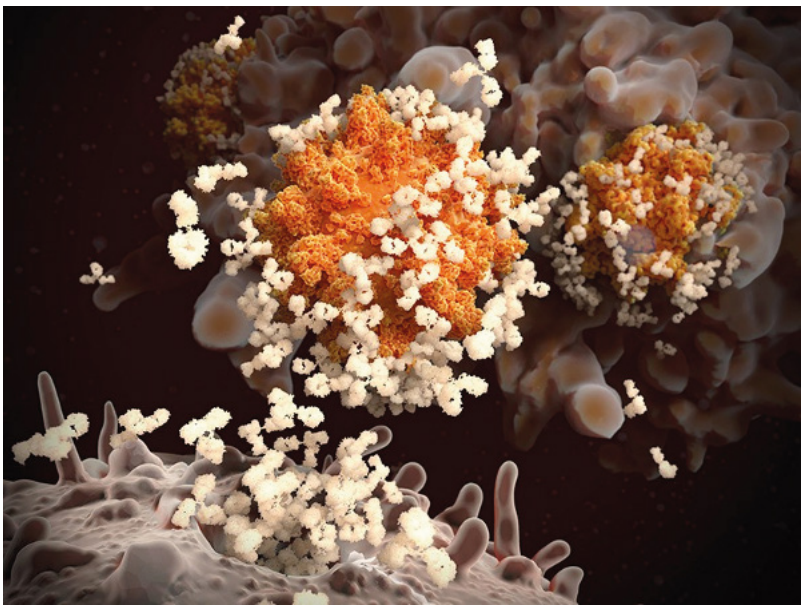
According to the study by **Leo Swadling** and colleagues *at University College* London, there are people with potential exposure to SARS-CoV-2 who do not necessarily develop C-reactive protein (CRP) or antibodies, suggesting that some may clear the subclinical infection before seroconversion.

Reference

Swadling, L., Diniz, M.O., Schmidt, N.M. et al. Pre-existing polymerase-specific T cells expand in abortive seronegative SARS-CoV-2. Nature (2021). https://doi.org/10.1038/s41586-021-04186-8

Search for people resistant to coronavirus

With very good judgment, an international group of scientists from 10 centers around the world has considered the search for people resistant to coronavirus, who have not had COVID-19 and whose genome prevents them from being infected. These people exist and the observation is not new. Many people have lived with tuberculosis, meningitis, or HIV-positive for AIDS and have not contracted the disease. These people differ from others in their genomic profiles, which protect them against invasive agents of various kinds. Identifying the genomic traits of coronavirus-resistant people can open a revolutionary avenue to fight COVID-19, prophylactically protect vulnerable people, and effectively treat infected patients.



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Antibodies that respond to SARS-CoV-2 particles.

Source:

Juan Gaertner / Science Photo Library. Nature 598, 393-394, 2021; doi: https://doi.org/10.1038/d41586-021-02795-x

The Promises of New Pills to combat COVID-19: Molnupiravir and Paxlovid

The pharmaceutical industry promises that the two new pills to fight the coronavirus, Molnupiravir and Paxlovid, will change the course of the pandemic. As reported by **Heidi Ledford** in *Nature (Nature 599, 358-359, 2021;* doi: https://doi.org/10.1038/d41586-021-03074-5), the antivirals Molnupiravir and Paxlovid may reduce COVID-19 hospitalizations when people are treated shortly after becoming infected with coronavirus.

On November 4, the UK became the first country to approve Molnupiravir, developed by Merck in Kenilworth, NJ, and Ridgeback Biotherapeutics in Miami, Florida. The approval came just over a month after companies announced that the antiviral, brand name Lagevrio, cut the risk of hospitalization in half for people with mild or moderate forms of COVID-19. Twenty-four hours after Molnupiravir was approved in the UK, Pfizer announced in New York that its antiviral drug Paxlovid reduced hospitalizations by 89%.

Previous antiviral options against SARS-CoV-2 were expensive and had to be administered in a hospital. The new drugs are small molecules and can be taken at home. However, little is known about the mechanisms of action of these drugs and their potential use in the infected population, as well as side effects in the medium and long term.

Molnupiravir is known to work by introducing mutations into the viral genome during viral replication. A metabolite of the drug is taken up by a viral enzyme, called RNA-dependent RNA polymerase, which is incorporated into the viral genome, eventually causing so many errors that the virus can no longer survive. Human cells have a DNA genome, rather than RNA, but some laboratory experiments have suggested that Molnupiravir may also cause mutations in human DNA. A full treatment with Molnupiravir is said to last about five days. The enigma of what to do with pregnant women and the drug's teratogenic effects persists.

Paxlovid works by inhibiting an enzyme that is needed to process some viral proteins into their final form. This drug is a combination of an antiviral and another drug, ritonavir, that helps prevent enzymes in the liver from breaking down the antiviral before it has a chance to inactivate the coronavirus. Ritonavir, a component of some HIV treatment cocktails, can cause significant side effects and serious drug interactions with treatments for heart, blood pressure, pain, and immune problems.

One concern of scientists is that the way Molnupiravir generates mutations in the coronavirus genome could lead to the emergence of new variants. Another concern is that the virus becomes resistant. Drug resistance is a common problem and is the reason that some viral infections, such as HIV and hepatitis C, are treated with combinations of antivirals. However, the most frequent reason for microbial resistance and toxic effects or therapeutic ineffectiveness of many drugs is the pharmacogenetic profile of each patient, commonly ignored by the medical community, who prefers bulk treatment.

As long as the pharmaceutical industry, public administrations and regulatory agencies for drug development do not realize that administering drugs in bulk, ignoring the individual genome of each person, is an anachronistic procedure, many political and administrative decisions will continue to be based on erratic criteria and mercantilists whose beneficiaries are not patients. The therapeutic failure rate without personalizing the treatments based on the genomic profile of each patient is over 60%.

Protein vaccines against SARS-CoV-2

The number of people who have had adverse effects with the anti-SARS-CoV-2 vaccines currently available on the market is not insignificant. Some of these effects are serious and the pharmaceutical industry has started looking for alternatives. The most feasible and affordable within a prudent time frame is the development of "protein vaccines" instead of mRNA vaccines with adenoviral vectors.

Unlike the relatively new technologies behind COVID-19 viral vector and mRNA vaccines, protein vaccines have been used for decades to protect people from hepatitis, shingles, and other viral infections. To elicit a protective immune response, these vaccines deliver proteins, along with immunity-stimulating adjuvants, directly to a person's cells, rather than a piece of genetic code that cells must read to synthesize proteins. Although protein vaccines are not yet in widespread use for COVID-19, late-stage clinical trial data so far looks promising, demonstrating strong protection with fewer side effects than those which other COVID-19 vaccines typically cause.

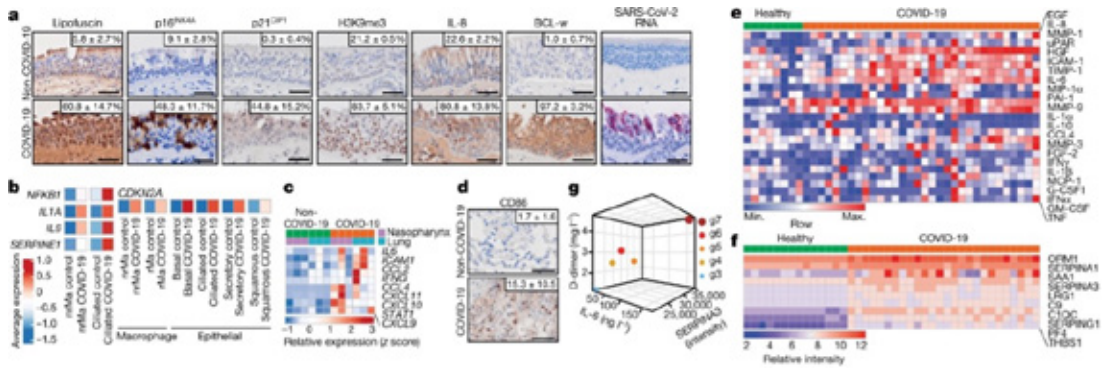
After months of quality control setbacks and manufacturing delays, the Novavax company of Gaithersburg, Maryland, is ready to submit its protein-based vaccine to the FDA before the end of the year. On November 1, Indonesia granted this company's vaccine its first emergency clearance, and regulatory filings have already been made to government agencies in Australia, Canada, the United Kingdom, the European Union, and other countries. Two vaccine manufacturers in Asia, *Clover Biopharmaceuticals*, based in Chengdu, China, and Biological E in Hyderabad, India, are in the process of submitting applications for approval of their protein vaccines to various national authorities in the coming months. Medicago in Quebec, Canada, Sanofi / GlaxoSmithKline in Paris (France) and Brentford (Great Britain), and *Seongnam* in South Korea are also developing new protein vaccines for immediate submission to drug development regulatory agencies for future approval.

Coronavirus infection ages tissues

Several studies show that the derailment of cytokine and immune cell networks may explain the organ damage and clinical severity caused by the coronavirus in COVID-19. A study by **Soyoung Lee**, from the group led by **Clemens A. Schmitt,** from the Department of Hematology, Oncology and Tumor Immunology at the *Molekulares Krebsforschungszentrum Charité - Universitätsmedizin* in Berlin, shows that SARS-CoV-2, like other viruses, evokes cellular senescence as a primary stress response in infected cells. Virus-induced senescence is indistinguishable from other forms of cellular senescence and is associated with a secretory phenotype associated with senescence, comprising pro-inflammatory cytokines, active extracellular matrix factors, and procoagulogenic mediators. Patients with COVID-19 show markers of senescence in the airway mucosa *in situ* and increased serum levels of factors related to the secretory phenotype associated with senescence. *In vitro* assays demonstrate activation of macrophages secreting senescence factors, complement lysis, and secondary amplifying senescence in endothelial cells, reflecting distinctive features of COVID-19, such as macrophage and neutrophil infiltration, endothelial damage, and generalized tissue thrombosis in affected lung tissue. Extracellular neutrophil traps, platelet activation and activation of the coagulation cascade appear in the supernatant of virus-induced senescent cells. Senolytics, such as Navitoclax, and a combination of Dasatinib and Quercetin selectively kill virus-induced senescent cells, mitigate lung disease caused by COVID-19, and reduce inflammation in animals infected with SARS-CoV-2.

Some of these pathogenic phenomena, associated with SARS-CoV-2, are also seen in some cases of people vaccinated with mRNA preparations and adenoviral vectors who develop serious side effects, such as brain microinfarcts, immune dysfunction, neurological damage and systemic decline.

This is a field that deserves further exploration due to the importance that viral infection has on phenotypes of cellular senescence and tissue aging, whether associated with COVID-19 or many other forms of viral infection, and with vaccines generated with mRNA sequences and adenoviral vectors. The neutralization of this pro-senescent viral effect could represent a new therapeutic target, both for prophylactic purposes and new treatment formulas in active infections.



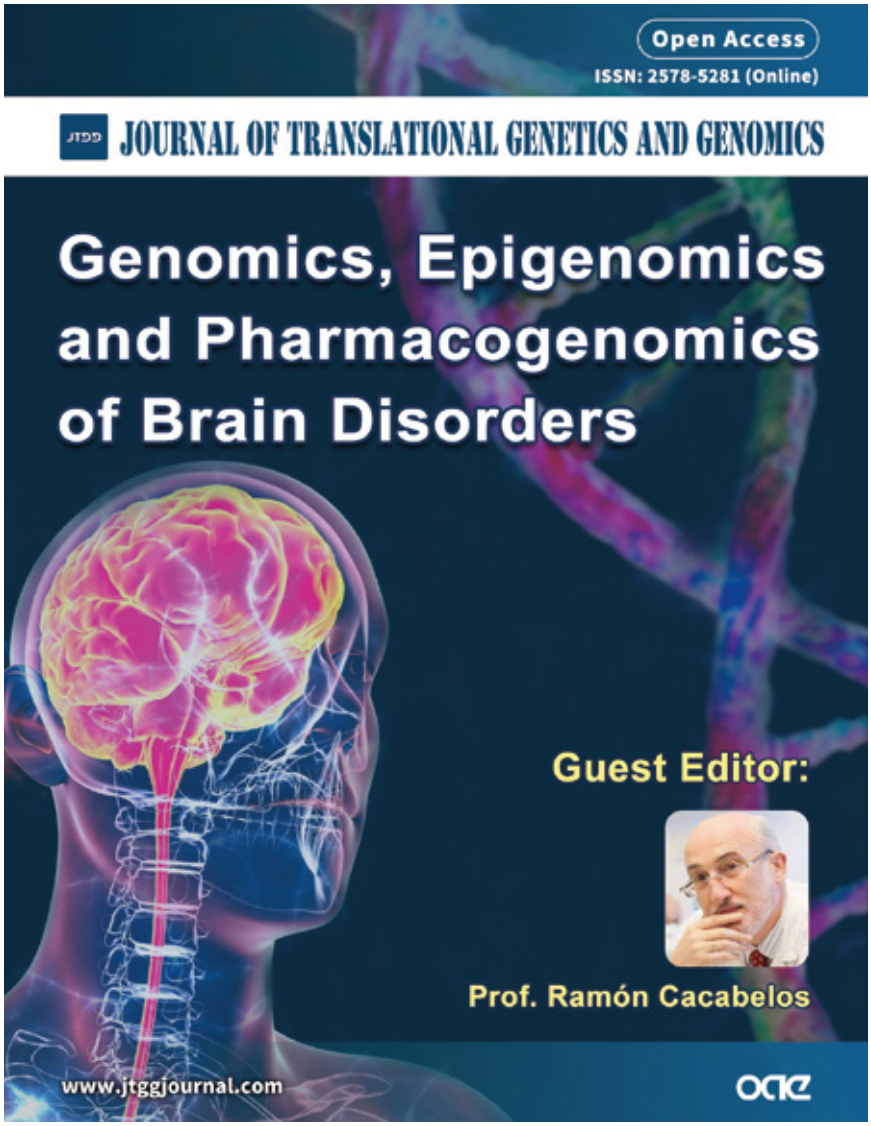
Tissue aging caused by SARS-CoV-2

Reference

Lee, S., Yu, Y., Trimpert, J. et al. Virus-induced senescence is a driver and therapeutic target in COVID-19. Nature 599, 283–289 (2021). https://doi.org/10.1038/s41586-021-03995-1.

Editorial News

Editions are open to the international scientific community for which Dr. Ramón Cacabelos is responsible, as Editor-in-Chief or Guest Editor for special issues dedicated to genomics, epigenetics, pharmacogenetics of diseases of the central nervous system and development of new pharmaceutical products.



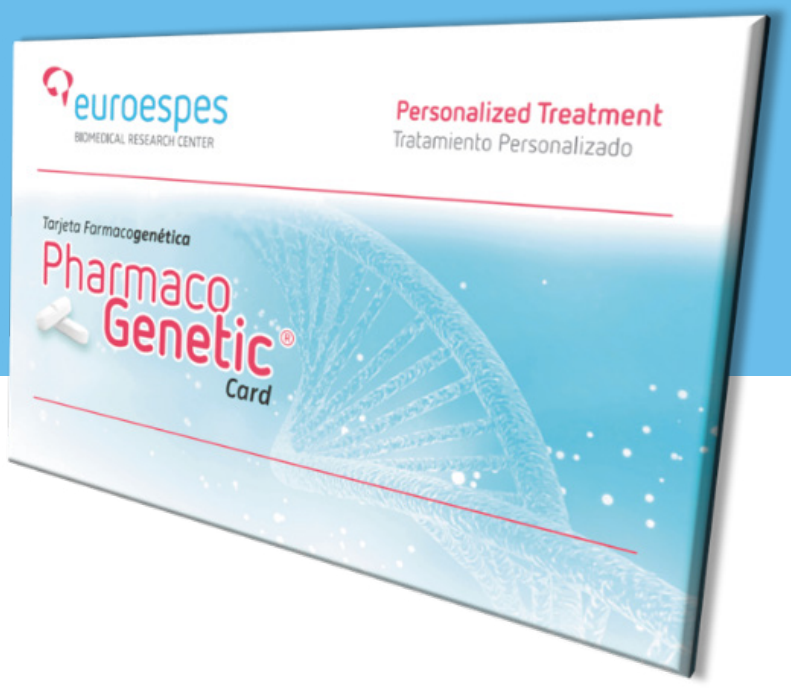
Promotional Section

Alzheimer's Prevention Plan (APP)
Home and Face-to-face

The APP identifies populations at risk of Alzheimer's disease (AD) and discriminates against other memory disorders and other forms of dementia. As the initial component of the APP is the identification of the genetic risk, in order to avoid unnecessary costs and discomfort due to the displacement of people, we have established a dual APP: (i) Home APP to perform genetic tests on a saliva sample that the interested person sends to the EuroEspes Medical Center with no need to travel; and (ii) face-to-face APP for those who wish to complete a complete diagnostic protocol, including genetic tests, at our Medical Center. Those people whose home APP detects an obvious risk can later join the face-to-face APP to complete the diagnostic set and enter the personalized prevention program through pharmacogenetic intervention.

Parkinson's Prevention Plan (PPP)
Home and Face-to-face

The PPP identifies the population at risk of suffering from Parkinson's disease, differentiating familial Parkinson's disease and other forms of parkinsonism (vascular, toxic or traumatic). The PPP also includes (i) a home PPP for all those asymptomatic people with a family history of Parkinson's or who detect incipient symptoms of tremor, rigidity or bradykinesia; and (ii) a PPP in person at the EuroEspes Medical Center where they would carry out the complete diagnostic protocol, including genomic screening. Patients following the home regimen who show genetic or environmental risk for Parkinson's would take the in-person PPP to complete the diagnostic set, and start the personalized prophylactic plan according to their pharmacogenetic profile.



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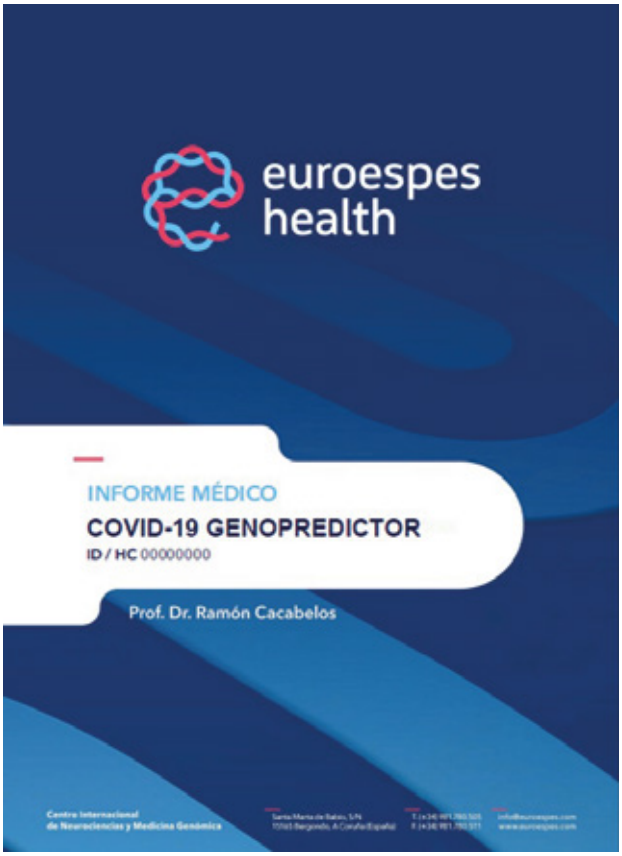
- so that your doctor knows which drugs to prescribe and which drugs harm you
- to avoid toxicity and side effects when you have to take medication for any health problem
- to avoid life-threatening drug interactions if you have to take several medications simultaneously for long periods of time
- to avoid unnecessary expenses on products that are not useful to you
- to preserve your health with the appropriate medication for your genomic profile
- for the health of their children, who share 50% of their genome
- for life, because your genome does not change



COVID-19 GenoPredictor

The COVID-19 GenoPredictor is the only genetic test in the world that allows predicting vulnerability to SARS-CoV-2 infection with potential lung damage, immunological status and immune response capacity to coronavirus infection, and pharmacogenetic profile that allows us to personalize the pharmacological treatment appropriate to the genome of each person in case of need for treatment.

Carrying out this genomic test is recommended for people at high risk (heart disease, lung disease, hypertension, diabetes, stroke, cancer, immunosuppressed), people exposed by the nature of their work (high public attendance centers, frequent trips), people with a family history of risk, people infected by coronavirus and health personnel.

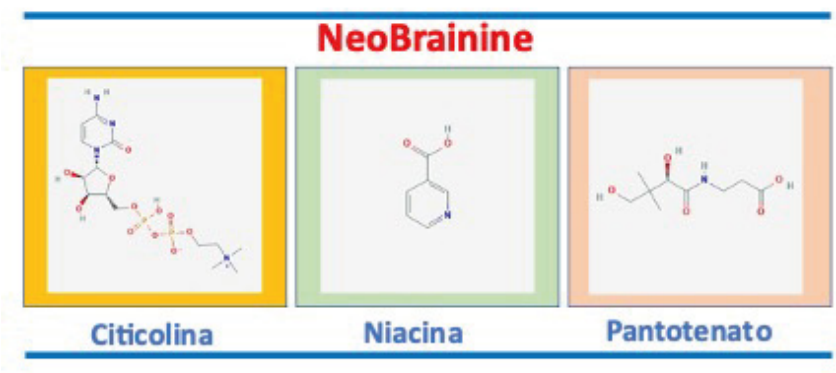
NeoBrainine

NeoBrainine is a new neuroprotective product for the prevention and treatment of various types of dementia and cerebrovascular risks (migraine, cerebral ischemia, thromboembolic events, stroke). NeoBrainine is a hybrid bioproduct, created by the team of scientists led by Dr. Ramón Cacabelos, that integrates citicoline, pantothenic acid and niacin molecules. Citicoline is a choline donor, acetylcholine precursor -an essential neurotransmitter for memory-; it is an essential component of the phospholipids of neuronal membranes and is an intermediate metabolite in nucleotide synthesis.

Pantothenic acid (D (+) - N- (2,4-dihydroxy-3,3-dimethylbutyryl) β-alanine) is an amide between pantoic acid with β-alanine; it is a water-soluble vitamin of the B complex, also known as vitamin B5 or vitamin W, essential for life. Pantothenic acid is a fundamental cofactor in the synthesis of coenzyme A (CoA) and in the metabolism and synthesis of carbohydrates, proteins and fats.

Niacin or nicotinic acid ($C_6H_5NO_2$) is another water-soluble vitamin of the B complex (vitamin B3, vitamin PP) involved in cell metabolism as part of the coenzyme NAD (nicotine-adenine-dinucleotide) and NAD-phosphate (NADP). Its derivatives (NADH, NAD+, NADPH, NADP+) are essential in energy metabolism and in DNA repair. Its main amide is nicotinamide or niacinamide ($C_6H_6N_2O$). Niacin is essential in the synthesis of steroid hormones and in the elimination of toxic xenobiotic agents.

The components of NeoBrainine (Citicoline, Niacin and Pantothenic Acid) exert essential neuroprotective functions for the normal functioning of the central nervous system.



Atremorine capsules

Atremorine has been approved by the European Patent Office for the prevention and treatment of Parkinson's disease.

In its usual presentation, Atremorine is dispensed as a powder to take with yogurt or other similar food, but not with water or liquids that can oxidize it or alter its properties. To avoid the use of powder and to facilitate the intake of Atremorine, EuroEspes Biotecnología (Ebiotec) launches Atremorine in capsules. The new presentation is now available nationally and internationally.

References

Cacabelos R, Fernández-Novoa L, Alejo R, Corzo L, Alcaraz M, Nebril L, Cacabelos P, Fraile C, Carrera I, Carril JC. 2016. E-PodoFavalin-15999 (Atremorine®) -Induced Dopamine Response in Parkinson's Disease: Pharmacogenetics-Related Effects. J Gen Med Pharm 1(1):1-26.

Cacabelos R, Fernández-Novoa L, Alejo R, Corzo L, Rodríguez S, Alcaraz M, Nebril L, Cacabelos P, Fraile C, Carrera I, Carril JC. 2016. E-PodoFavalin-15999 (Atremorine®) -Induced Neurotransmitter and Hormonal Response in Parkinson's Disease. J Exp Res Pharm 1(1):1-12.

Cacabelos R. 2017. Parkinson's Disease: From Pathogenesis to Pharmacogenomics. Int J Mol Sci 18(551):1-28.

Cacabelos R, Lombardi VRM, Fernández-Novoa L, Carrera I, Cacabelos P, Corzo L, Carril JC, Teijido O. 2018. Chapter 6 - Basic and Clinical Studies with Marine LipoFishins and Vegetal Favalins in Neurodegeneration and Age-Related Disorders, 59:195-225.

Cacabelos R, Carrera I, Alejo R, Fernández-Novoa L, Cacabelos P, Corzo L, Rodríguez S, Alcaraz M, Tellado I, Cacabelos N, Pego R, Carril JC. 2019. Pharmacogenetics of AtreMorine-Induced Neuroprotection and Dopamine Response in Parkinson's Disease. Planta Med., 85(17):1351-1362.

DefenVid-90

EuroEspes Biotechnology (Ebiotec) launches a new presentation of DefenVid with 90 capsules. This new presentation covers a complete monthly treatment regimen. Ebiotec continues to maintain the presentation of 30 capsules.

DefenVid is an immunity enhancer epinutraceutical to combat immunodeficiency states or the fall in natural defenses associated with the use of antibiotics for bacterial infections or chemotherapeutic agents in cancer patients.

DefenVid is a powerful enhancer of cellular immunity at any age against viral infections.

The two presentations of 30 and 90 capsules are already available nationally and internationally.

References

Lombardi VRM, Fernández-Novoa L, Corzo D, Zas R, Cacabelos R. 2002. Enhancement in Immune Function and Growth Using E-JUR-94013®. Methods Find Exp Pharmacol 24(9): 573:578.

Lombardi VRM, Fernández-Novoa L, Etcheverría I, Seoane S, Cacabelos R. 2005. Effects of fish-derived lipoprotein extracts on activation markers, Fas expression and apoptosis in peripheral blood lymphocytes. International Immunopharmacology 5: 253-262.

Cacabelos R. 2016. Novel Biotechnological Products from Natural Sources: Nutri/Pharmacogenomic Component. J Nutr Food Sci 6:6.

Cacabelos R. 2017. ProteoLipins and LipoFishins: Novel nutraceuticals and their effects. Adjacent Government. Health & Social Care Reports, January 20.

Cacabelos R, Carril JC, Teijido O. 2017. Chapter 5: Pharmacogenomics and Epigenomics of Age-Related Neurodegenerative Disorders: Strategies for Drug Development. In: Vaiserman AM (Ed). Anti-aging Drugs: From Basic Research to Clinical Practice. Royal Society of Chemistry, UK: 75-141.

Lombardi VRM, Corzo L, Carrera I, Cacabelos R. 2018. The search for biomarine derived compounds with immunomodulatory activity. J Explor Res Pharmacol, 3(1):30.

Cacabelos R, Lombardi VRM, Fernández-Novoa L, Carrera I, Cacabelos P, Corzo L, Carril JC, Teijido O. 2018. Chapter 6 - Basic and Clinical Studies with Marine LipoFishins and Vegetal Favalins in Neurodegeneration and Age-Related Disorders, 59:195-225.

Corzo L, Fernández-Novoa L, Carrera I, Martínez O, Rodríguez S, Alejo R and Cacabelos R. 2020. Nutrition, Health, and Disease: Role of Selected Marine and Vegetal Nutraceuticals. Nutrients, 12(3):747.

Complete Sequencing of the Human Genome

The team of geneticists from the Department of Genomics and Pharmacogenomics, led by Dr. Juan C. Carril and Dr. Óskar Martínez de Ilárduya Ruiz de Larramendi, Head of the Genomic Sequencing Unit, make available to users of medical services from the International Center for Neurosciences and Genomic Medicine, as well as from the national and international medical and scientific community, a service specialized in the complete sequencing of the human genome (> 20,000 genes) with NGS technology.

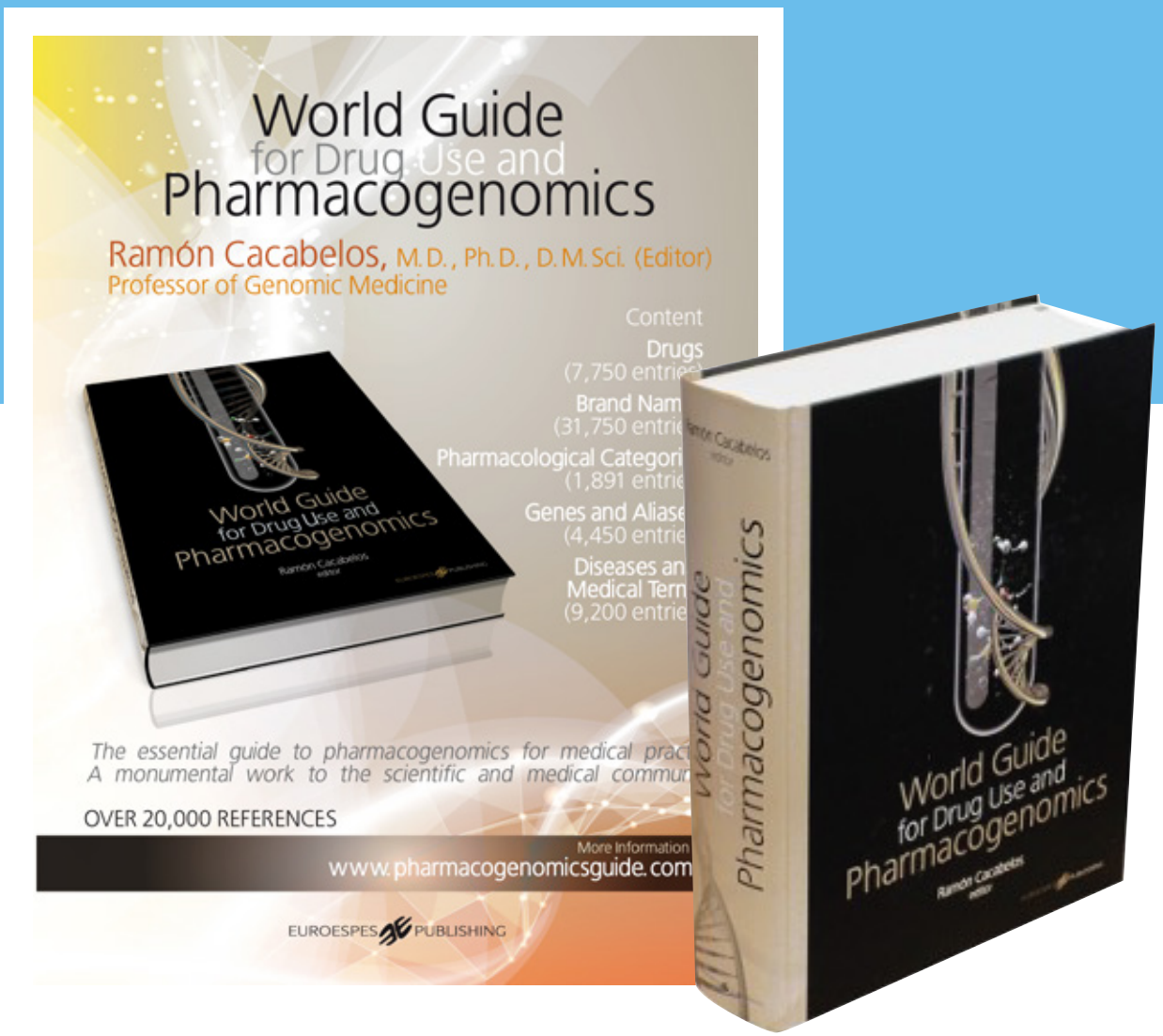
DermoGenetics Catalog

The Genomics and Pharmacogenomics Department of the EuroEspes Medical Center offers doctors and specialists in Dermatology the EuroEspes DermoGenetics Catalog. The Catalog includes the 1000 most relevant genes in skin diseases, from allergic reactions to skin cancer. This is the first Dermogenetics Catalog available in Europe.

Home Care: COVID-19 and Genetic Testing

Following our Community Care policy, facing the COVID-19 crisis, mobility restrictions in various national territories, and the difficulties of displacement of our national and foreign patients, the International Center for Neuroscience and Genomic Medicine has established a Home Care Service to our patients, to individuals and companies to carry out COVID-19 tests (PCR, Antigens, Antibodies) and genetic tests (see catalog at www.euroespes.com).

Phone No.: (+34) 981 780505.



World Guide for Drug Use and Pharmacogenomics

The First World Guide of Pharmacogenomics, edited by Dr. Ramón Cacabelos, incorporates for the first time the pharmacogenetic profile of commonly used drugs. In its more than 3000 pages the WGDUPGx catalogs (i) drugs approved by the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), Koseisho (Japan) and other international agencies, with their bioactive properties, side effects, metabolism and pharmacogenetic profile; (ii) genes of interest in human pathology and pharmacogenetics; and (iii) more than 9,000 illnesses and medical terms.

The World Guide for Drug Use and Pharmacogenomics is a fundamental reference in the library of universities, hospitals, medical departments and research centers.

Available from EuroEspes Publishing Co., Tel. (+34) 981 780 505.

EuroEspes Health Medical Bulletin

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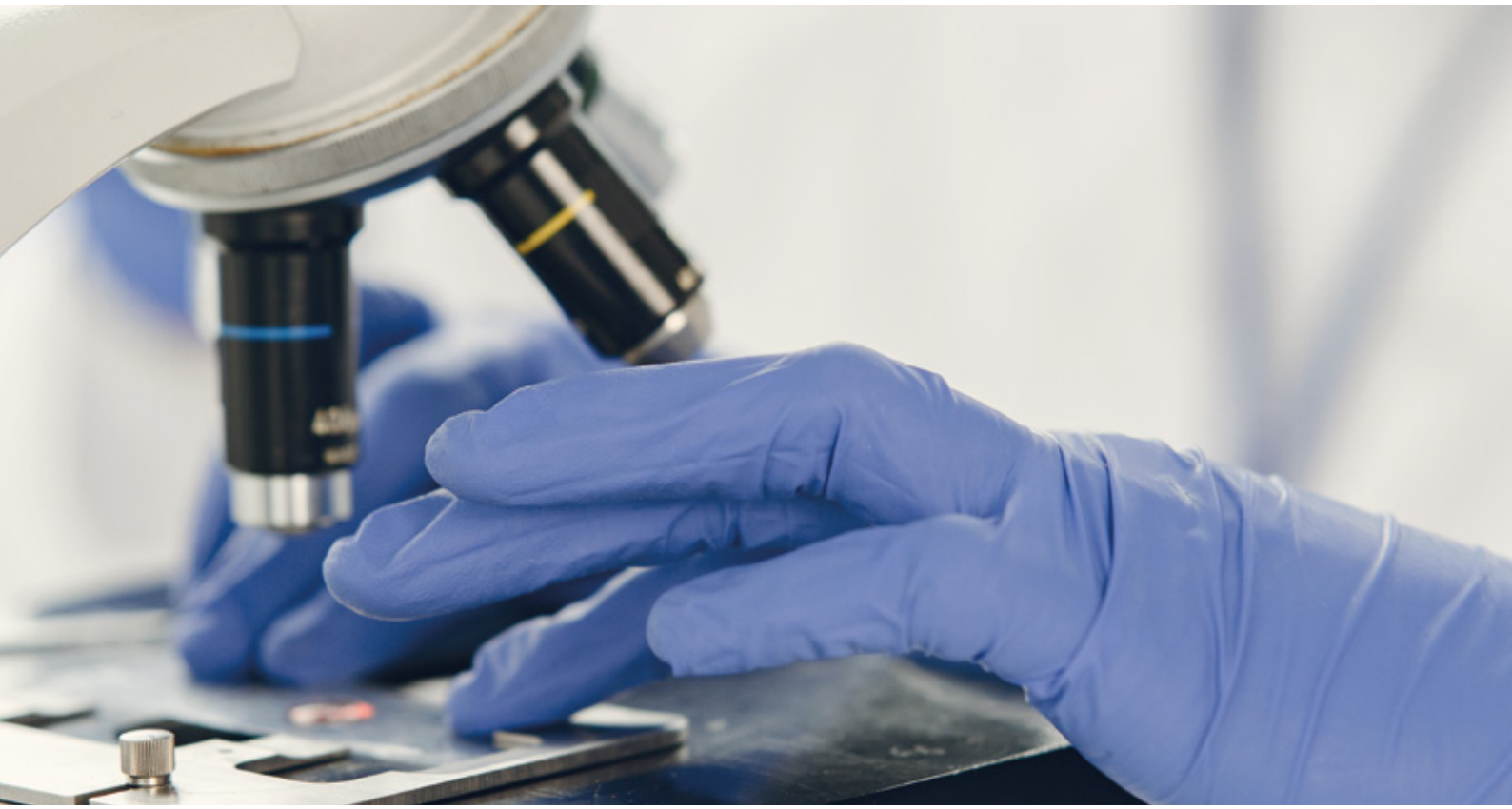

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