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PESKIN® PHARMACEUTICALS

The green drug company®

Novel Lipids-Based Pharmacognosy Solutions for Circulatory Diseases

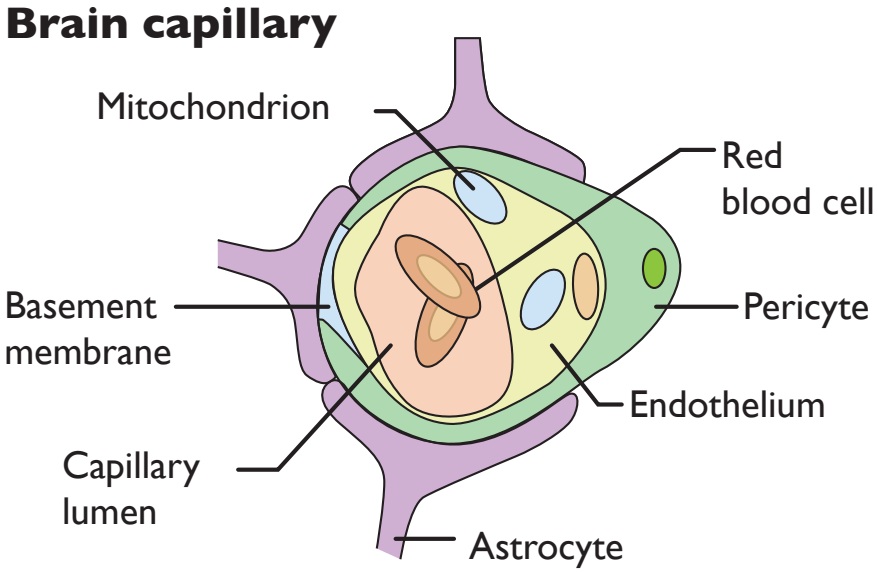
PSK003 and Alzheimer's

PSK003 & ALZHEIMER'S

PSK003 positively impacts the circulatory system, and that should translate into a profound impact on the progression of Alzheimer's disease and also on reversing the disease in existing patients.

Cardiologists know that the capillaries in the brain are essential for nutrient transfer. If nutrient transfer is impeded, then cognitive function suffers. PSK003 directly supports this key function via the circulatory system. We believe that the primary cause of Alzheimer's disease is circulatory, with the neurological issues resulting from circulatory dysfunction.

There are at least 40 million capillaries in the brain totaling some (approximately) 400 miles of capillary tissue, and it is estimated that every neuron has its own capillary (making the estimated number substantially greater).[1] These endothelial capillaries are extremely small—comprised of a single layer of rolled-up epithelial tissue (Parent omega-6)[2]—and if nutrient transfer and / or oxygen transfer is impeded because of decreased functionality, we would expect brain impairment, e.g., memory impairment and mental deterioration. This area of transfer is termed the microvascular.[3] There are also mitochondria in these endothelium-based structures:[4]



PSK003 is designed to specifically support and optimize the epithelial tissue, increase blood flow, eliminate hypoxic environments, decrease inflammation, increases nitric oxide (NO), and maximize mitochondrial functionality.

1 Cipolla, Marilyn, *Integrative Physiology—From Molecule to Function to Disease*: "The Cerebral Circulation," Editors: Granger, DN and Granger, JP, Morgan & Claypool Life Sciences, 2010.

2 http://faculty.stcc.edu/AandP/AP/AP2pages/Units18to20/vessels/capillar.htm.

3 Drewes, Lester, "Molecular architecture of the brain microvascular," *Journal of Molecular Neuroscience*, Volume 16, 2001, pages 93-99.

4 http://www.helsinki.fi/~tjrinne/artikkeleita_neuroI/Zlokovic_Alzheimer_nrn_2011.pdf (Zlokovic, B., "Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders," *Nature Reviews: Neuroscience*, Vol. 12, December 2011, pages 723-738).

Although many researchers consider Alzheimer's a neurologic condition with beta-amyloid plaque, we believe that focusing on cerebral circulation—both macro- and microcirculation—will lead to remarkable improvements in Alzheimer's patients. Other researchers share our view of the macro- and microcirculation being causal to Alzheimer's disease.

The 2011 *Nature Reviews: Neuroscience* article makes clear:[4]

"**Vascular pathology**. Patients with **Alzheimer's disease or other dementia-causing diseases** frequently show focal **changes in brain *microcirculation***. These changes include the appearance of string vessels (**collapsed** and acellular membrane tubes), a reduction in capillary density, a rise in **endothelial** pinocytosis, a decrease in **mitochondrial content, accumulation** of collagen and perlecans in the basement membrane, loss of tight junctions and/or adherens junctions, and **BBB [blood-brain barrier] breakdown** with leakage of blood-borne molecules. The time course of these **vascular alterations** and how they relate to **dementia and Alzheimer's disease** pathology remain unclear, as **no protocol** that allows the development of the diverse brain **vascular pathology** to be scored, and hence to be tracked with aging, **has so far been developed and widely validated**.

"**Increased levels of VEGF [*vascular endothelial* growth factor], a hypoxia-inducible angiogenic factor**, were found in **the walls of intraparenchymal vessels**, perivascular deposits, astrocytes and intrathecal space of patients with Alzheimer's disease, and were consistent with the **chronic cerebral hypoperfusion and hypoxia** that were observed in these individuals.

"The proposed neurovascular triad model of neurodegenerative diseases **challenges the traditional neurocentric view of such disorders**. At the same time, this model raises a set of new important issues that require further study. For example, the ***molecular basis of the neurovascular link with neurodegenerative disorders is poorly understood***, in terms of the adhesion molecules that keep the physical association of various cell types together, the molecular crosstalk between different cell types (including **endothelial cells**, pericytes and astrocytes) and how these cellular interactions influence neuronal activity. **Addressing these issues promises to create new opportunities not only to better understand the molecular basis of the neurovascular link with neurodegeneration but also to develop novel neurovascular-based medicines**."

The journal article makes the following statement regarding neurological impairment in Alzheimer's disease:

"Does vascular dysfunction cause neuronal dysfunction?

In summary, the evidence clearly indicates that vascular dysfunction is tightly linked to neuronal dysfunction."

There was early support (2000) for the notion that a vascular disease precedes Alzheimer's, but few inroads have been made:[5]

"**Evidence is fast accumulating** which indicates that **Alzheimer's disease is a vascular disorder with neurodegenerative consequences** rather than a neurodegenerative disorder with vascular consequences.

"It is proposed that CATCH—hemodynamic **microcirculatory insufficiency**—initiates AD by **distorting regional brain capillary structure involving endothelial cell shape changes and impairment of nitric oxide (NO) release** which affect signaling between the immune, cardiovascular and nervous systems." [Note: PSK003 facilitates NO release both directly through increase of PGE_1 and indirectly through its endothelium-derived relaxation factor (EDRF).]

It was stated in 2014:[6]

"Recent epidemiological and clinico-pathological data indicate **considerable overlap between cerebrovascular disease (CVD) and Alzheimer's disease (AD)** and suggest additive or synergistic effects of both pathologies on cognitive decline.

"Up to 84% of aged subjects show **morphological substrates of CVD** in addition to AD pathology. AD brains with **minor CVD**, similar to pure **vascular dementia**, show **subcortical vascular lesions in about two-thirds**, while in **mixed type** dementia (AD plus vascular dementia), **multiple larger infarcts are more frequent.** Small infarcts in patients with full-blown AD have no impact on cognitive decline but are overwhelmed by the severity of Alzheimer pathology, **while in early stages of AD, cerebrovascular lesions may influence and promote cognitive impairment, lowering the threshold for clinically overt dementia**.

"The burden of **vascular** and AD-type **pathologies** are **leading and independent causes of dementia in the elderly**, suggesting additive or synergistic effects of both types of lesions on cognitive impairment.

"In the Medical Research Council Cognitive Function and Aging Study, vascular risk factors were not associated with an increased burden of AD pathology at death in old age, ***whereas cerebral small vessel disease (SVD) and cardiovascular disease were interrelated***.

"AD has been reported to present frequently together with ***SVD, microvascular injury***, and microscopic CVLs [***cerebrovascular lesions***].

"**Vascular pathology** in aging and **Alzheimer's disease**—The types of vascular pathology in the aged human brain **include**:

5 de la Torre, J.C. and Stefano, G.B., "Evidence that Alzheimer's disease is a microvascular disorder: the role of constitutive nitric oxide," *Brain Research Reviews*, Vol. 34, Issue 3, 2000, pages 119-136.

6 Attems, Johannes and Jellinger, Kurt A.,"The overlap between vascular disease and Alzheimer's disease–lessons from pathology," (Vascular risk factors and Alzheimer's disease), *BMC Medicine*, 2014, 12:206, pages 1-12.

- "Cerebral **amyloid angiopathy** (CAA). Of note, **the majority** of cases with CAA-related ICH **had hypertension**, suggesting that **hypertension is an important additional causal factor in CAA-related ICHs**;

- "**Cerebral atherosclerosis**, SVD (in most cases **caused by hypertension**, i.e., hypertensive vasculopathy), or **microvascular degeneration** (tortuosity, fibro- and lipohyalinosis);

- "**Blood–brain barrier** (BBB) **dysfunction** causing white matter lesions (WMLs), **microinfarctions**, lacunes or lacunar **infarcts**, and **microbleeds**.

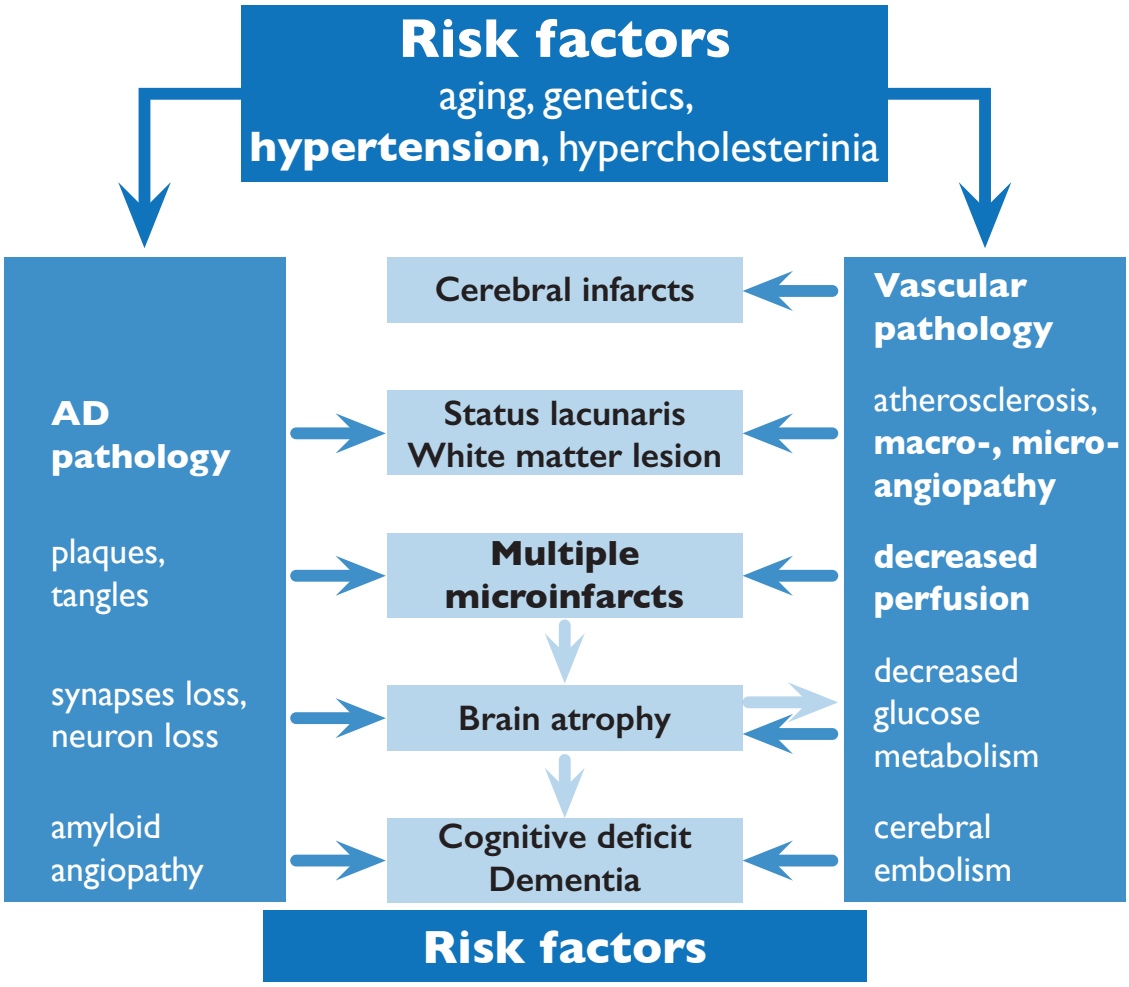
"**All of these pathologies may disrupt the integrity of cerebral vessels** and alter brain perfusion leading to neuronal injury and cognitive impairment. SVD ***affects small arteries and arterioles and refers to pathological changes similar to atherosclerosis that are termed small vessel arteriosclerosis / atherosclerosis***, lipo- or fibrohyalinosis, or **hypertensive arteriopathy**.

"As opposed to large and lacunar infarcts, **cortical microinfarcts** (CMI) are ***usually not visible*** at gross neuropathological examination. Due to the location of the underlying vessel disorder, multiple cortical CMIs are often associated with CAA, whereas subcortical microinfarcts are mainly linked to SVD or atherosclerosis-related embolism.

"In a series of 300 autopsy cases of AD, Kalaria and Ballard reported 98% CAA [cerebral amyloid angiopathy], **100% microvascular degeneration**, 31% infarcts of all sizes, and 7% intracerebral hemorrhage, while Olichney, in a cohort of 248 autopsy cases of AD, revealed a total of 48% CVLs [cerebrovascular lesions], with 31% microinfarcts, 12.5% large infarcts, and 13.5% hemorrhages.

"**Microvascular changes** in the aged brain and in AD induce impairment of cerebral perfusion, **in particular decrease of regional blood flow**, reduction of glucose transport and utilization, **loss of vascular innervation** with special impact on the cholinergic and transmitter deficits in AD, impairment of neurovascular regulation, ultrastructural **changes in capillaries** and **basement membranes** due to deposition of Aβ, with breakdown of the BBB and impairment of amyloid clearance.

"The role of vascular pathology as a factor contributing to AD is a topic of current interest, with a wide overlap between both disorders."



We believe that PSK003 has the potential to become the first-in-class drug for Alzheimer's disease.