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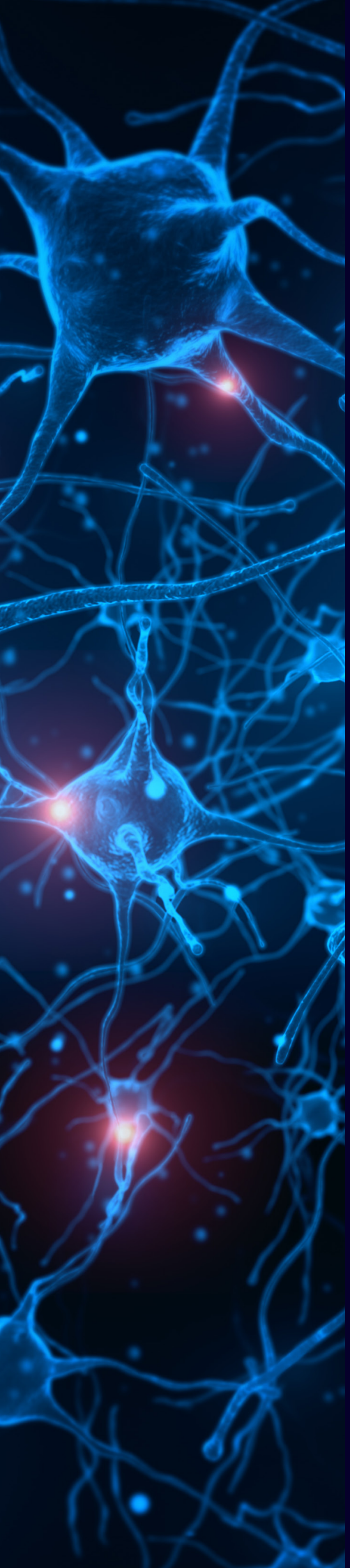
ALF5755: A NEW THERAPEUTIC AVENUE FOR ALZHEIMER'S AND DIABETIC NEUROPATHY

Prof. Christian Bréchot

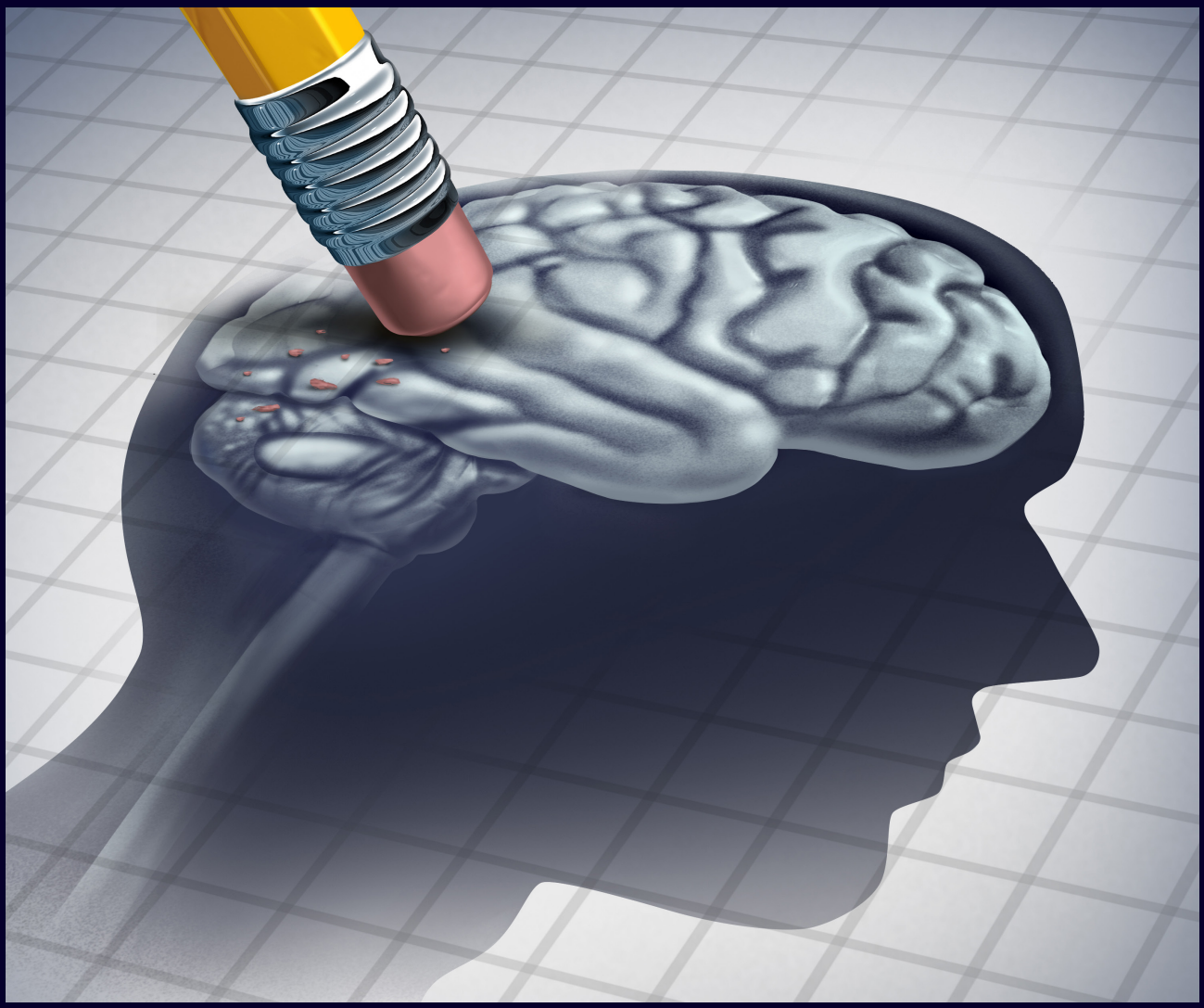


ALF5755: A New Therapeutic Avenue for Alzheimer's and Diabetic Neuropathy

Many diseases become more likely to emerge as we age, with metabolic disorders such as diabetes, and neurodegenerative conditions, such as Alzheimer's disease, representing two frequent manifestations of poor health in old age. While many age-related diseases present very differently, many share common underlying mechanisms. These include inflammation, a build-up of reactive oxygen molecules that can damage cellular components, and a lack of sensitivity to insulin. Treatments that can effectively target these mechanisms could have transformational effects on the age-related diseases that are fueled by them, including potentially preventing such diseases from developing in the first place. Prof. Christian Bréchot and colleagues at The Healthy Aging Company have developed a drug candidate: ALF5755, the pharmacological name of a protein called Hepatocarcinoma-Intestine-Pancreas, or HIP for short, also named Reg3A, that has shown exciting evidence of effectiveness on the cognitive disorders which occur during Alzheimer's disease and the peripheral nerve damage that often occurs in diabetes, which is called diabetic neuropathy.

Maintaining health into old age is a key priority for many, but time is not kind to the body. As we age, complex biochemical mechanisms in our body can begin to malfunction, leading to chronic health problems. For instance, in many people, tissues can become less sensitive to the action of insulin, the hormone that controls blood glucose levels. This can potentially pave the way for diabetes, and serious complications such as diabetic neuropathy, which involves painful lesions and ulcers that typically appear on the legs and feet. Insulin sensitivity deficits, inflammation and oxidative stress can also play a significant role in neurodegenerative diseases, such as Alzheimer's disease. In fact, Alzheimer's is sometimes described as diabetes type 3.

There are currently no effective treatments for either diabetic neuropathy or Alzheimer's disease. However, Prof. Christian Bréchot and colleagues have accumulated a wealth of pre-clinical data for a new therapy for potential use in both conditions. This is ALF5755, a protein originally discovered in the liver, and which has demonstrated exciting efficacy in a range of disease states. The protein can directly bind and inactivate reactive oxygen molecules that cause cellular damage. It acts as a tissue repair molecule, which means it drives tissue regeneration and counterbalances tissue lesions and it also has significant anti-inflammatory effects and can help to reduce insulin sensitivity deficits.



Interestingly, ALF5755 tends to have the greatest effect on unhealthy and inflamed tissues. It binds to another protein called fibrin that forms long strands on the outside of cell membranes. Once bound to extracellular fibrin, ALF5755 has a local anti-oxidant effect by binding reactive oxygen molecules, and then this affects large protein bundles called receptors that are studded in the cell membrane. The receptors then transmit these changes inside the cell itself, helping to amplify the effectiveness of HIP treatment.

However, healthy cells tend to be covered with another protein called fibrinogen, and have less fibrin, meaning that HIP is less likely to affect them. This mechanism forms a serendipitous ALF5755 targeting effect for inflamed tissues, and may help to avoid off-target effects in healthier tissues.

One of the most painful and debilitating conditions for which ALF5755 has significant potential is diabetic neuropathy. Up to one third of patients with diabetes may experience foot ulcers, and up to 60% of such wounds become infected, with a significant associated risk that the affected limb will need to be amputated. In diabetes, high blood glucose levels lead to small vascular lesions which can become inflamed, leading to an increase in reactive oxygen molecules. These processes can damage and destroy nearby nerves, and the lesions can degenerate to form painful ulcers that are very difficult to treat. At present, no treatments exist that can slow or prevent diabetic neuropathy.

However, ALF5755 has shown exciting pre-clinical effectiveness in addressing the mechanisms underlying diabetic neuropathy. For instance, one study in mice showed that ALF5755 treatment could protect neurons in the brain from being killed through overstimulation, by exerting its anti-oxidant effects. In a second study in diabetic mice, ALF5755 treatment enhanced skin wound healing, in part by reducing levels of inflammatory proteins in the wound margin.

Impressively, in a sophisticated rat model of type 2 diabetes in which diabetic neuropathy arises as the rat grows older, ALF5755 treatment enhanced nerve sensitivity and associated muscle function.
The ALF5755 protein has also shown significant potential in pre-clinical models of Alzheimer's disease. Alzheimer's involves characteristic protein plaques and tangles within the brain, but it also involves inflammation and oxidative stress, providing an opportunity for HIP to provide therapeutic benefit.

The researchers used a mouse model of Alzheimer's in which mice demonstrate characteristic protein plaques in their brains, along with memory and learning defects. They used genetic techniques to overexpress the ALF5755 protein in the mice, and successfully demonstrated that it could significantly reverse learning and memory defects over 6 months, and that it also increased levels of anti-oxidant enzymes in the brain. In a key aspect, the study demonstrated that ALF5755 could cross the blood-brain barrier, a specialized lining found in the blood vessels within the brain that often prevents therapies from entering.

In terms of the safety of ALF5755 therapy, so far, phase 1 and 2 studies in healthy men and patients with acute liver diseases who received intravenous administration of ALF5755, at a range of concentrations, showed no adverse effects, suggesting that this drug is safe for clinical use. At present, the therapy is designed to be delivered as a subcutaneous injection, but Bréchot and colleagues are working to develop a capsule formulation that patients could take orally.

Both diabetic neuropathy and Alzheimer's are significant sources of suffering for many in old age, with no currently available treatment options to alleviate this. Finding new treatments that can help people to increase their health span and live happy lives into old age would be transformative. Therapies such as ALF5755 look to be a step in the right direction.

For further information, you can connect with Prof. Christian Bréchot at cbrechot@usf.edu