

Dear Sirs!

I think we should move in the direction of the fastest commercialization of Cryomelt.

As a first step in this direction, I see additional research for positioning Cryomelt as a medicine for the prevention and treatment of Alzheimer's disease. My reasons are simple. Alzheimer's disease case is a big challenge and a lot of money at the same time. From the point of view of society, Alzheimer's disease is the most burdensome disease. Thus, according to American experts, the total cost of treatment and care for patients with Alzheimer's disease in the United States by 2017 will reach \$ 259 billion. And according to patient organizations, the burden of disease for the US economy by 2050 could exceed one trillion US dollars.

On the one hand, such amounts are an unbearable burden for the economy, on the other hand - a gigantic market for pharmaceutical companies.

It should be especially noted that a new product in this area have not appeared since 2003.

How do I see this work?

The characteristic histological signs of Alzheimer's disease are  $\beta$ -amyloid plaques and neurofibrillary tangles in the cortex.

Neurofibrillary tangles consist of hyperphosphorylated tau protein.

Obviously, an effective medicine should reduce the concentration of  $\beta$ -amyloid and tau protein in the brain.

To confirm this effect, it is necessary to conduct clinical studies in humans. It is difficult, expensive and time consuming. However, there is another way.

If we look at existing medicines to treat the Alzheimer's disease, we will see that most of them are ACh- inhibitors, the first of which, Tacrine, was approved for use in 1993. These drugs increase the amount of acetylcholine in the brain of patients. Nevertheless, in this class of drugs, we can conduct a study of the Cryomelt effect on the secretion of acetylcholine in the brain of rats. It is fast and inexpensive. A positive result obtained in a reputable international laboratory will allow an IPO to succeed. I am confident of a positive result. My confidence is based on the results of the research conducted on the properties of Cryomelt.

There is, of course, a question. How is Cryomelt better than other inhibitors? The answer is simple. All drugs in this group have the same strong side effects, which often lead to discontinuation of therapy.

These are decrease in heart rate, lower blood pressure, trouble sleeping, nausea, vomiting, loss of weight. Cryomelt does not have any identified side effects.

Of course, Cryomelt can be attributed to the ACh-inhibitor drug group only conditionally, since Cryomelt clearly has a different mechanism of action, which explains the absence of side effects.

It is very important that our studies on rat neurons in Russia showed an increase in the expression of neurotrophins BDNF and NGF under the influence of Cryomelt. These studies need to be continued in an internationally certified laboratory. This, again, is fast and inexpensive. The obtained result allows to expand the scope of Cryomelt for ALL neurodegenerative diseases, including multiple sclerosis.

This is a clear advantage for the commercialization of Cryomelt.

Here is an example that might be interesting.

Axovant was established in October 2014 by Vivek Ramaswami, the hedge fund manager. The company acquired from the pharmaceutical industry giant GlaxoSmithKline for \$ 5 million of the right to develop the molecule RVT-101 - a substance that helps alleviate some of the symptoms of Alzheimer's disease, but does not affect the rate of its progression.

Six months later, in June 2015, the company entered the NASDAQ exchange. At this point, the RVT-101 molecule was the only asset of Axovant. On the first day of the sale of shares, Axovant's market capitalization reached almost \$ 3 billion.

At one time, GSK suspended the development of this drug because it showed no effect on the progression of the disease. Ramaswami suggested that RVT-101 is probably not really effective as monotherapy, but may enhance the effects of already approved drugs sufficiently for regulatory approval. Axovant used this strategy by combining the already approved drug donepezil with the molecule purchased from GlaxoSmithKline. Preliminary research data suggest that such a combination can actually give better results than using one donepezil.

I can not fail to note that, firstly, Cryomelt reliably relieves the symptoms of Alzheimer's disease, secondly, it enhances the effect of other drugs during complex therapy.

If you have additional questions, I will try to answer them as soon as possible.

Sincerely yours, Serge Afanasyev.