Lord of the Folate

SCIENCE A man founded a life science start-up at the age of 60 and now, almost ten years later, could be on the verge of a breakthrough. There is a shortfall: 50 million Swiss francs for a phase 3-study.

Sharon Saameli (Text) und Robin Kohler (Bild)

Martin Ulmann would actually have retired at the age of 69. "Many colleagues tell me I'm crazy. I'd better go travelling," he says. Instead, on this rainy morning, he sits in the "Munot" room of the Schaffhausen Generis and tries to explain to the *AZ* journalist the difference between folic acid and methylfolates. It is not easy to see the structures printed on his papers.

But in these papers lies the secret why Ulmann has been running a start-up here in Schaffhausen for ten years. And why the trained chemist is not thinking about quitting for at least the next five years – but, on the contrary, senses his company's breakthrough right now.

The company is called Aprofol AG, and in addition to its headquarters in Appenzell, it also has premises and a cooperation with Generis. It deals with the research into folates and the development of new products for the healthcare market. Folate – or methylfolate – is a water-soluble vitamin that plays pretty much everywhere in the human organism. In the language of Martin Ulmann: "Folate are the carrier for the smallest building blocks in the body, namely «one carbon units»."

Folate is particularly needed in cell division and growth and is therefore indispensable for health. Accordingly, the "life vitamin" has experienced a veritable hype in recent decades. In several dozen countries (all outside the EU), it is added to basic foodstuffs such as flour to avoid widespread malnutrition. Among other things, such an insufficiency before and during pregnancy can lead to so-called neural tube defects (NTD) in the fetus.

Nerve damage, paralysis or spina bifida, a splitting of the spinal column, are the consequences.

More recently, however, medicine has also discussed connections to folates that go far beyond this knowledge. And with this diversity, you can get dizzy: Folates should not only reduce cardiovascular diseases and prevent chronic skin diseases, but also reduce the risk of dementia, improve sperm quality and help with allergies, depression or even an attention-deficit hyperactivity syndrome (ADHD).

The vitamin B9 is better known under the term folic acid. This is quite correct

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but not: Folic acid refers to the synthetic, i.e. artificially produced form of folates. "Folic acid must first be activated and converted in the body," explains Martin Ulmann, "and there are currently growing fears that unmetabolised folic acid (UMFA) can even be harmful to health." This is central to Aprofol's work: it delivers folates in a way that can be absorbed directly by the body.

The «Appenzellerkopf»

It is no coincidence that Ulmann, who grew up in Appenzell and completed his training in Basel and later at the technical university in Zurich, conducts folate research in Schaffhausen. This is where Drs. Hans Suter and Fulvio Bracco founded Eprova AG 70 years ago; they succeeded in developing leucovorin (a specific form of folate) in such purity as the world has never seen before. In the company, which was firmly rooted in the region and was taken over by the German Merck in the early 70s, Ulmann also made a career from 1978 on. "I was infected by Hans Suter," he says today, the longer he let go, the less, and in 2002 he became managing director of the affiliate.

When his contract was not extented after ten years in the upper management and 35 years overall, Martin Ulmann was 59. Elsewhere, to find a comparative job in the field was considered difficult or impossible.

Subordinating oneself to a new hierarchy too. "That's when the «Appenzellerkopf» intervened," says Ulmann. That's why he started his own business at the age of 60 and founded Aprofol. The start-up euphoria gripped Ulmann. His declared goal: to be able to move on the folate center that Doctor Suter once founded, independent from big pharma.

The first station of the young company was the eye. This small organ, responsible for our vision, requires the most energy per volume – and therefore reacts very sensitively to a lack of vitamins and other nutrients. In 2018, Aprofol launched the vitamin product Ocufolin, which supplies the folates directly to the retina. However, the founder and CEO of Aprofol feels the definitive kick-off of the company (and the topic Martin Ulmann prefers to talk about) elsewhere: is the treatment of autism spectrum disorder (ASD).

The extent to which people with autism have a lack of folate in the brain was investigated in 2004 at the Children's Hospital in Zurich. However, it was not until 2016 that the US-American pediatric neurologist Richard E. Frye conducted a first pilot study in which children with autism were treated with folates. The result: compared to the control group, the children's communication behaviour improved considerably. This has been deepened since 2021 in other studies with very young children – and Aprofol supplies the drug product for three clinical studies, manufactured in Schaffhausen.

The study was financed, again led by Richard Frye, incidentally by the foundation "Autism Speaks". It is the largest non-profit organization in the entire USA that specifically promotes autism-specific research. Social movements such as NGO's that want to strengthen the rights of people with disabilities, are criticizing "Autism Speaks" for pathologizing autism, stirring up prejudices and ultimately advocating a "cure" instead of seeing autism as part of a neurodiverse society.

Eight patents pending

The Schaffhausen entrepreneur Martin Ulmann notes that the treatment method with folate cannot be said to be a cure anyway. Rather, it seems to be about further researching symptoms and insufficiencies, and then treating them.

For the approval of the drug used in the study – and thus for the breakthrough of Aprofol – this research would have to be further deepened. Ulmann speaks of a phase III study, i.e., of around 50 million Swiss francs would be needed.

One reason that makes it difficult to acquire these funds is that science is rarely completely free of doubt. Ulmann, who is repeatedly confronted with skepticism, is aware of this. "What we often hear," he explains, "is that our solution is too simple. Especially because folates are so diverse in their application – many do not trust them to play this central role as we are proposing." Ulmann, however, believes in the case. In the meantime, his company has applied for eight patents, two of which have already been granted. "It's not that easy to get pass the little Aprofol today," he says, not without pride. The man obviously dares to do his job.

Martin Ulmann is therefore now looking for investors for such a study. He is well connected for this: he is in contact with researchers and professors from all over the world. This is demonstrated not only by the experts and researchers listed on the Aprofol website, but also by a symposium held at the University Hospital in Zurich at the end of September. Martin Ulmann and Gerd Wiesler, Head of Operations at Aprofol, were among the eight experts who exchanged views on "Folates in Health and Disease".

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High expectations

The fate of the Folate Centre in Schaffhausen is therefore similar to that of all start-ups: to become profitable soon – or to fail altogether. After one and a half hours of bending over structural formulas and studies, it is clear to one person: Martin Ulmann knows how to sell the idea. This is not only out of personal conviction; high expectations are also placed on him.

"My family and those around me have put a lot of money into this company. For me, Aprofol is a personal investment. Profession and hobby at the same time. I hardly received any wages during this time," he says. Being a start-up has its price.