

People with autoimmune diseases suffer from a hyper-active immune system, which has spiralled out of control and attacks them by mistake.
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SWISS
START-UPS

+ AUTOIMMUNE DISEASES

AlloCyte – New Hope for Patients Suffering from Autoimmune Diseases

AlloCyte Pharmaceuticals AG is developing a new class of small molecule drugs for patients suffering from severe autoimmune diseases. AlloCyte's orally available "integrin silencers" are designed to restore patients' self-protective immune balance, translating into lasting disease control.

ELSBETH HEINZELMANN

Whether our body is attacked by bacteria, viruses, toxins or cancer cells, our immune system's army of white blood cells is always ready to protect us from these dangerous aggressors known as antigens. However, if we are suffering from an autoimmune disease, it is precisely this immune system that spirals out of control and attacks us by mistake.

Action Required for Novel Medications

Almost any organ can fall victim to this kind of immune attack. As a result, over 80 different autoimmune diseases are known. A growing number of patients suffer from these diseases, which are often chronic, debilitating and sometimes life-threatening. The underlying cause of autoimmunity is an overactive immune response of our body against structures that occur naturally in the body and do not normally elicit immune responses. Integrins (a class of trans-membrane receptors) are known to play decisive roles in triggering and sustaining these aberrant and excessive immune responses.

In 2011, a small group of Swiss- and US-based pre-clinical and clinical researchers, intrigued by recent insights into the roles of integrins in aberrant immune processes, decided to tackle the challenge of developing novel integrin-targeting medications. These medications are designed to restore the patient's protective immune balance and, in consequence, to provide lasting disease control.

AlloCyte's co-founders were well-positioned to meet this challenge. They brought with them a detailed understanding of integrin structural biology, an in-depth knowledge of the roles of integrins in health and disease and, importantly, considerable expertise in pre-clinical and clinical drug development.

Opportunities and Challenges of Integrins as Therapeutic Targets

Integrins are a family of 24 heterodimeric cell membrane glycoproteins composed of α - and β -chain subunits. Different cell types express different integrins – or combinations of integrins – on their surfaces. Therefore, integrins are attractive therapeutic targets that offer the potential to modulate the function of distinct cell populations and thus to selectively target cellular processes driving autoimmune diseases. »

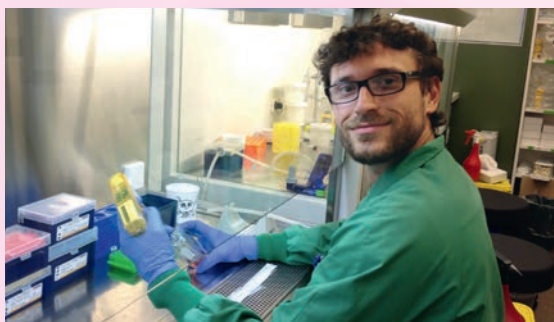


The Basel Inkubator provides space, infrastructure and support for young start-up companies such as AlloCyte Pharmaceuticals AG. From left to right: Dr Albrecht Schmidt, PD Dr Gabriele Weitz-Schmidt (both AlloCyte) and Dr Peter Burckhardt (EVA and Basel Inkubator). (Pictures: AlloCyte)



Professor Marianne Hürzeler and Martin Gut (B.Sc. in Molecular Life Sciences) at the School of Life Sciences, FHNW Basel, examine the purity of newly synthesized LFA-1 inhibitors.

Riccardo Mancuso (M.Sc. Biotechnology), PhD student at the University Hospital Basel, isolates and cultures white blood cells, which are critical for testing biological activities of novel small molecule LFA-1 inhibitors.





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Integrins are difficult targets from a pharmacological perspective, however. This is because integrins are normally expressed on cell surfaces in an inactive or “silent” state. Intracellular signals are required to activate integrins. This activation is associated with massive conformational changes of the α/β heterodimers. Subsequent ligand binding to the activated integrins triggers complex signalling cascades that fundamentally change the cells’ morphology and behaviour.

It is a central pharmacological challenge to inhibit integrins without triggering unwanted signalling into the cells. Unwanted signalling is of major clinical concern because it could aggravate, rather than treat the disease. This phenomenon is also known as paradoxical agonism, a risk associated with all modalities that interact with the ligand-binding site of integrins. Paradoxical agonism has haunted integrin pharmacology for decades. AlloCyte aims to avoid paradoxical agonism by pursuing an elegant pharmacological approach in which integrins are stabilized in their inactive state, referred to as “integrin silencing”. By their small molecule nature, steerability, selectivity and their avoidance of paradoxical effects, AlloCyte’s integrin silencers are expected to support innovative therapeutic concepts that could not be realized with earlier integrin-targeting pharmacological approaches.

AlloCyte’s first integrin target is the leukocyte receptor lymphocyte function-associated antigen-1 (LFA-1). LFA-1 controls leukocyte migration and T cell activation during inflammatory and immune responses. Furthermore, LFA-1 plays an important role in directing the fate of young T cells towards disease-driving (pro-inflammatory) or protective (regulatory) populations.

Experts join Forces and roll up their Sleeves

When AlloCyte started, the team already had a detailed understanding of the molecular site within the LFA-1 heterodimer that they wanted to target, based on prior research by Timothy Springer, Harvard Medical School Boston and Gabriele Weitz-Schmidt, AlloCyte Basel. This very high level of understanding allowed for a virtual screening approach for identifying compounds that bind to this site and potentially inhibit (silence) LFA-1.

AlloCyte’s virtual screening performed by Gisbert Schneider’s group at the ETH Zurich (ETHZ) rapidly led to the identification of virtual hits. They became the starting points of a focused chemistry programme conducted by Marianne Hürzeler’s group at the School of Life Sciences of the University of Applied Sciences and Arts Northwestern Switzerland (FHNW) Basel. The pre-clinical pharmacological profiling of the compounds was performed by the groups headed by Daniel Gyax at FHNW Basel, and Stephan Krähenbühl at the University Hospital Basel. This efficient collaboration of leading research groups from different Swiss academic institutions rapidly advanced the initially virtual hits to produce a new chemical class of potent, selective and orally available LFA-1 inhibitors with the desired mode of action.

Working hand in hand with the company’s pre-clinical research consortium, Albrecht Schmidt, AlloCyte Basel, an experienced internist and clinical drug developer, reached out to leading clinicians to develop and advance AlloCyte’s innovative translational concepts, thus building the second pillar of therapeutic innovation – right from the company’s start.

Partners sharing the Vision and accepting the Risks

As a start-up company, AlloCyte needed financial partners who shared the company’s vision and were prepared to accept inherent risks. The young company was lucky to gain the almost immediate support of NTN Swiss Biotech and the Swiss Commission for Technology and Innovation (CTI). The Basel Incubator/EVA (see box) also stepped in to provide AlloCyte with an attractive home and the

BASEL INKUBATOR – the high-tech incubator in Basel

The Basel Inkubator, founded in 2009, is a service provided for start-ups by the University of Basel and the University of Applied Sciences and Arts Northwestern Switzerland (FHNW), MuttENZ. Created on the initiative of the University of Basel, the FHNW and EVA – the Basel life sciences start-up agency – as well as the AWA (Office of Economy and Labour) Basel, the incubator offers coaching and low-cost business accommodation. The start-up companies benefit from subsidized employment and consulting services in order to further develop their business idea.

stimulating environment of other start-up companies. Moreover, i-net Innovations Network Switzerland provided the company with access to expertise not available elsewhere. In addition, private help was provided at an early stage, supplemented later on in the project by the

support of a Basel-based pharmaceutical company that joined the CTI consortium.

"Initially, it proved impossible to attract venture capital, as we did not own any substantive intellectual property," states Gabriele Weitz-Schmidt. She appreciates the generous financial sup-



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DR GABRIELE WEITZ-SCHMIDT.

CSO and co-founder of AlloCyte

Questions to Gabriele Weitz-Schmidt, PhD and co-founder of AlloCyte

Interview conducted by Elsbeth Heinzelmann

Lifesciences plus: *As a pharmacist and biochemist you led global interdisciplinary projects in cardiovascular disease, transplant rejection and autoimmunity. What is your personal motivation as a Chief Scientific Officer at AlloCyte?*

Gabriele Weitz-Schmidt: AlloCyte brings together an international team of experienced researchers with the common goal of exploiting the therapeutic opportunities offered by integrins. It is a major motivation to work within such an interdisciplinary team and to translate research into therapeutic benefits for patients. AlloCyte is a young company with a very productive and open-minded atmosphere. It's fun to be a part of it.

What role does the inclusion of Daniel Gygax, President of biotechnet, in the AlloCyte team play and – thanks to him – the access to innovative technology and methodology infrastructure at FHNW?

AlloCyte could not have started without Daniel Gygax's early support. Daniel recognized the potential of AlloCyte's pharmacological concept and joined the initial team that went on to found the company. He also provided AlloCyte with critical infrastructure during the start-up phase and helped AlloCyte's consortium to gain the support of NTN Swiss Biotech and CTI. AlloCyte is privileged to have Daniel Gygax on board as a senior advisor, development partner and shareholder.

Before founding AlloCyte, you spent a sabbatical in the laboratory of Timothy Springer, a further co-founder of AlloCyte. The Boston area has a worldwide reputation in identifying innovative companies and putting them on a sound footing. Why did you decide to found AlloCyte in Basel?

Indeed, the Boston area provides an attractive and stimulating environment for start-up companies. We decided to found AlloCyte in Basel for a number of reasons: Firstly, the Basel location provided us with immediate access to exceptional medicinal chemistry and biology infrastructure and expertise. We could hardly have found this expertise anywhere else. Secondly, the concept of public-private partnership (which made great sense from the co-founders' perspectives) could be realized in Switzerland thanks to the generous support of CTI and NTN Swiss Biotech. Last but not least, the Basel area is an exceptionally privileged location for innovative drug development. There are major international pharmaceutical companies in close proximity, as well as successful budding biotech companies. The momentum that can be derived from this constellation should not be underestimated.

port of CTI all the more, since it enabled rapid progress during AlloCyte's start-up phase, resulting in the prompt discovery of a new chemical class of integrin inhibitors leading to AlloCyte's first patent application. CTI's support was also critical in initiating the kind of public-private partnership that worked so productively in AlloCyte's case. "The FHNW Basel, as well as the ETHZ and the University of Basel, provided competencies that synergized with our own expertise, not to mention infrastructures that would not have otherwise been accessible to AlloCyte," remembers Weitz-Schmidt, who contributes her expertise in pharmacology and project management. There was another important element shaping the environment within AlloCyte's team: The involvement of highly motivated and practice-oriented Bachelor, Master and PhD students. "They helped to create the 'can do' spirit that characterizes our young company," adds Weitz-Schmidt.

Meanwhile, AlloCyte has initiated collaborations within Switzerland and internationally to further assess its LFA-1 silencers. These activities will be an important next step in translating AlloCyte's integrin pharmacology into innovative therapeutic concepts, expected to provide patients suffering from severe autoimmune diseases with sustained therapeutic benefit and, ultimately, freedom from disease. 