Development of a new generation of integrin targeting drugs for the treatment of immune-mediated diseases

Gabriele Weitz-Schmidt¹, Riccardo Mancuso², Marianne Huerzeler³, Stephan Kraehenbuehl⁵, Gisbert Schneider⁴, Albrecht-Georg Schmidt¹

¹AlloCyte Pharmaceuticals AG, Switzerland, ²University Basel, Switzerland, ³School of Life Sciences Muttenz, Switzerland, ⁴ETH Zuerich, Switzerland

Integrins are a family of cell surface receptors which mediate cell-to-cell or cell-to-extracellular matrix interactions. They have been recognized as important therapeutic targets for immune-mediated, fibrotic, malignant and cardiovascular diseases. Despite their well-characterized roles in key disease processes, only six integrin therapeutics are approved to date, targeting four of the 24 known human integrins. The limitations of these current integrin inhibitors reflect the challenges associated with integrin targeting pharmacologies, in general. These include paradoxic agonism (i.e. the elicitation of effects the inhibitors were designed to prevent), lack of selectivity as well as limitations related to antibody or peptidomimetic natures. New pharmacologic strategies are needed to overcome these limitations and to fully exploit the potential of integrins as therapeutic targets. Here we report the discovery and development of a new generation of small molecule inhibitors targeting the integrin lymphocyte function associated antigen-1 (LFA-1). LFA-1 is an attractive therapeutic target for immune-mediated inflammatory diseases.

A virtual screening approach was utilized to identify allosterically acting compounds which stabilize LFA-1 in its inactive, non-ligand binding state. These micromolar hits were turned into potent, orally available LFA-1 inhibitors by a focused chemical derivation program. Selected compounds are currently profiled in appropriate disease models of immune-mediated diseases. Moreover, the novel allosteric LFA-1 inhibitors have been demonstrated to be truly selective over other members of the integrin family, in contrast to previous antibody or ligand mimetic-based LFA-1 pharmacologies. Further, they do not induce unwanted paradoxic agonistic effects as associated with other LFA-1 targeting modalities.

The differential effects observed at cellular and molecular levels to date indicate that the newly discovered class of allosteric, non-peptidomimetic small molecule LFA-1 inhibitors may have the potential to resolve unwanted effects associated with previous LFA-1 targeting pharmacologies and may allow to fully exploit the potential of LFA-1 as a therapeutic target for immune-mediated diseases, in the future.