

Curing causal mechanisms instead of treating symptoms in autoimmune diseases and inflammation

Prof. Sylviane Muller

CNRS-University of Strasbourg Unit Biotechnology and cell signaling,
University of Strasbourg Institute for Advanced Study (USIAS)/ Chair Therapeutic Immunology,
Strasbourg Drug Discovery and Development Institute (IMS)
Strasbourg, France

Nowadays, pharmacologic treatments of inflammatory and autoimmune diseases are largely palliative rather than curative. They result in non-specific immunosuppression, which can be associated with disruption of natural and induced immunity with significant, sometimes dramatic, adverse effects. Among the novel strategies that are under development, tools that target specific molecular pathways and cells, and more precisely modulate the immune system to restore normal tolerance mechanisms, are central. In these approaches, peptides represent a class of therapeutic drugs that display many physicochemical advantages in terms of stability, toxicity, absence of immunogenicity and unwanted side effects. In this context, the peptide P140, which is currently evaluated in phase III-clinical studies worldwide, is very promising for treating patients with systemic lupus. This peptide targets key elements of endo-lysosomal autophagy, which is hyperactivated in lupus. We also obtained beneficial effects in animal models mimicking Sjögren's syndrome, inflammatory bowel disease, chronic inflammatory demyelinating polyneuropathy and asthma. In an induced mouse model of periodontitis, we showed that P140 normalizes the dysregulated expression of several autophagy-related genes in the gingiva of sick mice, with an effect on bone loss. Our most recent data suggest that P140 may act as a blocker of pro-inflammatory cells towards targeted tissues. After the era of drugs classified as "disease-modifying" therapeutics, a new type of safe "mechanism-guided" therapies are emerging for treating inflammatory diseases.

-Wang, F., Tasset, I., Cuervo, A.M. & Muller, S. (2020) *In vivo* remodelling of altered autophagy-lysosomal pathway by a phosphopeptide in lupus. *Cells* 9:2328

-Akiyama, K., Aung, K.T., Talamini, L., Huck, O., Kuboki, T. & Muller, S. (2022) Therapeutic effects of peptide P140 in a mouse periodontitis model. *Cell. Mol. Life Sci* 79:518

-Gros, F. & Muller, S. (2023) Role of lysosomes in metabolic and autoimmune diseases. *Nature Rev Nephrol.* 19:366–383

-Bonam, S.R., Mastrippolito, D., Georgel, P. & Muller S. (2024) Pharmacological targets at the lysosomal autophagy-NLRP3 inflammasome crossroads. *Trends Pharmacol Sci.* 45:81-101