LS18-058 - Systems medicine analysis of sarcoidosis by targeting mTOR in a co-clinical trial in patients and mice

Abstract

Sarcoidosis is a chronic disease of unknown etiology affecting multiple organs and lacking targeted therapies. The mechanistic target of rapamycin (mTOR) pathway is a key regulator of immune cell metabolism and highly upregulated in granuloma-associated cells.

In our WWTF-funded joint project, we defined the molecular architecture of granulomas with novel techniques and found that macrophages, T-cells and fibroblasts are granuloma-driving cell populations. Pathways associated with these cell populations with the granulomas are potential new treatment options, which we confirmed in a mouse model for sarcoidosis. When mice were treated with a small molecule blocking the matrix metalloproteinase (MMP) 12, there was a reduction of sarcoidosis-associated clinical symptoms in mice, corroborating an important role for extracellular matrix proteins in granuloma formation and maintenance.

Within the scope of this project, we treated patients with persistent cutaneous sarcoidosis with the mTOR inhibitor sirolimus in an investigator-initiated trial with an overall response rate of 70%. Importantly, we found a long-lasting improvement of symptoms in responders of the 4- months treatment. In addition, we used patient-derived macrophages to introduce a new ex vivo model for granulomas, which will be important for future studies with this patient cohorts.

By combining a clinical trial and a unique mouse model with single-cell and spatial RNAseq technology, this proposal connected mechanism-based and high-throughput research to patient needs for an underserved disease, revealed mTOR inhibition in sarcoidosis patients as save and effective therapy and validate targets for future clinical studies.

Scientific disciplines:
Immunology (50%) | Bioinformatics (30%) | Dermatology (20%)

Keywords:
sarcoidosis, granuloma formation, mTOR, macrophages, n-of-1 clinical trial

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Further links to the persons involved and to the project can be found under
https://www.wwtf.at/funding/programmes/ls/LS18-058/