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Development of peptidomimetics to target CRAC channel complex

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Calcium ion is the most ubiquitous intracellular messenger in eukaryotic cells and is responsible for different biological processes including cell proliferation, growth, muscle contraction, exocytosis, immune cell activation, and apoptosis. The main plasma-membrane Ca2+ entry route in non-excitable cells involves calcium-release activated Ca2+ channels (CRAC), localized in the endoplasmic reticulum membrane junctions. CRAC has two molecular key components, the plasma membrane highly selective Ca2+ channel Orai1 and the endoplasmic reticulum resided Ca2+ sensor protein, stromal interaction molecule 1 (STIM1), which binds to Orai1 in response to ER Ca2+ depletion. The STIM1 binding site to Orai1 C-terminus is crucial upon the activation of store-operated Ca2+ entry (SOCE). This channel complex is involved in several diseases and channelopathies, therefore it is an attractive therapeutic target. The aim of this PhD project pursues the design, the synthesis and the biophysical characterization of peptidomimetics to target Stim1-Orai1 interaction. Here I will describe first achievements that are currently conducted. Based upon the available NMR complex between STIM1-Orai1, different peptidomimetics have been proposed by modifying the chain length and the linker for macrocyclization. Then, the potential binding of the STIM1-derived -helical macrocycles (MCXs) proposed against Orai1 have been assessed by means of Molecular Dynamics simulations. The MCXs were obtained by solid phase peptide-synthesis and protein expression. As a result, some MCXs have been already obtained and their activities are under investigation. Overall, these abstract aims to show the rationalize behind the proposed strategy on the design of MCXs and on the early obtained results.