MSc Thesis in Computational Chemistry

Computer-aided design of thrombolytic enzymes

We are looking for a motivated **MSc Student** to join our laboratory of **Computer-Aided Molecular Design** (Division of Physiological Chemistry) at the Medical University of Graz. The successful MSc Student candidate will participate in the **computational part** of the project **Computer-aided design of thrombolytic enzymes.**

Background: Amongst different actors, the von Willebrand factor (vWF) and its physiological partner, the metalloproteinase ADAMTS13 (a disintegrin-like and metalloprotease with thrombospondin type 1 motif 13), have been proven to mediate the thrombolysis of occlusions in ischemic stroke that are resistant to the tissue plasminogen activator (tPA), the standard drug in thrombolytic enzymes. ADAMTS13 is a metalloprotease that counterbalances the von Willebrand factor (vWF) by means of cleaving it into smaller, less adhesive multimers within nascent platelet-rich thrombi. vWF bridges subendothelial collagen at the site of vascular injury with platelets' glycoprotein Ibα during the initiation of hemostasis. Upon presence of vessel injury, the circulating globular form of vWF anchors to collagen via its A3 domain and - like a flag in the wind - stretches and exposes its A1 domain for the binding of platelets and its A2 domain to ADAMTS13. Thus, ADAMTS13 has emerged as an attractive enzyme that could be used as thrombolytic drug in the clinic.

Goal: The MSc Project will consist of the **modeling and molecular dynamics (MD) simulation of the full-length zinc metalloprotease ADAMTS13**, a key player in the regulation of blood clots formation. The 3D structure of the full-length ADAMTS13 has not been completely determined. Thus, techniques like homology modeling will be used in this project to build those domains whose structure is not known. The structure for the full-length ADAMTS13 will be refined by means of MD simulations using Amber20 or Gromacs. Aspects like the impact of the glycosylation pattern and/or the redox state of the protein on its structure and its flexibility will be evaluated within these studies. As outcome, the gained knowledge on the structure and dynamics of this protein will be used to help our team to design advanced ADAMTS13 variants with improved properties.

Timing and facilities: We offer a position for the MSc Thesis for 6 months starting from now. As part of our group, the successful MSc Student will count with a working station in Linux and full access to our scientific cluster equipped with the new GPU RTX3090.

Questions? Feel free to visit **CAMDgraz.com** or to send an Email to: **pedro.murcia@medunigraz.at**

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