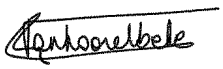
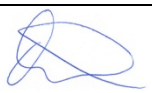
CELSA
Central Europe Leuven Strategic Alliance

CELSA - Collaborative research project - Application form - COVER PAGE

1. Identification of the principal investigator of the CELSA application – co-ordinator of the CELSA research project (from partner university *OR* KU Leuven)
Full name: Karen Vanhoorelbeke
Faculty/Department: Faculty of Sciences/Department of Biochemistry
Research unit within Faculty/Department: Laboratory for Thrombosis Research
Address: E. Sabbelaan 53, 8500 Kortrijk
University: KU Leuven Campus Kulak Kortrijk
Tel: 003256246061
Fax : 003256246997
email : karen.vanhoorelbeke@kuleuven.be
Signature[1]: 

2. Identification of the second investigator
Full name: Zoltán Prohászka
Faculty/Department: Faculty of Medicine/3rd Department of Medicine
Research unit within Faculty/Department: Research Laboratory
Address: Kútvölgyi st 4, 1125 Budapest, Hungary
University: Semmelweis University
Tel: +361-2129351
Fax : +3612253899
email : prohaszka.zoltan@med.semmelweis-univ.hu
Signature[1]: 

3. Identification of third and fourth co-investigator(s) (if applicable) Expand table if more than four research units are involved.	
Third co-investigator	**Fourth co-investigator**
Full name: Nick Geukens	Full name:
Faculty/Department: Chemistry	Faculty/Department:
Research unit within Faculty/Department: PharmAbs, the KU Leuven antibody Center	Research unit within Faculty/Department:
Address: Etienne Sabbelaan, 53 8500 Kortrijk & Herestraat 49 box 820, 3000 Leuven	Address:
University: KU Leuven	University:

Tel: 003216377177	Tel:
Fax: 003256246997	Fax:
email: nick.geukens@kuleuven.be	email:
Signature[1]: 	Signature[1]:

[1] Faxed signatures will be accepted.

3. Non confidential and public friendly summary (max. 2000 characters)

Project title: Autoantibodies in autoimmune-mediated thrombotic thrombocytopenic purpura: from mechanistic insights towards the first steps in targeted therapy

Summary:

More than 2.5% of the population is affected by autoantibody-driven autoimmune diseases. The mechanism of autoantibody-induced deficiency of the autoantigen is different for every autoimmune disease. However, there is only one general treatment for all those diseases and that is systemic immune suppression. As a consequence, side effects, morbidity and mortality are high in these patients. An unmet need in the field is the availability of targeted immune therapies to neutralize the pathogenic autoantibodies. A targeted therapy can only be developed when the exact mechanism on how autoantibodies cause autoantigen deficiency is known. A targeted neutralization of the pathogenic antibodies could then be realized by specific drugs like anti-idiotypic antibodies or small molecules.

Immune–mediated thrombotic thrombocytopenic purpura (iTTP) is a rare and life-threatening autoimmune disease caused by a severe deficiency in the plasma metalloprotease ADAMTS13 (A Disintegrin and Metalloprotease with Thrombospondin Type 1 repeats, member 13). Hyperactive ultra-large von Willebrand factor (UL-VWF) multimers in circulation cannot be cleaved when this metalloprotease is absent or dysfunctional. Consequently, microthrombi are formed by spontaneous binding of UL-VWF multimers to platelets, depriving organs from oxygen supply. The immune response in iTTP patients is polyclonal with an immunodominant epitope in the ADAMTS13 spacer domain. The exact mechanism how anti-ADAMTS13 autoantibodies induce ADAMTS13 deficiency is unknown. Unravelling this mechanism is, however, an unmet need to allow development of a targeted therapy for iTTP patients. The aim of the current project is to identify which group of anti-ADAMTS13 autoantibodies are the pathogenic ones and cause ADAMTS13 deficiency. Blocking the specific group of pathogenic antibodies would lead to the first steps in developing a targeted therapy for iTTP.

4. List 5 key words

Thrombotic thrombocytopenic purpura, autoimmune disease, ADAMTS13, autoantibodies, structure