CeNT CENTRE OF NEW TECHNOLOGIES

UNIVERSITY OF WARSAW

invites to a seminar by

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Rice University, Houston, USA

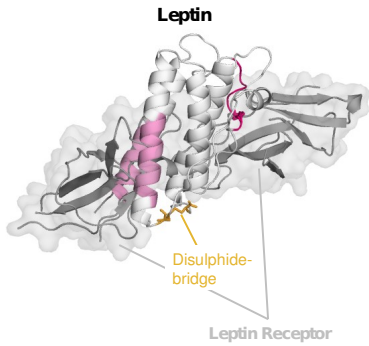
Uncovering the Molecular Details Behind the Disease-Associated Mutations Identified in Leptin, and the role of the Pierced Lasso Topology

26th July 2017 at 2:30 p.m.

Venue: Centre of New Technologies, Banacha 2C,
Seminar room 4050 (4th floor)

Host: Ass. Prof. Joanna I. Sułkowska

Is Obesity Caused By Leptin Deficiency?



A Pierced Lasso Topology (PLT) is a new class of "knotted" proteins discovered in the satiety hormone leptin. Here, a single disulphide bridge holds the knotted topology together where part of the backbone is threaded through the covalent loop. Thus, the knot can easily be manipulated in vitro/in vivo by the chemical environment and thus act as an on/off switch to control the biological activity. Interestingly, homozygous mutations are identified in the leptin gene associated with extreme obesity, marked hyperphagia and impaired immune function. While these mutations have been characterized in vivo, a detailed understanding of their structural and functional integrity remains elusive. We characterized the structural effects of the full-length mutations identified in patients with congenital leptin deficiency. Our results show that disease not only occurs from misfolding and/or aggregation of the protein, but also are due to changes in the receptor-binding interface. Therefore, we hypothesize that leptin deficiency is a combined effect of different mechanisms including: (i) blockage of receptor interface II, (ii) decreased affinity in the second step of receptor interaction, (iii) protein destabilization, and (iv) unsuccessful threading through the covalent-loop leading to protein misfolding/aggregation. We anticipate that our current findings create a framework for systematically designing therapeutics for diseases associated with leptin.