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Targeting IL-23/Th17 pro-inflammatory axis by novel non-immunoglobulin protein binders with an immunosuppressive potential

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IL-23 receptor-mediated signaling has recently been closely associated with development of several chronic autoimmune diseases such as psoriasis, psoriatic arthritis, inflammatory bowel disease and multiple sclerosis. Recently we generated novel IL-23 receptor antagonists (called REX ligands) derived from scaffold of albumin-binding domain (ABD) that exhibited immunosuppressive control over IL-23-driven ex vivo expansion of primary human Th-17+ T-cells. Due to small size, excellent tissue penetration and self-refolding activity, these binders represent a valuable non-immunoglobulin alternative for development of topically-administrated anti-psoriatic biologicals. As the structure of IL-23/IL-23R complex is unavailable and a precise mode of interaction remains unknown, designing more efficient IL-23 inhibitors is cumbersome. Following our concept, we generated a novel class of binding proteins targeting p19 subunit of human IL-23 cytokine. These unique proteins, called ILP binders, were selected from high-complex ABD-derived combinatorial library in combination with ribosome display. From 214 clones analyzed by ELISA, Western blot and DNA sequencing, 53 provided 35 different sequence variants that were further characterized. Using *in silico* docking in combination with cell-surface competition binding assay we identified a group of inhibitory candidates that substantially diminished binding of recombinant p19 to the IL-23 receptor on human monocytic THP-1 cells. Several found p19-blocking variants inhibited IL-23-driven expansion of IL-17-producing primary human CD4+ T-cells. Thus, these novel binders represent unique IL-23-targeted probes useful for IL-23/IL-23R epitope mapping studies and could be used for designing novel p19/IL-23-targeted anti-inflammatory biologics.

Biography

Petr Maly is the Head of Laboratory of Ligand Engineering at the Institute of Biotechnology, Czech Academy of Sciences in Vestec near Prague, Czech Republic. He has studied at the Department of Biochemistry, Faculty of Science, Charles University in Prague and completed his Doctorate at the Institute of Molecular Genetics, ASCR in Prague. He has completed his Postdoctoral fellowship at the Department of Pathology and Howard Hughes Medical Institute, The University of Michigan Medical School, USA, in the laboratory of Professor John B. Lowe where he has published several substantial papers related to *in vivo* role of mammalian glycosyltransferases. Since 1998 to 2005 he was a Research Group Leader at the Institute of Molecular Genetics in Prague. He has also worked as Visiting Scientist at the Department of Biochemistry and Molecular Biology of Oklahoma Center for Medical Glycobiology, College of Medicine, the University of Oklahoma, USA. He was a Participating Investigator of Consortium for Functional Glycomics, USA (2001-2008) and Member of Editorial Board (2001-2005) and Editor (since 2003) of the Czech Journal *"Biologicke listy"*. Since 2008, he has been working on development of combinatorial protein libraries derived from small protein scaffolds and construction of novel high-affinity protein binders with therapeutic and diagnostic potential.

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