

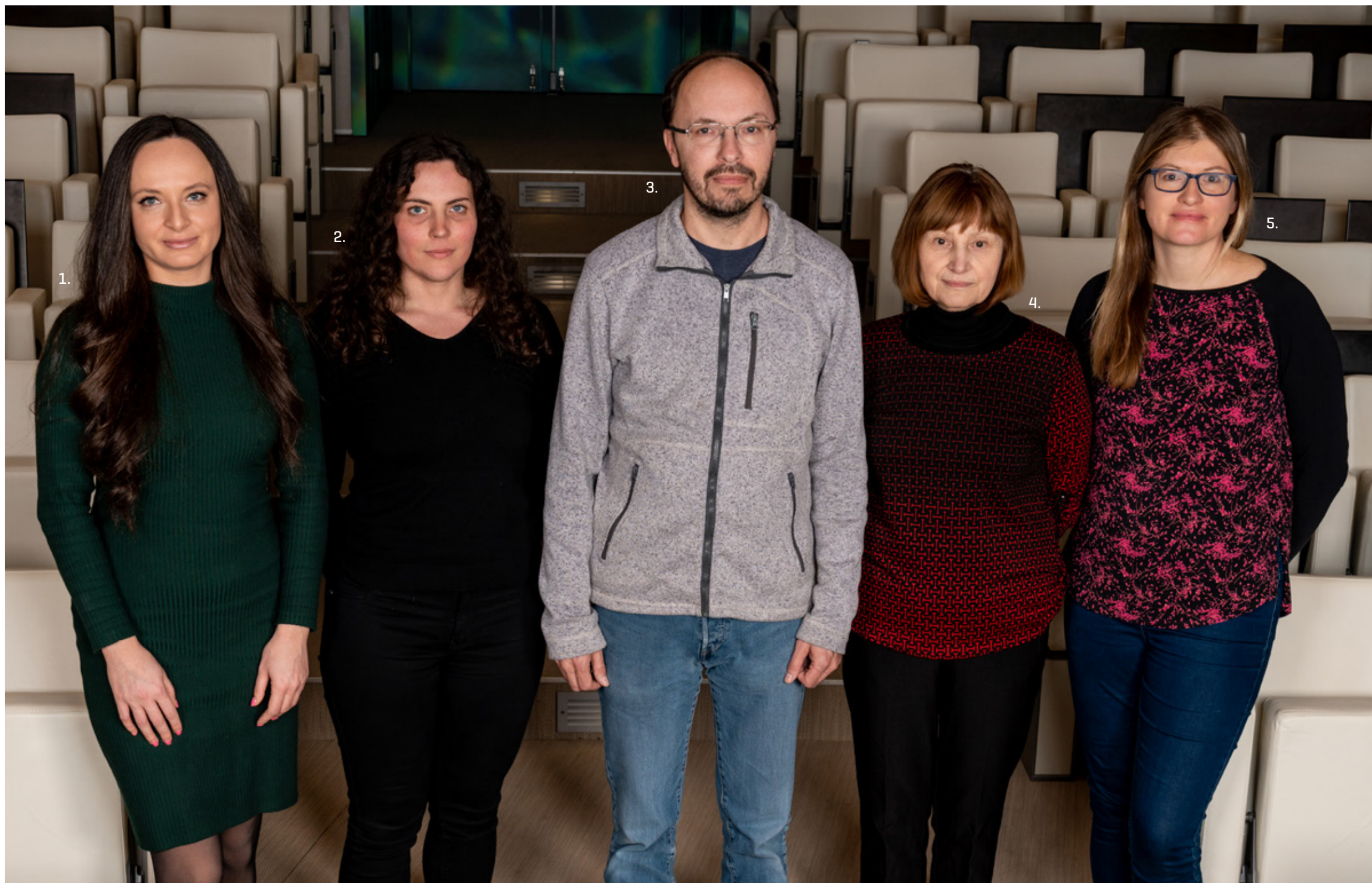


LABORATORY OF

LEUKOCYTE SIGNALLING

Leukocyte signal transduction, inflammation, immune response, autoinflammatory diseases, membrane adaptor proteins

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In the picture: 1. Pavliuchenko Nataliia | 2. Durić Iris | 3. Brdička Tomáš | 4. Angelisova Pavla | 5. Skopcová Tereza

The Laboratory of Leukocyte Signalling is studying the molecular mechanisms of how various leukocyte proteins regulate signal transduction by surface receptors and how their dysfunction triggers disease. Within this relatively broad field, our research focuses mainly on membrane adaptor proteins and Src-family kinases [SFK] and on their roles in inflammation and haematopoiesis.

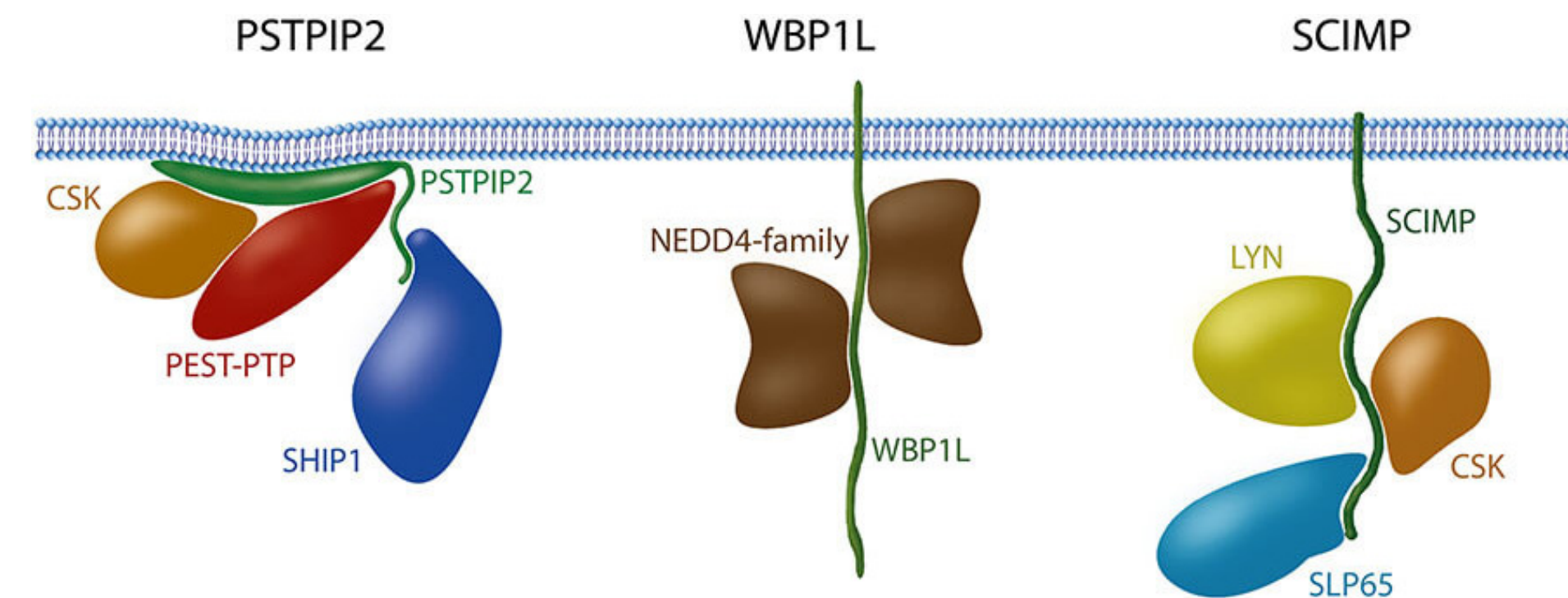
Membrane adaptor proteins are membrane-associated proteins, which are responsible for organizing networks of signalling molecules near cellular membranes. Some of these proteins have key roles in propagation of the signal generated by leukocyte surface receptors, while others have important regulatory functions. One of the most interesting membrane adaptors is known as PSTPIP2. Its deficiency in the mouse model leads to the development of chronic multifocal osteomyelitis. It is an autoinflammatory disease characterized by spontaneous bone and skin inflammation, which closely resembles several human disorders. We are studying the molecular mechanisms of how the complex of proteins organized by PSTPIP2 in neutrophil granulocytes regulates inflammatory processes and how its absence leads to impaired control of inflammation. Our most interesting discoveries include the finding

that dysregulated reactive oxygen species production by NADPH oxidase is specifically important for inflammatory bone damage in this disease and that the disease progression is very likely dependent on SFK and the receptors they regulate.

Another membrane adaptor protein we are extensively studying is WBP1L, aberrantly expressed in certain types of childhood leukaemia and potentially affecting the treatment outcome. We have found that WBP1L regulates haematopoiesis, in part via regulation of several key cytokine/chemokine receptors in haematopoietic stem and progenitor cells. We are currently analysing the molecular mechanisms of this regulation and its effects on the biology of the haematopoietic system.

Apart from membrane adaptors, we are also investigating the roles of Src-family kinases in leukocyte signalling and disease. Within this topic, we are analysing their roles in the regulation of antigen receptor signalling and mutations in their genes causing diseases in humans.

Finally, part of our team engages in research of the methods of detergent-free membrane disintegration and their utilization in the analysis of organization of plasma membrane lipids, membrane adaptors, and Src-family kinases into membrane nanodomains.



Examples of molecular signalling complexes organized by leukocyte membrane adaptors PSTPIP2, WBP1L, and SCIMP at cellular membranes.

Selected publications:

1. Pavliuchenko N, Duric I, Kralova J, Fabisik M, Spoutil F, Prochazka J, Kasperek P, Pokorna J, Skopcova T, Sedlacek R, and Brdička T*: Molecular interactions of adaptor protein PSTPIP2 control neutrophil-mediated responses leading to autoinflammation. *Front Immunol* 2022 13: 1035226.
2. Kralova J, Pavliuchenko N, Fabisik M, Ilievska K, Spoutil F, Prochazka J, Pokorna J, Sedlacek R, and Brdička T*: The receptor-type protein tyrosine phosphatase CD45 promotes onset and severity of IL-1 β -mediated autoinflammatory osteomyelitis. *J Biol Chem* 2022 297: 101131.
3. Kanderova V, Svobodova T, Borna S, Fejtikova M, Martinu V, Paderova J, Svatou M, Kralova J, Fronkova E, Klocperk A, Pruhova S, Lee-Kirsch MA, Hornofova L, Koblizek M, Novak P, Zimmermannova O, Parackova Z, Sediva A, Kalina T, Janda A, Kayserova J, Dvorakova M, Macek M, Pohunek P, Sedlacek P, Poh A, Ernst M, Brdička T*, Hrusak O*, and Lebl J*: Early-onset pulmonary and cutaneous vasculitis driven by constitutively active SRC-family kinase HCK. *J Allergy Clin Immunol* 2021 149(4): 1464-1472.
4. Kralova J, Drobek A, Prochazka J, Spoutil F, Fabisik M, Glatzova D, Borna S, Pokorna J, Skopcova T, Angelisova P, Gregor M, Kovarik P, Sedlacek R, and Brdička T*: Dysregulated NADPH Oxidase Promotes Bone Damage in Murine Model of Autoinflammatory Osteomyelitis. *J Immunol* 2020 204: 1607-1620.
5. Borna S, Drobek A, Kralova J, Glatzova D, Splichalova I, Fabisik M, Pokorna J, Skopcova T, Angelisova P, Kanderova V, Starkova J, Stanek P, Matveichuk OV, Pavliuchenko N, Kwiatkowska K, Pratty MB, Tomlinson MG, Alberich-Jorda M, Korinek V, and Brdička T*: Transmembrane adaptor protein WBP1L regulates CXCR4 signalling and murine haematopoiesis. *J Cell Mol Med* 2020 24: 1980-1992.