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Lisa Westerberg's group: <https://ki.se/en/mtc/lisa-westerberg-group>

### **Internship description**

This position will be based in Lisa Westerberg's group at Karolinska Institutet, Stockholm, Sweden.

Lisa Westerberg's group focuses on primary immunodeficiencies caused by mutations in actin cytoskeleton regulators such as the Wiskott-Aldrich syndrome protein (WASP) and Megakaryoblastic leukemia 1 (MKL1). The spatio-temporal activation of the immune system is essential for the efficient immune response and relies on actin cytoskeleton dynamics. The actin cytoskeleton is composed of actin filaments (F-actin) that are generated from the polymerisation of actin monomers (G-actin). Hundreds of proteins tightly regulate the polymerisation and depolymerisation of G-actin into F-actin. While WASp induces the formation of branched actin filaments, MKL1 senses cytoplasmic level of globular actin (G-actin). When actin polymerisation is stimulated, cytoplasmic G-actin level decreases and MKL1 is retained in the nucleus where it binds Serum Response Factor (SRF) to regulate the transcription of actin and actin-related genes.

It has recently been shown that a nonsense mutation in the MKL1 gene resulted in a loss of polymerised actin and impaired immune function in patient immune cells. These results highlight the importance of MKL1 in regulating the immune cytoskeleton and function.

The student will be involved in an on-going project aiming at studying the effect of mutations in WASp and MKL1 on the actin cytoskeleton of immune cells and will focus on Natural Killer cells and Cytotoxic T lymphocytes. The student will use genetically modify cell lines and primary cells and assess the impact of the mutations on the actin cytoskeleton and function of the cells by time-lapse microscopy, confocal microscopy, super-resolution microscopy and flow cytometry.

- Record J., Malinova D. *et al*: Immunodeficiency and severe susceptibility to bacterial infection associated with a loss-of-function homozygous mutation of MKL1. *Blood* 2015; 126 (13): 1527–1535. doi: [10.1182/blood-2014-12-611012](https://doi.org/10.1182/blood-2014-12-611012)
- Keszei M., Record J. *et al*: Constitutive activation of WASp in X-linked neutropenia renders neutrophils hyperactive. *J Clin Invest*. 2018 Aug 31;128(9):4115-4131. doi: [10.1172/JCI64772](https://doi.org/10.1172/JCI64772).
- Record J, Sendel A *et al*: An intronic deletion in megakaryoblastic leukemia 1 is associated with hyperproliferation of B cells in triplets with Hodgkin lymphoma. *Haematologica*. 2020 May;105(5):1339-1350. doi: [10.3324/haematol.2019.216317](https://doi.org/10.3324/haematol.2019.216317).