

# Looking for clinical biomarkers through the integration dynamic modelling and *omics* data in severe bacterial infections

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**Type of thesis:** Computational

**Required competences:** Basic statistics, Basic knowledge of R and possibly Python, Basic of dynamic modelling (differential equations)

**Acquired competences:** Dynamic modelling, Network analysis, Multivariate statistics, analysis of (metabol)omics data, Phenotyping of human metabolism.

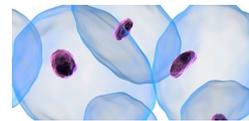
**Date:** 10-10-2019

## Description

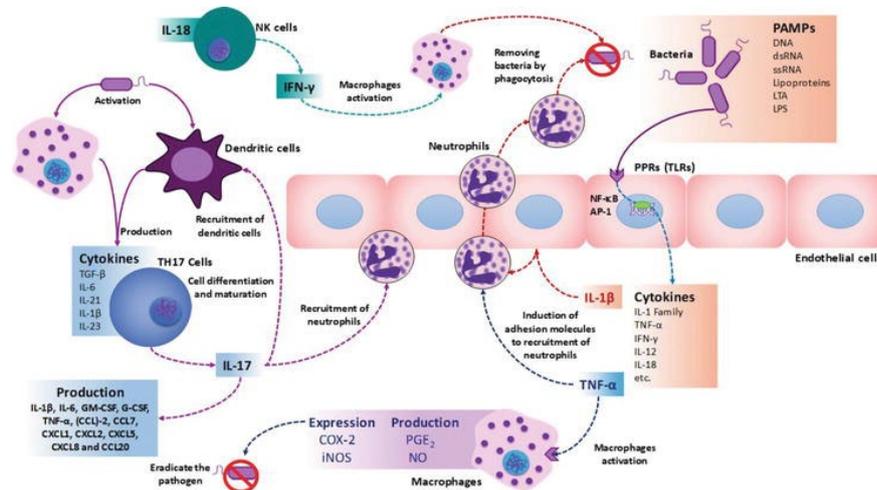
Early detection is crucial in Necrotizing Soft Tissue Infections (NSTI, sometimes called flesh eating bacterial infection), a devastating type of bacterial infection (Hansen, Rasmussen et al. 2017, Stevens and Bryant 2017). NSTI is becoming increasingly more common, and continue to be associated with a fulminant course and high mortality rates. These infections comprise a spectrum of diseases ranging from necrosis of the skin to life-threatening infections involving the fascia and muscle with systemic toxicity. They vary in predisposing and causative factors, anatomic location, offending bacteria, and tissue level of involvement.

Early diagnosis of necrotizing soft tissue infections is important for timely surgical intervention, but presenting physical exam findings can vary, so misdiagnosis is common.

A promising set of biomarkers is constituted by cytokines. Cytokines are very important in the host defense system, and play a critical role in protection against bacterial and viral infections. Cytokines are also involved in the pathogenesis and development of symptoms in infections. Exposure to micro-organisms commonly elicit



the production of cytokines. These soluble factors enhance several innate immune functions that aim to limit the spread of infection. Further, many of the pro-inflammatory cytokines regulate the ensuing specific immune response.

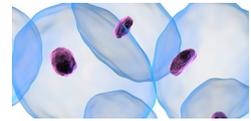


**Figure 1.** Cytokines profile in bacterial infections. In response to bacterial infection, the IL-1 family cytokines, such as IL-1 $\beta$ , potently induces the expression of adhesion molecules in the endothelial cells and promotes the recruitment of neutrophils to the site of inflammation. TNF- $\alpha$  plays an important role through the recruitment of neutrophils and macrophages, besides inducing the expression of proinflammatory mediators to the site of infection. Th17 cells produce IL-17A, which induces the production of inflammatory mediators such as IL-1 $\beta$ , IL-6, GM-CSF, G-CSF, and TNF- $\alpha$ , as well as adhesion molecules. IL-18 also promotes the secretion of other proinflammatory cytokines like TNF- $\alpha$ , IL-1 $\beta$ , IL-8, and GM-CSF and consequently enhancement, migration, and activation of neutrophils during infections. From (Muñoz-Carrillo, Cordero et al. 2018)

In addition to their effects on cells of the immune system, cytokines also are important regulators in the so called immune-neuroendocrine network. The microbial structures that are necessary for induction of cytokine production are not conclusively determined but in general, bacteria preferentially induce the production of IL-1, TNF-alpha, IL-6, and IL-8. The onset of production of these cytokines is rapid, and several of them may reach systemic levels during a short period after infection.

Thus, cytokines can serve as markers for ongoing infections and to discriminate among different type of infections.

Scope of the thesis is to identify critical molecular mechanisms underlying cytokine production release through the integration of existing dynamic models (base on ordinary differential equations) and cytokines profiles acquired on healthy subjects, patients



affected by The analysis will be complemented through the integration of gene expression data.

At the end of this project the student will have gain knowledge in (bio)logical network analysis, integration of different data type, modelling of individual responses and the analysis of large metabolomics data sets.

This project is collaboration with the Karolinksa Institut

## References

1. Hansen, M. B., L. S. Rasmussen, M. Svensson, B. Chakrakodi, T. Bruun, M. B. Madsen, A. Perner, P. Garred, O. Hyldegaard, A. Norrby-Teglund, I. s. group, M. Nekludov, P. Arnell, A. Rosén, N. Oscarsson, Y. Karlsson, O. Oppegaard, S. Skrede, A. Itzek, A. M. Wahl, M. Hedetoft, N. F. Bærnthsen, R. Müller and T. Nedrebø (2017). "Association between cytokine response, the LRINEC score and outcome in patients with necrotising soft tissue infection: a multicentre, prospective study." Scientific Reports **7**: 42179.
2. Muñoz-Carrillo, J. L., J. F. C. Cordero, O. Gutiérrez-Coronado, P. T. Villalobos-Gutiérrez, L. G. Ramos-Gracia and V. E. Hernández-Reyes (2018). Cytokine Profiling Plays a Crucial Role in Activating Immune System to Clear Infectious Pathogens. Immune Response Activation, IntechOpen.
3. Stevens, D. L. and A. E. Bryant (2017). "Necrotizing Soft-Tissue Infections." New England Journal of Medicine **377**(23): 2253-2265.