EDITOR'S CHOICE OF RECENT PAPERS FROM RADBOUDUMC RESEARCHERS

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Summary

With over 3,000 publications per year, scientific research is a cornerstone of the Radboud university medical center [1]. In this section, recent high-impact papers with an impact factor higher than five – published by researchers from the Radboudumc – will be discussed.

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Inhaled tigecycline is effective against *Mycobacterium abscessus in vitro* and *in vivo*

In collaboration with researchers at Colorado State University, Camron Pearce, with leading investigator Jakko van Ingen, PhD, published a new effective treatment of *Mycobacterium abscessus* (*M. abscessus*) tested both *in vitro* and *in vivo* in the Journal of antimicrobial chemotherapy (impact factor 4,940). *M. abscessus* is a bacterium that can cause severe, chronic, pulmonary infections in its host. The paper refers to *M. abscessus* as 'an antibiotic nightmare' as it is resistant to most classes of antibiotics, making treatment complex. Furthermore, the cure rate of this micro-organism is only 45%. This study explored whether *M. abscessus* pulmonary disease is treatable with 0.25, 1.25 and 2.5 mg doses of tigecycline in human macrophages inserted in mice for 28 days. Inhaled tigecycline proved to be highly effective against *M. abscessus* infection in GM-CSF (stimulating factor) knockout mice in a dose-dependent manner. Interestingly, the paper suggests that the effect of the inhaled tigecycline may have been underestimated in the mouse model experiment due to rapid degradation of the drug in aqueous environments. This inaccuracy means that the drug is expected to be even more effective than estimated in this study. From this study can be concluded that inhaled tigecycline could represent a viable treatment option for *M. abscessus* pulmonary disease, a disease where treatment outcomes are currently very poor. To proceed with this drug as a treatment for *M. abscessus* pulmonary disease infections, a stable and safe formulation is required to continue to further pharmacodynamic studies and, ultimately, clinical trials [2].

Catecholamines induce trained immunity in monocytes *in vitro* and *in vivo*

Catecholamine (e.g. noradrenaline and adrenaline) levels rise when an individual is subjected to stress, anxiety or pain. This explains the evolutionary function of catecholamines in the fight or flight response. Interestingly, high concentrations of catecholamines have also been found to be associated with a pro-inflammatory effect. Fellow researchers from the Radboudumc studied whether the pro-inflammatory effects of noradrenaline and adrenaline can in part be explained by the induction of immunological memory in innate immune cells, also known as 'trained' immunity. The rationale of this study is that it is known that exposure to high catecholamine levels is associated with inflammatory changes of myeloid cells (progenitor cell of various cells within the blood plasma) and atherosclerosis, but underlying mechanisms are only partly understood. Primary human monocytes were used, which are cells that are directly isolated from a biopsy and used for experiments. These monocytes were exposed to catecholamines, after which they differentiated into macrophages. Subsequently, these exposed macrophages were re-stimulated with lipopolysaccharide, an endotoxin. This re-stimulation showed that cells that were exposed to (nor)adrenaline had an increased tumour necrosis factor α (TNF-α) production. Furthermore, an *in vivo* study was performed on monocytes isolated from pheochromocytoma and paraganglioma patients, which are rare tumours that cause abnormal catecholamine levels in the blood. This study showed that catecholamines induce long-lasting pro-inflammatory changes in monocytes *in vitro* and *in vivo*. Research such as this helps us understand specific pathways that drive inflammatory changes which are characterised by catecholamine levels. In the end, the authors proposed that trained immunity underlies the increased cardiovascular event rate in certain patients. This paper was published in the Journal Circulation Research with an impact factor of 15,862 [3].

Assessment of placental disposition of infliximab and etanercept in women with autoimmune diseases and in the *ex vivo* perfused placenta

Various autoimmune diseases are known to affect women in their reproductive years, such as rheumatoid arthritis and inflammatory bowel disease. Infliximab and etanercept are TNF-α inhibitors that are used for the treatment of these autoimmune diseases in order to reduce inflammation. These therapies are increasingly applied to patients during pregnancy, even though little is known about their effect on the placenta and the foetus. Eliesen *et al.* from the Department of Pharmacology and Toxicology used both *in vivo* experiments and *ex vivo* placenta perfusion experiments to study the placental transfer of both these drugs. These experiments allowed greater insight into whether these drugs could pass the placental barrier and at which rate. This is important for the treatment of pregnant women since both the unborn child and the placenta could be negatively affected by the administration of the drug(s). In the placenta perfusion setup, the umbilical cord and a vein from a single cotyledon (functional unit foetal side of the placenta) are brought back into the circulation. With this technique, the drug concentration before and after passage through the placenta can be determined and the rate in which they pass the placenta can be calculated. In this study, they found that both drugs can be transferred into the cord blood and placenta, *in vivo* and *ex vivo*. However, tissue was exposed in a higher concentration to infliximab than etanercept, due to a higher transfer. In the future, it would be of interest to study the occurrence of placental TNF-α inhibition and what the possible consequences could be thereof. This research was published in the Journal of Clinical Pharmacology and Toxicology, a journal with an impact factor of 7,266 [4].

References

1. Radboudumc. Jaardocument 2018. (2018).
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3. Van Der Heijden, C., *et al.* Catecholamines Induce Trained Immunity In Monocytes In Vitro and In Vivo. *Circulation research* (2020).
4. Eliesen, G.a.M., *et al.* Assessment of Placental Disposition of Infliximab and Etanercept in Women With Autoimmune Diseases and in the Ex Vivo Perfused Placenta. *Clinical pharmacology and therapeutics* (2020).