RECENT HIGH-IMPACT 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 ten – published by researchers from the Radboudumc – will be discussed.

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Mutations in *TLR7* are associated with severe acute respiratory syndrome (SARS) in young male patients suffering from COVID-19

Severe acute respiratory syndrome is a life-threatening complication of the coronavirus disease 2019 (COVID-19) often requiring mechanical ventilation at the intensive care unit. When four males under 35 were admitted to the intensive care unit at Radboud and Maastricht University medical center, attention of the physician was caught, as the occurrence of this complication in young patients is rare and suggests a possible genetic component. Therefore, van der Made *et al*. analysed genetic variants in these four male patients that originated from two different families. The researchers performed whole-exome sequencing in the patients and compared the results with a control group. In all of the patients, a mutation in the X-chromosomal *Toll-like receptor 7* (*TLR7*) gene was found, albeit the mutations differed per family. In the first family, a four nucleotide hemizygous deletion, meaning that only one copy of the chromosome is present, was identified, leading to a total loss of function of TLR7 in both patients. Noteworthy, a heterozygous form of the deletion was observed in the mother. In the second family, a missense variant was found in *TLR7*. Furthermore, *TLR7* mRNA expression in peripheral blood mononuclear cells, derived from the patients, did not increase after stimulation with imiquimod, an agonist of TLR7. As TLR7 is involved in the generation of a type 1 interferon-γ response, these mutations will result in a diminished type 1 interferon-γ response. In addition, the fact that these mutations were detected on an X-chromosome bound gene could explain the observation that SARS is more frequent in male COVID-19 positive patients, as the male gender only has one X-chromosome. However, it is important to note that the detected hemizygous mutations are most likely quite rare. The question remains what the clinical effect of a heterozygous (carrier) mutation consists of, and if there are any genetic mutations associated with a mildly severe development of COVID-19. This research paper was published in the Journal of American Medical Association (impact factor 47.7) [2].

A phase I/IIa trial with a malaria vaccine using genetically attenuated *Plasmodium berghei*

Roestenberg *et al.* published a phase I/II clinical trial of a possible candidate vaccine against malaria in Science Translation Medicine (impact factor: 11.6). This is one of the first clinical trials using a live, genetically engineered strain of *Plasmodium berghei*, which is a malaria strain that causes malaria in rodents. A knock-out variation of this strain was created, lacking two proteins that are crucial for the development and growth of the sporozoites of *Plasmodium berghei* in the liver. This clinical trial consisted of phase I stage (n=19), assessing the safety of different dosages of the vaccination and a IIA stage (n=48) to establish the immunological effect and preliminary efficacy of the different doses. In order to assess the safety, the volunteers of the first group received three possible different doses of the vaccination or a placebo, with a follow-up lasting 100 days. The volunteers in the second group received the same varying dosages or placebo as the first group, after which a controlled human malaria infection (CHMI) was administered. The total follow-up in this group lasted 321 days. No serious side-effects were found in either group. The volunteers in the stage IIa-group receiving the lowest dose of the vaccination all developed parasitemia after CHMI. This pattern was seen as well for the volunteer group receiving the higher dosages, in which the majority also developed parasitemia. Nevertheless, 10% and 20% remained sterile, in the two groups receiving the highest dosages. All of the immunised volunteers showed an increase in antibody titers and an increase in interferon-γ-producing CD4+ and CD8+ T-cells, although only 35% and 32% of all volunteers were full responders in the production of CD4+and CD8+ T-cells, respectively. This clinical trial was one of the first to use a live genetically attenuated vaccine and proved that this could be administered safely, although further research is needed to truly establish and increase its efficacy [3].

Dolutegravir as a possible alternative to standard antiviral therapy in the third trimester of pregnancy in HIV positive women

The antiviral medication efavirenz is the current first-line treatment for human immunodeficiency virus (HIV) infection, although dolutegravir, an integrase inhibitor, has shown to lower the viral load in a significantly shorter time than efavirenez. However, the safety and efficacy of dolutegravir in pregnant, HIV-positive women, has not been evaluated properly. Therefore, Kintu *et al.*, part of an international consutim of scientists, published their clinical trial evaluating the use of dolutegravir as antiviral therapy in pregnancy in Lanclet HIV (impact factor: 14.8). A total of 268 pregnant HIV-positive women from Uganda and South-Africa, ranging from 29 to 34 weeks pregnant without prior treatment with antiviral therapy, were recruited. The volunteers received either dolutegravir or efavirenz, with a follow-up lasting until zero to fourteen days postpartum. With a median exposure time of 28 days needed to decrease viral loads to less than 50 copies per mL (95% confidence interval (CI) 28-34 days), dolutegravir was more efficient than efavirenz, which needed a median exposure time of 82 days to lower viral loads under 50 copies per mL (95% CI 55-97). The difference was smaller when looking at median time needed to decrease viral loads to less than 1000 copies per mL. The median exposure time needed was seven days in the dolutegravir group (95% CI 7-20) and 23 days in the efavirenz group (95% CI 21-27). More adverse effects occurred in the dolutegravir group in comparison to the efavirenz group, as 22% of women receiving dolutegravir and 14% of women receiving efavirenz developed at least one or more serious side-effect (p<0.013). However, in three volunteers treated with dolutegravir, *in utero* mother-to-child transmission of HIV occurred. Nonetheless, no significant difference was observed when looking at drug-related adverse effects. Therefore, in general, the medications were well tolerated. This research has provided the first step towards a possible new standard therapy for all patients with HIV, including HIV-positive women in late pregnancy [4].

References

1. Radboudumc. Jaardocument 2018. (2018).
2. Van der Made, CI., Simons, A., Schuurs-Hoeijmakers, J., Van den Heuvel, G., Mantere, T. et al. Presence of Genetic Variants Among Young Men With Severe COVID-19. *JAMA* **324**, 663-73 (2020).
3. Reuling, IJ., Mendes, AM., De Jong, GM., Fabra-García, A., Nunes-Cabaço, H. *et al.* An open-label phase 1/2a trial of a genetically modified rodent malaria parasite for immunization against Plasmodium falciparum malaria. *Science Translational Medicine* **12**, 2578 (2020).
4. Kintu, K., Malaba, TR., Nakibuka, J., Papamichael, C., Colbers, A., et al. Dolutegravir versus efavirenz in women starting HIV therapy in late pregnancy (DolPHIN-2): an open-label, randomised controlled trial. *The Lancet HIV* **7**, 332-9 (2020).