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Can electroporation push the cancer immunotherapy even further?

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Immunotherapy for cancer treatment has shown remarkable results in the last years, especially in some of the most aggressive cancer types, such as melanoma, where more than 20 % of patients receiving adjuvant immunotherapy survive more than 5 years – a result previously unheard of. Immunotherapy is a broad category of cancer therapies designed to stimulate the body's immune system to better recognize and fight cancer. The best results are currently achieved with so-called immune checkpoint inhibitors that work by disrupting the cancer cells' signals telling the immune system that they are normal cells, consequently exposing the cancer cells for attack from the immune system. Currently, the majority of these immunotherapies are based on antibodies targeting either Cytotoxic T-lymphocyte antigen 4 (CTLA-4), Programmed death-ligand 1 (PD-L1), or Programmed cell death protein 1 (PD-1). Of a note, the discovery of therapies targeting these three immune checkpoints was awarded the 2018 Nobel Prize in Physiology or Medicine. Although, these therapies are effective, and a large proportions of patients respond favourably, there are still some that do not. Moreover, because they are given systemically they can cause immune cells to attack healthy cells resulting in severe adverse effects. Lastly, the cost of these immunotherapies, due to the production requirements of the antibodies, can reach over 100.000 € per patient per year which puts them amongst the most expensive therapies currently on the market.

The team led by Dr Kevin Hollevoet from Laboratory for Therapeutic and Diagnostic Antibodies, KU Leuven has realized that electroporation, specifically gene electrotransfer of plasmid DNA coding for antibodies against immune checkpoints into tissues and tumours, could resolve some of the major issues with current immunotherapies targeting immune checkpoints. With their approach the costs of therapies could be substantially reduced, and even more importantly, due to the local delivery of the plasmid DNA, the majority of severe adverse effects caused by systemic exposure to therapeutic antibodies could be evaded.

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The team has recently published their findings in a high impact journal Molecular Therapy (Jacobs et al., 2020)* where they show the effectiveness of gene electrotransfer of plasmid DNA coding for antibodies against CTLA-4 and PD-1 into muscles and tumours for treatment of murine colon carcinoma. They have successfully created plasmid DNA that upon delivery into the cells by electroporation alters them to start producing anti-CTLA-4 or anti-PD-1 antibodies, a task that can usually be done only by specialized immune cells called B lymphocytes. With this approach, the team of Dr Hollevoet shoved that muscles as well as tumours can be successfully transfected, becoming a body's own antibody factory. In case of muscles, this production of antibodies can last for at least 6 months, which would – in case of cancer immunotherapy – circumvent the need for repetitive dosing of systemically given antibodies, thus substantially reducing the cost of immunotherapy. In either cases, transfecting muscles or tumours, a good anti-tumoral effect was also achieved. Moreover, in case of muscle transfection, a prophylactic action of the expressed antibodies was also detected, implying that this approach could also have an anti-metastatic action.

Dr Hollevoet and his team are now pursuing this approach further through collaboration with the Faculty of Health Sciences from University of Ljubljana, and Department of Experimental Oncology from the Institute of Oncology Ljubljana. In this collaboration the teams led by Dr Kevin Hollevoet and Prof Gregor Serša joined their forces to obtain funding from the Central Europe Leuven Strategic Alliance (CELSA), in order to further develop this promising approach and explore new avenues how it could be combined with standard cancer therapies.

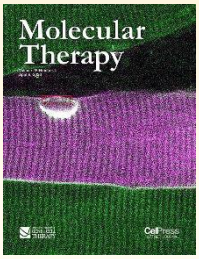
*Jacobs L., De Smidt E., Geukens N., Declerck P., and Hollevoet K. (2020). DNA-Based Delivery of Checkpoint Inhibitors in Muscle and Tumor Enables Long-Term Responses with Distinct Exposure. Mol Ther. DOI: 10.1016/j.ymthe.2020.02.007.

Forthcoming events

7th School on Pulsed Electric Field Applications in Food and Biotechnology
Zaragoza, **new dates**: September 7 – 11, 2020
http://pefschool2020.electroporation.net/

8th European Medical and Biological Engineering Conference – EMBEC 2020
Portorož, **new dates**: November 29 – December 3, 2020
http://embec2020.org/

Electroporation-Based Technologies and Treatments
Ljubljana, November 15 – 21, 2020
http://2020.ebtt.org



Read the article in the current (Vol. 28, No. 4) issue of the journal Molecular Therapy, DOI: https://dx.doi.org/10.1016/j.ymthe.2020.02.007

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