

# Viro-immunotherapy for Triple Negative Breast Cancer

Investigator

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## **Abstract**

Triple negative breast cancer (TNBC) is the most aggressive type of breast cancer with the poorest prognosis. Chemotherapy is used for the treatment of patients with metastatic TNBC. However, patients often develop resistance to chemotherapies and recurrence of cancer is common after initial response. Hence, there is an urgent need for improved therapies. We believe that an optimal therapeutic should not only eradicate tumors but also prevent tumor recurrence. Immunotherapy has shown unprecedented long-lasting efficacy in several types of malignancies. Therefore, we propose to study a novel therapeutic approach called “viro-immunotherapy”, which is a combination of two novel therapeutic approaches: Oncolytic virotherapy and Immunotherapy. Oncolytic viruses are live viruses “tamed” to replicate in and kill cancer cells while leaving normal cells unharmed. We have generated an artificial oncolytic poxvirus (CF33) that is very potent in killing breast cancer cells. This virus can further be armed with immune-stimulatory genes to act as immunotherapy for better treatment of TNBC.

Central hypotheses: We hypothesize that a chimeric poxvirus (CF33) can be engineered to selectively replicate in and kill triple negative breast cancer cells. Furthermore, the virus can be modified to produce two immune-stimulatory proteins, LIGHT and IL-15, which can further increase anti-tumor effectiveness of the virus by provoking anti-tumor immune response. Finally, virally produced immune-stimulatory proteins will prevent the cancer from recurrence by long-term maintenance of cancer-specific memory immune cells. The general methodology: We have already created a potent oncolytic poxvirus (CF33) that can kill triple negative breast cancer cells. We have also armed this virus with the immune-stimulatory genes LIGHT and IL-15 (CF33-LIGHT-IL-15). We will explore safety and anti-tumor efficacy of CF33-LIGHT-

IL-15 in mouse models. Innovative elements and potential impacts: The main innovation of this project is the development of a next-generation immunocytolytic virus that combines the direct cancer killing ability of a chimeric poxvirus with enhancement of anti-tumor immunity through immune-stimulatory proteins produced by the virus. Our innovative project has the potential of developing a novel therapeutic for improved treatment, with less resistance and recurrence, of TNBC.

## **Progress Report Abstract**

Our working hypothesis was that an oncolytic poxvirus (CF33) modified to make 2 immune-stimulatory proteins (mLIGHT and interleukin-15 or IL-15), could specifically kill cancer cells and optimally activate immune system to eliminate cancer. We first inserted the gene for mLIGHT protein in the CF33 to make CF33-mLIGHT. The next step was to insert gene for IL-15 in this virus to get the doubly-armed virus (CF33-mLIGHT-sIL15). However, it was challenging to insert the gene for IL-15 in CF33-LIGHT to get the doubly-armed virus (CF33-mLIGHT-sIL15). Therefore, for initial studies we decided to study the efficacy of the singly-armed viruses (CF33-mLIGHT and CF33-sIL15) in combination. In the murine TNBC model (E0771), the combination treatment significantly increased survival of tumor bearing mice, however, the anti-tumor efficacy in terms of tumor regression was only moderate. The viruses were more potent against TNBC tumors of human origin in immune-compromised mice.

After trying different strategies of virus construction, we were able to finally construct the doubly-armed virus (CF33-mLIGHT-sIL15). After construction of this virus, we first confirmed the ability of this virus to produce the immunomodulatory proteins (mLIGHT and IL-15) in cultured cancer cells. Next, we tested the anti-tumor efficacy of this virus in the mouse TNBC model (E0771). Because immune checkpoint inhibitors such as PD-1 have shown impressive therapeutic efficacy in many tumor types, we also combined our oncolytic viruses with anti-PD-1 to study their combined therapeutic efficacy. While the virus as a single therapeutic agent showed minimal therapeutic advantage, combination of anti-PD1 with the doubly-armed virus (CF33-mLIGHT-sIL15)

showed the highest therapeutic efficacy with complete tumor regression in 4 out of 9 treated mice. Our study suggest that this virus may work well in combination with checkpoint inhibitors. In future, we plan to test our virus in combination with PD-1 and other checkpoint inhibitors in different models of TNBC.

## Publications

Publication Type	Publication Title	Identifier	Authors	Publication Year	Publication Status
Journal Article	A comprehensive preclinical study supporting clinical trial of oncolytic chimeric poxvirus CF33-hNIS-anti-PD-L1 to treat breast cancer	<a href="https://doi.org/10.1016/j.omtm.2021.12.002">https://doi.org/10.1016/j.omtm.2021.12.002</a>	Shyambabu Chaurasiya Annie Yang Zhifang Zhang Jianming Lu Hannah Valencia Sang-In Kim Yanghee Woo Suanne G. Warner Tove Olafsen Yuqi Zhao Xiwei Wu Seymour Fein Linda Cheng Maria Cheng Nicholas Ede Yuman Fong	2022	Published
Journal Article	Viroimmunotherapy for breast cancer: Promises, problems and future directions		Shyambabu Chaurasiya & Yuman Fong	2021	