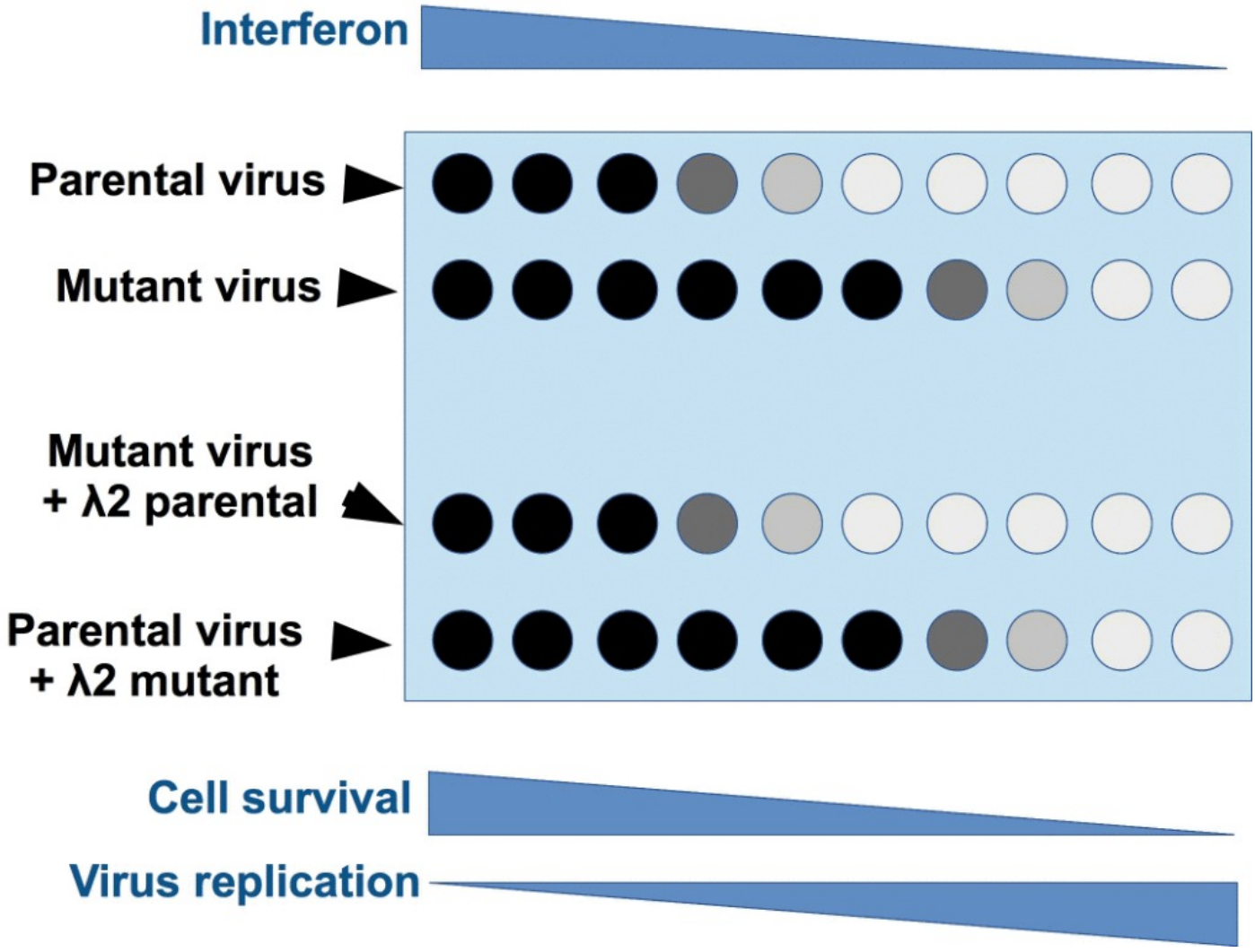
A novel reovirus mutant: toward the next generation of viruses for cancer treatment?

In the last decade or so, it has been realized that viruses are not only foes to fight, but possible therapeutics against diseases such as cancer. Most of these so-called *oncolytic viruses* are engineered to acquire desirable properties: preferential infection, replication or propagation in cancer cells, or preferential killing of these cells. In contrast, mammalian reovirus is among the few viruses naturally exhibiting an oncolytic activity. It also presents the added advantage of not being associated with any known human disease. However, even though clinical trials have generated promising results in cancer treatment, it cannot be excluded that mutant virus could become more selective toward tumor cells or more potent in their ability to kill them.



The interferons are small molecules produced by virus-infected cells as a first line of defense against viruses. The *interferon response* of infected cells is one important factor that could

determine both the fate of the infected cells and the ability of the virus to propagate to other cells. However, cancer cells are often deficient in their ability to secrete interferons or to be protected against viruses in the presence of interferons. The sensitivity of a given virus to interferon response could thus be critical in determining its ability to preferentially infect, replicate in, or destroy cancer cells. With this idea in mind, a chemical mutagenesis approach was initially used in our laboratory to isolate a reovirus mutant exhibiting increased sensitivity to interferon.

In the present study, sequencing of the nucleic acids that constitute the viral genetic material of this mutant (the viral genome) revealed mutations in 4 out of 10 viral genes. A powerful technique called *reverse genetics* then allowed to examine the importance of each of these mutations by separately introducing them in the viral genome. It turns out that introduction of the mutant gene for the ?2 protein is sufficient to confer interferon sensitivity to the parental virus and reciprocally. This is schematically illustrated below. Addition of relatively small concentrations of interferon to wells containing infected cells is sufficient to block virus replication and protect the cells with the mutant (or a parental virus harboring the mutant ?2); surviving cells being stained in the wells. Higher concentrations are required for the same effect on the parental virus (or the mutant harboring the parental ?2).

The ?2 protein was previously suspected of a role in determining sensitivity of reovirus to interferon response but this has never as clearly shown as in the present study. Furthermore, our work allowed to identify a mutation that can significantly alter interferon sensitivity while allowing replication of the virus. The change to the ?2 protein, consecutive to this mutation, is consistent with an effect on the synthesis of the so-called *cap structure* of the viral nucleic acid. Further work will be needed to confirm that it is actually the case. Furthermore, other reovirus genes are also known, or are suspected, to control interferon response upon viral infection or sensitivity of the virus to this response. We thus believe that combining different mutations could allow to generate a panel of viruses varying in interferon sensitivity. Those viruses could then be further examined for their ability to exert an oncolytic activity against various cancer cell types, depending on the exact interferon response of these cells. This could eventually allow to examine if some of them could be adequate for the development of second-generation oncolytic viruses.

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Publication

A single amino acid substitution in the mRNA capping enzyme ?2 of a mammalian orthoreovirus mutant increases interferon sensitivity.
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