Repurposing of Kinase Inhibitors to Fight the Flu – MEK Inhibitors Efficiently Block Influenza Virus Replication in Mice with a Prolonged Therapeutic Window

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Influenza A virus (IAV) infection results in the activation of a variety of intracellular signaling responses. IAV exploit some of these activities to support efficient replication. This dependence of IAV on cellular signaling factors provides opportunities for a novel antiviral strategy that targets essential host factors instead of viral components.

We have identified the cellular mitogenic Raf/MEK/ERK kinase cascade to be suitable for antiviral intervention. We have employed several inhibitors, which block the pathway on the level of MEK and that are under advanced clinical evaluation or even licensed for clinical use for other diseases. We have analyzed their antiviral potential on a broad range of influenza viruses in vitro and in vivo, including studies on resistance development and therapeutic treatment window, and have unraveled their antiviral mode of action.

We could demonstrate that inhibition of this pathway efficiently blocked virus replication in cells and animals. MEK inhibitors are now under advanced clinical evaluation or even licensed for clinical use for other diseases. We show that these novel signaling blockers (a) efficiently inhibit influenza virus replication *in vitro* and *in vivo*, (b) are broadly active against all influenza A and B viruses analysed so far, (c) are active against oseltamivir resistant viruses, (d) are not toxic for cells or animals in the concentration and time line used, (e) display an enhanced therapeutic window compared to standard of care, and (e) confirm the postulated mode of action: blockade of the export of viral genomes from the nucleus.

Repurposing of clinically tested MEK inhibitors is a promising approach to develop safe and efficient anti-influenza viruses with a prolonged treatment window and a high barrier towards development of resistance.