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Recombinant viruses that replicate in response to specific biochemical signals

Stanford researchers have designed an oncolytic virus that replicates only within cells that are driven by hyperactive biochemical signals, such as constitutively active kinases driving and maintaining tumors, which can minimize off-target activity and support higher dosing. The only currently approved viral therapy, T-vec (Talimogene laherparepvec), suffers from off-target effects that limit its use to intratumoral injection, toxicity to normal tissues, and limited antitumor efficacy. Other viral treatments under development suffer from the same limitations of off-target toxicity and lack of on-target efficacy.

The Lin Lab integrated a synthetic signaling construct (ErbB-RASER) that drives activity only in the presence of constitutively active ErbB, a kinase mutated to be hyperactive in numerous cancer types. ErbB-RASER by design does not block ErbB but it re-directs the signal activity to therapeutic response which reduces the occurrence of the resistance. The construct was integrated into the vesicular stomatitis virus (VSV), where only ErbB-positive cells replicated the virus, with specific cell-killing ability across breast, ovarian, and pancreatic cancer cells. Research is ongoing.

This technology for controlling viruses from the Lin Lab is the only engineered method for controlling viral replication based on hyperactive biochemical signaling in cancer cells.

Stage of Development
Research *In Vitro*

Applications

- Targeted cancer therapy
- Oncolytic viral therapy

Advantages

- Greater specificity and antitumor efficacy than existing oncolytic viruses
- Minimizes off-target toxicity
- Retains wild type signaling from mutated kinases

Publications

- Chung, H. K., Zou, X., Bajar, B. T., Brand, V. R., Huo, Y., Alcudia, J. F., Ferrell Jr., & Lin, M. Z. (2019). A compact synthetic pathway rewires cancer signaling to therapeutic effector release. *Science, 364*(6439), eaat6982. DOI: 10.1126/science.aat6982

Patents

- Published Application: WO2023077009

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