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Recombinant viruses that replicate in response to specific biochemical signals

Engineered viruses have great potential as cancer treatments. However, the only currently approved viral therapy, T-vec (Talimogene laherparepvec), suffers from off-target effects that limit its use to intratumoral injection. In addition, it is attenuated to reduce its toxicity to normal tissues, which also limits its antitumor efficacy. Other viral treatments under development suffer from the same limitations of off-target toxicity and lack of on-target efficacy.

Researchers at Stanford 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 tumor, which can minimize off-target activity and enable higher dosing. Inventors from the Lin lab have 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.

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.

Applications

- Targeted cancer therapy

- Oncolytic viral therapy

Advantages

- Greater specificity than existing oncolytic viruses
- 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
- Lin, M. Z., Zou, X., & Chung, H. K. (2023). *U.S. Patent Application No. 63/272,515,*

Patents

- Published Application: WO2023077009

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