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A Novel Method for Detecting Lytic Human Herpesvirus 6 in T cell Therapies to Identify Patients at Risk of Encephalitis and Enable Safety Screening of T cell Products

Stanford scientists have developed a method to detect reactivated human herpesvirus 6 (HHV-6) in T cell therapies using genomics technologies, including single-cell sequencing. Detecting lytic herpesvirus 6 in T cell therapies can identify patients at risk of encephalitis and assist in ensuring the safety of T cell products.

Cell therapies have yielded durable clinical benefits for patients with cancer but have been accompanied by unexpected side effects. For instance, approximately 1 in 40-100 patients who undergo CAR T cell therapy suffer from HHV-6 encephalitis. Unexpectedly, the source of the lytic HHV-6 virus can come from the cell therapy itself. Therefore, the detection of lytic HHV-6 in T cell therapies can serve as a diagnostic tool to identify patients at risk of encephalitis and as a safety screening method for T cell products.

Using single-cell sequencing, a rare polyclonal population of HHV-6 'super-expressors' (~1 in 360-10,000 cells) that possess high viral transcription and lytic activity late in chimeric antigen receptor (CAR) T cell culture were identified in vitro. Further, through the reanalysis of single-cell sequencing data from FDA-approved cell therapy products, the presence of CAR+, HHV-6+ super-expressor T cells were detected in vivo. Together, this implicates the T cell therapy as a potential source of lytic HHV-6 reported in multiple clinical trials and has broad implications for the design, screening, and diagnosis of unexpected toxicities in cell therapies.

Stage of Development:
Preclinical – in-vivo data

Applications

- Identification of patients likely to develop HHV-6 encephalitis who receive T cell therapies
- Safety screening autologous and allogenic CAR T cells for HHV6 virus in vitro for HHV-6 via genomics technologies
- Screening of patient samples to detect HHV6 in cells, including the cell therapies, *in vivo*

Advantages

- In cell therapies, there is no standard / routine screening for HHV-6, so this represents a significant conceptual advance
- Utilizes standard / widely-available tools (experimental and computational) to identify HHV6 expression in cells
- Uses easily-adoptable molecular biology reagents (including genomics tools) and informatics pipelines with custom downstream analyses to confidently call HHV6 expression.

Publications

- Lareau, C. A., Yin, Y., Maurer, K., Sandor, K. D., Daniel, B., Yagnik, G., ... & Satpathy, A. T. (2023). Latent human herpesvirus 6 is reactivated in CAR T cells. Nature, 623(7987), 608-615.

Patents

- Published Application: WO2024035951

Innovators

- Caleb Lareau
- Ansuman Satpathy

Licensing Contact

Minxing Li

Licensing and Strategic Alliances Manager

Email