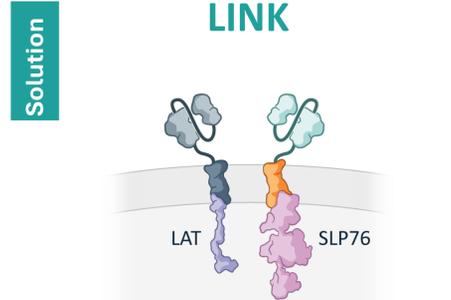


# Discovery, Validation, and Biomarkers Strategy for Clear Cell Renal Cell Carcinoma (ccRCC) Directed Dual-Targeting AND-Gated CAR (LNK001)

Bryan A Smith<sup>1</sup>, Colin Farrell<sup>1</sup>, Angeles Estellés<sup>1</sup>, Janette E Sutton<sup>1</sup>, Zeynep C Wheeler<sup>1</sup>, Kazuteru Hasegawa<sup>1</sup>, Benjamin Bauer<sup>1</sup>, Jakob McBroome<sup>1</sup>, Diego A Vargas-Inchaustegui<sup>1</sup>, Regina J Lin<sup>1</sup>, Mark Wallet<sup>1</sup>, and Alexander J Bankovich<sup>1</sup> <sup>1</sup>Link Cell Therapies, Inc.

## LINK exploits downstream TCR signaling machinery to optimize and customize CAR T cell responses

**Problem**  
Limited number of tumor-specific antigen targets

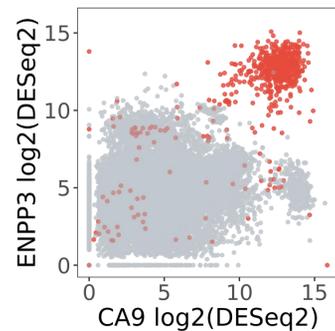


**Solution**  
**LINK**  
Safety of chimeric antigen receptor (CAR) targets, such as CA9, in solid tumors can be compromised by target expression in normal tissues (Lamers et al., 2013 Mol Ther). High-fidelity AND-gated CAR T cells (LINK CAR T) can overcome this issue by co-opting the combined downstream T cell signaling proteins, SLP76 and LAT (Tousley et al., 2023 Nature). LINK CARs will only exhibit cytotoxic activity when both antigens are present, sparing healthy tissue with single target expression. Here we de-risk CA9, a target for clear cell renal cell carcinoma (ccRCC) by identifying a second target antigen ENPP3 which displays high tumor-specific expression, with a different subset of healthy tissue liabilities. Combined, co-expression of these antigens is limited to ccRCC tumor. Targeting both antigens with LINK CAR T cells eliminates on-target, off-tumor toxicity and potentially could be a safe and efficacious therapeutic.

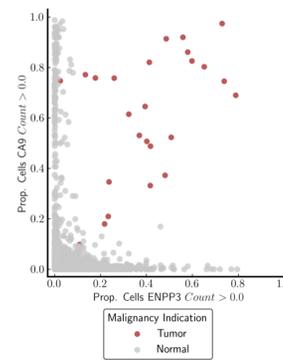
Rapid and direct Boolean logic AND-gating

## LNK001 targets are highly selectively and co-expressed in ccRCC (bulk RNA and scRNA-seq), but not in normal tissues

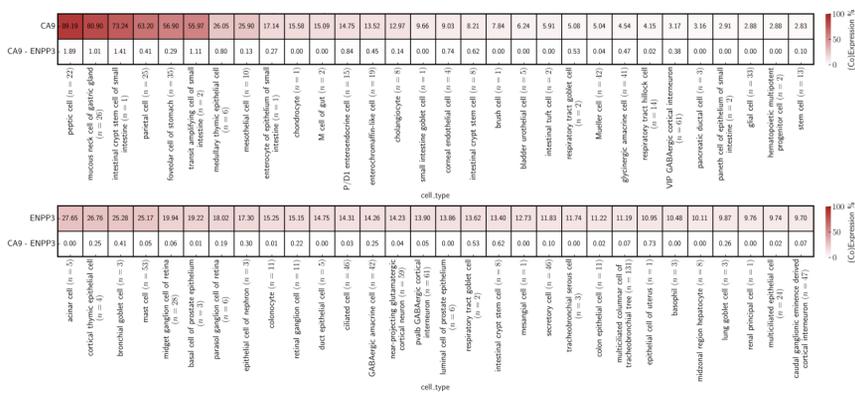
**Transcriptomics ccRCC & normal bulk RNA**



**Transcriptomics single cell RNA-seq**

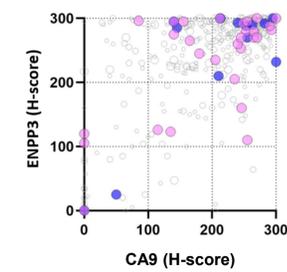


**scRNA-seq showing highest single target expression and co-expression on normal tissue**

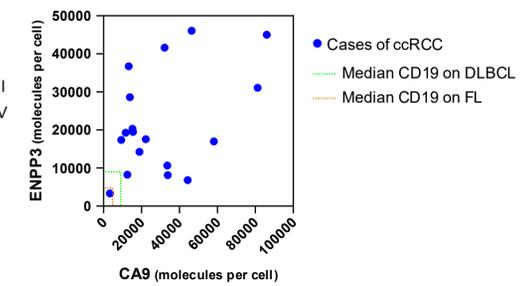


## LNK001 targets are highly co-expressed in ccRCC (IHC and flow cytometry) supporting a potential biomarker strategy

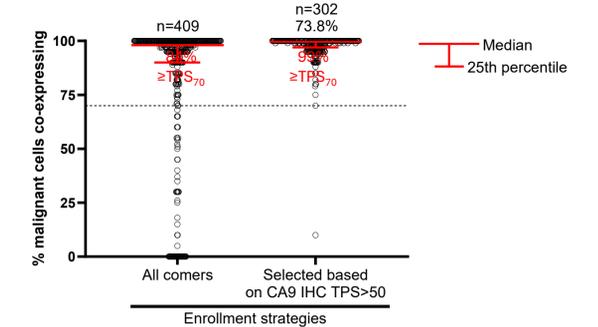
**IHC (ENPP3xCA9) 409 ccRCC cores**



**Flow cytometry (FC) 18 fresh ccRCC samples**

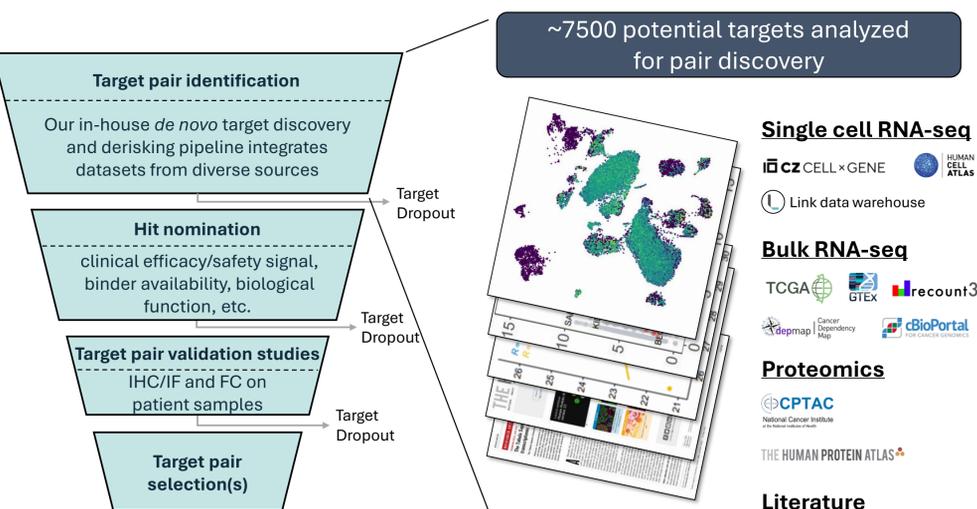


**IHC analysis of 409 ccRCC cores**

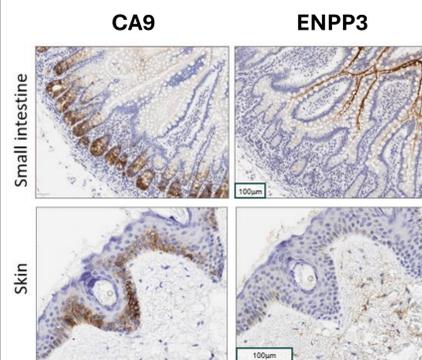


## Target pair selection pipeline

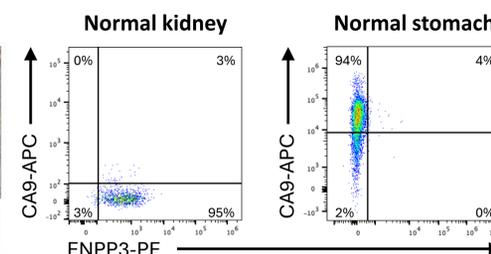
~7500 potential targets analyzed for pair discovery



**Histology Normal tissues**



**Flow cytometry (FC) Normal tissues**



## LINK AND-gate expands the target opportunity when enhanced with proprietary discovery efforts

- We have advanced a fundamental discovery on the LINK AND-gate into a clinical candidate
- To identify targets, we built a robust pipeline, which leverages the best qualities of RNA and protein measurement to identify exquisite target pairs
- We have begun to advance this system into new indications internally and as partnered research plans

## Disclosures

All authors are employees of Link Cell Therapies and hold equity in the company. Many authors are on patents related to this work.