Washington University in St. Louis
Office of Technology Management

POTENT, LOCALLY-ACTING CHEMOKINE BINDING PROTEINS TO PROTECT ORGAN TRANSPLANTS AND TREAT ISCHEMIC OR INFLAMMATORY DISEASES

Fremont, Daved, Lu, Yun Hsuan, Lubman, Olga

Miller, Qian

T-017443

Researchers in Prof. Daved Fremont's laboratory have identified two potent, soluble proteins that could prevent damage to transplanted organs and potentially treat other autoimmune and inflammatory diseases by evading the immune response instigated by chemokines.

In organ transplants, chemokines act as a danger signal to recruit immune cells to the transplanted tissue. This aggravates ischemia reperfusion injury (IRI) and could result in the organ being rejected. The process can be evaded by blocking chemokines, but systemic immune suppression has serious side effects. These chemokine binding proteins, R17 and T17, could potentially prevent organ damage and rejection while avoiding those systemic effects because not only do they act as decoy receptors for a wide array of chemokines, they also remain at the site of the transplant by selectively binding to cell surface markers (glycosaminoglycans, "GAGs"). R17 and T17 are derived from rodent herpesviruses and can potently sabotage chemokine-mediated immune surveillance with chemokine binding affinities 10-1000 fold higher than naturally occurring receptors. This immune evasion strategy could be used in organ preservation solutions to protect solid organs prior to transplant or prevent IRI and rejection of organs, tissues of cells after transplant. In addition, R17 or T17 could potentially be used more broadly in other chemokine-related disorders such as ischemic heart disease or inflammatory disorders.

Stage of Research

- *In vitro validation* – The inventors characterized the chemokine binding profile of these proteins and demonstrated that they also bind to cell surface glycosaminoglycans (GAGs). In addition, they showed that T17 blocks chemotaxis of human T cells and monocytes.
- *In vivo* - Using a mouse model for lung transplant, the inventors demonstrated that treating donor lungs with R17 protein sharply reduced ischemia reperfusion injury immune response in recipient mice.

Disease Indication/Applications

- **Organ preservation –** chemokine decoy receptors could be used in organ preservation solutions for preconditioning to prevent damage from ischemia reperfusion injury (IRI) by blocking chemokine effects that lead to rejection
- **Transplant immunosuppression –** prevent inflammation and rejection of solid organ, tissue, stem cell and embryonic stem cell transplants
- **Ischemic heart disease –** prevent or treat post myocardial infarction ischemic heart disease
- **Immune/inflammatory disease** – immunomodulation by blocking chemokines could be used to treat a range of inflammatory and autoimmune diseases

Key Advantages

- **Local immunosuppression - t**hese decoy receptor proteins bind to selective cell surface markers as well as chemokines, therefore they are likely to remain near the graft/tissue and avoid systemic side effects
- **Broad, potent activity:**
  - decoy receptors are expected to prevent a wide array of early immune response events because they recognize a diverse range of chemokine families (CXC, CC and C)
  - binding affinities 10-1000 fold higher than any endogenous chemokine-receptor pair
- **First in class -** no current FDA-approved treatment that prevents or effectively resolves ischemia reperfusion injury after transplantation

Publications

- Lubman, O. Y., Cella, M., Wang, X., Monte, K., Lenschow, D. J., Huang, Y. H., & Fremont, D. H. (2014). Rodent herpesvirus Peru encodes a secreted chemokine decoy receptor. *Journal of virology*, 88(1), 538-546.
- Lubman, O. Y., & Fremont, D. H. (2016). Parallel evolution of chemokine binding by structurally related herpesvirus decoy receptors. *Structure*, 24(1), 57-69.

Patents

- Chemokine decoy receptors of rodent gammaherpesviruses and uses thereof (PCT Application Publication No. WO2018201091)