Washington University in St. Louis
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TARGET AND METHOD TO TREAT ALPHAVIRUS INFECTIONS

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Technology Description

Researchers at Washington University in St. Louis have identified a target for therapeutic development and created methods to potentially treat arthritogenic alphavirus infection. Arthritogenic alphaviruses, including chikungunya (CHIKV), Ross River, Mayaro and O'nyong nyong (ONNV), are RNA viruses transmitted by mosquitos that cause debilitating acute and chronic musculoskeletal disease. These viruses are emerging beyond their historical boundaries and have epidemic potential. Currently, there are no vaccines or antiviral therapeutics to treat alphavirus infection. To help meet the need for therapeutics the inventors took advantage of recent work from their lab. They identified the cell adhesion molecule Mxra8 as the critical entry receptor for allowing alphavirus to gain access to the cytoplasm. Mxra8 is shared by multiple arthritogenic alphaviruses including CHIKV, Ross River, Mayaro and ONNV. This work enabled the inventors to develop methods of treating such infections by inhibiting Mxra8. Further, the inventors defined the structural basis for the interaction between Mxra8 and CHIKV thus providing insight to develop additional inhibitors. This technology provides a much-needed therapeutic target and approach for treating many types of arthritogenic alpha virus infection.

Stage of Research

The inventors showed Mxra8-Fc fusion protein or anti-Mxra8 monoclonal antibodies blocked CHIKV infection in multiple cell types including primary human cells. Further, in mice, administering Mxr8a-Fc protein or Mxra8 blocking antibodies reduced CHIKV or ONNV infection and associated clinical disease. In addition, they have generated C57BL/6 mice that are genetically engineered to lack expression of Mxra8.

Applications

- Treatment of arthritogenic alphavirus infection including:
  - Chikungunya
  - Ross River
  - Mayaro
  - O'nyong nyong
- Research studies on alphavirus infection
  - Blockade of alphavirus infection

Key Advantages

- Solves an unmet need- provides potential therapeutics to treat many arthritogenic alphavirus infections
- New target for therapeutic development to prevent alphavirus infection

Publications

- Zhang R, Kim AS, Fox JM, Nair S, Basore K, Klimstra WB, Rimkunas R, Fong RH, Lin H, Poddar S, Crowe JE Jr, Doranz BJ, Fremont DH. Diamond MS. Mxra8 is a receptor for multiple arthritogenic alphaviruses. Nature. 2018 May;557(7706):570-574. doi: 10.1038/s41586-018-0121-3. Epub 2018 May 16.
- Basore K, Kim AS, Nelson CA, Zhang R, Smith BK, Uranga C, Vang L, Cheng M, Gross ML, Smith J, Diamond MS, Fremont DH. Cryo-EM Structure of Chikungunya Virus in Complex with the Mxra8 Receptor. Cell. 2019 Jun 13;177(7):1725-1737.e16. doi: 10.1016/j.cell.2019.04.006. Epub 2019 May 9.
- Zhang R, Earnest JT, Kim AS, Winkler ES, Desai P, Adams LJ, Hu G, Bullock C, Gold B, Cherry S, and Diamond MS. Expression of the Mxra8 receptor promotes alphavirus infection and pathogenesis in mice and Drosophila. Cell Reports. 2019. Sept 3 (in press).

Patents

- **PCT patent application**

Website

- **Dr. Diamond profile**