Peptide immunotoxin for efficient kill of CMV-infected cells

Specifically targeting the viral G protein-coupled receptor US28 with a highly potent chemokine-based toxin, efficiently killing CMV-infected cells
Background

Cytomegalovirus (CMV) is an important human pathogen, which emerges to cause disease in immuno-compromised subjects, such as AIDS patients, neonates, and individuals who have been given immunosuppressive drugs e.g. as part of a transplantation regimen. In immuno-competent hosts, CMV establishes a persistent lifelong infection, which has been linked to a variety of inflammatory conditions including coronary artery occlusion following heart transplant or atherectomy and restenosis following angioplasty. CMV infection is currently treated with antivirals that target and inhibit viral replication. They halt CMV disease progression in immuno-compromised or immunosuppressed patients but cannot eradicate the infection. So, there is currently no cure for CMV infection.

With this invention, we hope to change that by treating CMV infection with an immunotoxin. An immunotoxin is a receptor-binding ligand combined with a toxin that can kill cells expressing the receptor.

The invention

The figure on the front page shows a Human Cytomegalovirus (HCMV)-infected cell expressing the virus receptor US28 along with the human receptors CX3CR1 and CD91. It also shows our experimental new medicine, SYNx, which is a recombinant fusion protein composed of two functional domains: one derived from the human chemokine fractalkine (the ligand) and one derived from the Pseudomonas aeruginosa Exotoxin A (the toxin). Exotoxin A would normally enter the cell via binding to CD91, and fractalkine would normally bind to CX3CR1. By slightly altering the CX3CR1-binding domain, we designed SYNx to have ultra-high affinity for US28 and to lose affinity for CX3CR1. Moreover, we deleted the Exotoxin A receptor-binding domain, so SYNx cannot enter the cell through CD91, but retains the toxic effect.

As a result, SYNx targets only HCMV-infected cells, and can therefore be used in the treatment of CMV-infection or CMV-associated diseases. The technology also enables targeting of latent CMV infections, thus offering complete CMV eradication.

Key selling points

- Specific targeting of cell toxin to CMV-infected cells only
- Uniquely enables targeting of both active and latent CMV infection
- The global CMV market across the 7 major markets (7MM) was valued at $246M in 2017
- The market is expected to grow at a Compound Annual Growth Rate of 4.5%, to about $383M in 2027

Development status

The drug substances have been produced in 2.5 L scale, at approximately 5–10 mg/L of bacterial cell culture, to high purity using FPLC techniques. The constructs have been characterized using a number of biophysical techniques, in vitro pharmacological and cell killing assays. Further development and testing will be needed prior to selecting a lead candidate.

Intellectual property rights