Human Cytolitic Fusion Proteins

Novel human cytolytic fusion protein (hCFPs) suitable to induce apoptosis in human cells using a target cell-specific binding component

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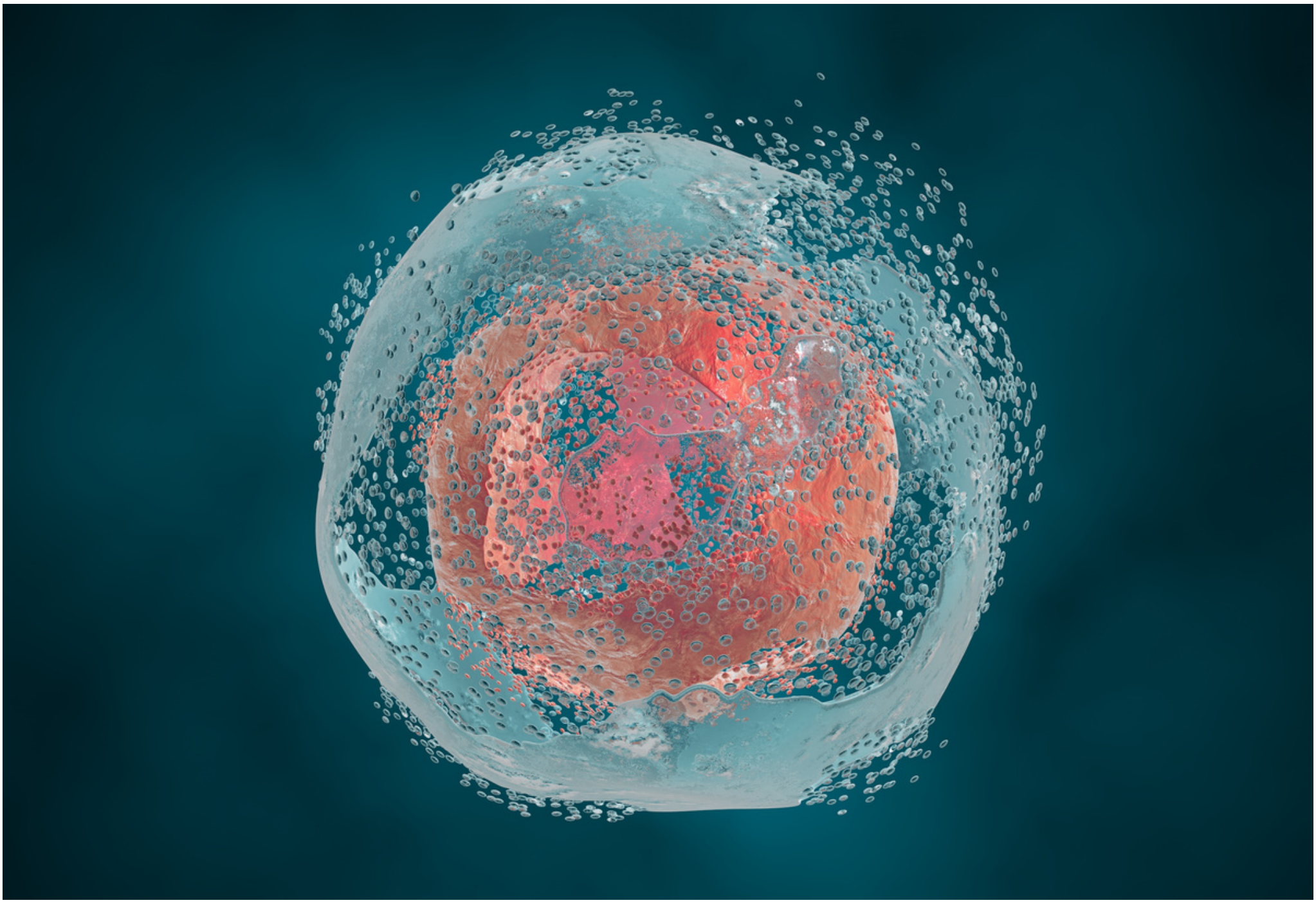

Dr_Microbe, stock.adobe.com

Background

Immunotoxins (ITs) are recombinant fusion proteins originally developed for the treatment of malignant diseases. They comprise a toxic effector domain fused to a tumor cell-specific binding component, which is usually an antibody or a derivative thereof. Initially the antibody components were derived from mice and the toxins were derived from bacteria or plants, e.g. Pseudomonas aeruginosa exotoxin A (ETA), diphtheria toxin (DT) or ricin A. The major advantage of ITs compared to traditional chemotherapy is their exceptional target cell specificity, but their disadvantages include side effects caused by potential immunogenicity. Furthermore, the development of neutralizing antibodies against the toxins or murine parts of binding moieties limits the impact of long-term treatment due to accelerated clearance from the circulation. Highly toxic drugs and heterologous toxins conjugated to antibodies have been extensively tested, but for example the ADC gemtuzumabozogamicin (Mylotarg ®), approved by the US Food and Drug Administration for treatment of CD33+ acute myeloid leukemia was voluntarily withdrawn from the market because of increased occurrence of fatalities caused by hepato-occlusive disease upon treatment.

The technology provided herein relates to novel human cytolytic fusion proteins (hCFPs) suitable to induce apoptosis in human cells comprising a target cell-specific binding component and a human effector domain, wherein the binding component comprises an antibody or an antibody fragment with an antigen-binding site for binding to the cellular surface receptor CD64 and the effector domain comprises a variant of wild type human angiogenin (Ang) or a functional fragment thereof; to nucleic acid molecules encoding said recombinant hCFPs, vectors and host cells containing said nucleic acids and methods for preparation and producing these hCFPs.

Technology Overview

The invention includes a method of preparing the recombinant human cytolytic fusion protein and isolating the fusion protein from the cell. The molecule is a member of the fusion proteins that consist of a disease specific binding component (e.g. cytokines or peptide ligands) fused to a human pro-apoptotic enzyme and are therefore known as ‘human cytolytic fusion proteins’ (hCFPs).

In the current hCFPs, the first component is an antibody fragment that allows binding to the cellular surface receptor CD64 of the targeted cells. The second component is the effector domain comprises a mutated human angiogenin (Ang), which has therapeutic properties when delivered to the targeted cells in a patient. When delivered to the targeted cells, angiogenin inhibit protein biosynthesis and thus resulting in programmed cell death.

In order to circumvent the side effects caused by potential immunogenicity, the murine antibody components have been replaced by humanized or fully human counterparts and the bacterial and plant toxins have been replaced by human pro-apoptotic enzymes such as granzymes or ribonucleases (RNases).

Benefits

The hCFPs have become highly preferred in treating most of the above-mentioned maladies because they do not elicit side effects compared to most of the immunotoxins with bacterial/plants fused proteins.

Applications

This IP covers a human cytolytic fusion protein (hCFPs) as a therapeutic molecule for the treatment of malignant chronic inflammatory diseases, such as acute myeloid leukemia, arthritis, COPD including emphysema, intrinsic and extrinsic asthma; cutaneous disease including atopic dermatitis, polymorphic light eruption, SLE; autoimmune diseases, multiple sclerosis, macrophage activation syndrome, rheumatoid arthritis, juvenile arthritis; intestinal diseases including Crohn's disease and chronic bowel disease.

Opportunity

Opportunity for a development/commercial/license partner to take the invention forward.

Patents

- PCT/EP2015/063282

IP Status

- Patented

Seeking

- Development partner
- Commercial partner
- Licensing
- Seeking investment
- University spin out