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Method to improve effectiveness of gene therapy for Duchenne muscular dystrophy

Researchers at Stanford University have developed a method to induce antigen-specific immunological tolerance to allow for more effective gene replacement therapy for Duchenne muscular dystrophy (DMD). DMD is a fatal, inherited, x-linked recessive disorder that affects 1 out of 3,600 males. Due to a defect in the dystrophin gene, there is progressive muscle wasting leading to skeletal muscle loss, and late stage cardiac and respiratory failure. With no known cure, tremendous efforts have been made towards gene therapy approaches. The goal for adeno-associated viral (AAV) gene replacement therapy in DMD is to achieve persistent transgene expression of dystrophin at therapeutic levels. However, an unfortunate side effect of gene therapy is an aggressive immune response to the introduced gene and AAV vector. This immune response severely limits the effectiveness of gene replacement therapy. Thus, there is an urgent need to find treatments with limited side effects. To help meet this need, the inventors have developed methods of suppressing the immune response to DMD gene replacement therapies. They have developed a tolerizing vaccine that can be used as an add-on to DMD gene replacement therapy to reduce the immune response and restore effectiveness of the therapy. The investigators also reduced immunity to the AAV vector. This technology helps overcome the limitations of gene therapy and provides the potential for more effective treatment of DMD.

Stage of research

Using the mdx/mTR mouse model of DMD, the inventors have shown their microdystrophin tolerizing vaccine can effectively reduce the immune responses against microdystrophin and against AAV, and thereby help to restore the effectiveness of microdystrophin gene replacement therapy.

Applications

- Gene therapy for DMD- add on to improve the effectiveness of gene replacement therapy

Advantages

- Reduces unwanted immune response that limits the effectiveness of gene therapy
- Add on to gene replacement therapies
- Focused approach- induces immunological tolerance to DMD gene therapy without further affecting the adaptive immune system
- The gene used in the tolerizing vaccine can be modified to match that used in the gene replacement therapy
- The tolerizing vaccine can also be generated to reduce the immune response to the AAV vector

Publications

- Ho PP, Lahey LJ, Mourkioti F, Kraft PE, Filareto A, Brandt M, Magnusson KEG, Finn EE, Chamberlain JS, Robinson WH, Blau HM, Steinman L. Engineered DNA plasmid reduces immunity to dystrophin while improving muscle force in a model of gene therapy of Duchenne dystrophy. Proc Natl Acad Sci U S A. 2018 Sep 4.
- Goldman, B. Scientists engineer way to prevent immune response to gene therapy in mice. Stanford News. 2018 Sept 3.

Patents

- Published Application: 20170021000
- Issued: 10,543,260 (USA)

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