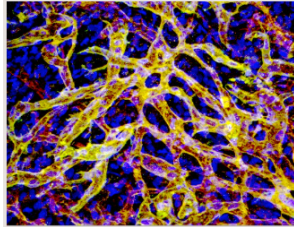


Adventures in gene therapy: Getting our own blood vessels to make drugs

Posted on June 18, 2014 by Juan Melero-Martin

Posted in Innovation, Therapeutics

More On: drug delivery, gene therapy, tissue engineering



A bioengineered network of blood vessels

Juan Melero-Martin, PhD, runs a **cell biology and bioengineering lab** in the department of Cardiac Surgery at Boston Children's Hospital. In May, he received an **Early Career Investigator Award** from Bayer HealthCare, part of the prestigious Bayer Hemophilia Award.

In 1982, insulin became **the first FDA-approved protein drug created through recombinant DNA technology**. It was made by inserting the human insulin gene into a bacterial cell's DNA, multiplying the bacteria and capturing and purifying the human insulin in bioreactors. Today, recombinant proteins are widely used in medicine, but life for patients who rely on

these drugs isn't pleasant: they must often endure injections several times a week, or visit a medical facility for intravenous therapy.

Back in 2011, we put forward an idea to make recombinant protein therapies less taxing for patients, by applying gene therapy to make a patient's own cells produce the drugs, rather than bacteria in a reactor. This idea has been around since the advent of gene therapy research few decades ago, but creating actual clinical therapies has turned out to be more difficult than anticipated. One of the many challenges is an insufficient understanding of how to engraft patients' cells back into their bodies in a controlled and stable fashion.

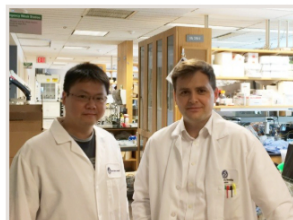
Some of my colleagues at the **Dana-Farber/Boston Children's Cancer and Blood Disorders Center** are optimistic about gene therapy's potential in **blood and immune disorders**, finding that patients' blood stem cells, genetically corrected, do a good job engrafting themselves into the bone marrow. Our laboratory, meanwhile, has focused its efforts on endothelial colony-forming cells, precursors of the cells that line our blood vessels.

Engineered blood vessels

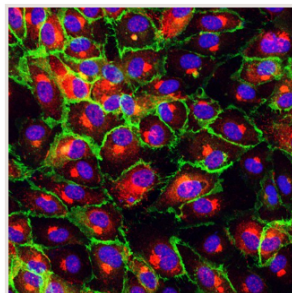
We first learned that endothelial colony-forming cells circulate in the bloodstream and are easily isolated from a simple blood draw. Later, we learned that they can be manipulated in the laboratory and transplanted into animals, and that they're particularly good at assembling themselves into stable blood vessels.

We soon found ourselves exploring this idea: What if we could insert instructions into these endothelial precursors, directing them to build vessels capable of producing drugs?

Proving the idea's feasibility was not straightforward. We initially tried it with "blockbuster" protein drugs such as insulin, only to realize that success would take more than inserting genes into the cells. Indeed, we learned that insulin production needs to be timed properly and coupled to blood glucose sensing, requiring more layers of genetic engineering than we initially realized. Other proteins needed their own particular refinements.



Juan Melero Martin (R) with postdoctoral fellow Ruei-Zeng Lin



Endothelial colony-forming cells engineered to produce EPO (shown in red). All images courtesy Melero-Martin lab.

We ended up focusing on production of the anemia drug erythropoietin (EPO), which had some \$2 billion in U.S. sales in 2011. Timely release is not crucial, and EPO produces a physiological response that is easily tracked—namely, an increase in hematocrit. Thanks to the incredible work and talent of Ruei-Zeng Lin, PhD, the postdoctoral fellow leading this project, we quickly made our first breakthrough, showing increased hematocrit levels in mice receiving implants of EPO-producing vascular networks. Soon after, we **demonstrated** that the implants were stable and able to correct anemia in mice.

Turning drug delivery on and off

Given that we've become interested in elements of endothelial drug delivery, it felt like we had a built-in

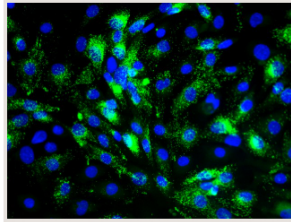
Thanks for your interest in *Vector*. Our science content has now moved to *Boston Children's Discoveries*, our new all-hospital hub. Visit us there.

Since then, we've become interested in elements for regulating drug delivery. Initially, we had a built-in genetic switch so that the EPO-making gene turned on only when the mice received the drug doxycycline. While this enabled us to precisely control EPO release, doxycycline is an antibiotic and probably should not be taken regularly. So we then sought to harness regulatory systems used naturally by the body.

Last year, we received funds from Boston Children's Hospital to develop a system that senses blood oxygen levels, stimulating EPO production when oxygen levels dip. Our goal is to incorporate multiple sensing elements into the EPO gene's "switch" or promoter region so that the modified endothelial precursor cells will activate EPO production on their own. If this succeeds, it could be the first self-governing protein drug delivery system that responds to physiologic demands.

Beyond this proof-of-concept effort, we hope to address a wider range of therapeutic applications. A little over a year ago, we began a collaboration with [Ellis Neufeld, MD, PhD](#), director of the Boston Hemophilia Center and associate chief of hematology at Boston Children's, to apply our system to the treatment of hemophilia A.

Patients with this inherited bleeding disorder, caused by mutations in the gene for factor VIII (a coagulation factor), currently undergo intravenous infusions of recombinant factor VIII two to three times a week—for life. This therapy is extremely expensive and creates tremendous discomfort. A system that could continuously supply the drug could significantly improve patients' quality of life and potentially reduce cost.



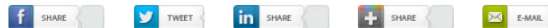
Endothelial colony-forming cells engineered to make Factor VIII (in green)

Our preliminary studies look encouraging: we have successfully genetically engineered blood endothelial precursors from four patients with severe hemophilia A to produce a corrected form of factor VIII. We are currently evaluating this approach in animal models.

iPS cells and gene editing

With funding from the Bayer Hemophilia Awards Program, we are also exploring the possibility of creating induced pluripotent stem cells (iPS cells) from hemophilia A patients to derive all the cells needed to build drug-producing vascular implants. This exciting effort is already generating encouraging results in the laboratory.

Despite some successes, the realization of gene therapy as an alternative to IV administration of recombinant drugs has been sluggish to say the least. In recent years, the advent of gene editing technologies and increased understanding of stem cell biology have brought new excitement and expanded possibilities in gene therapy. Time will tell whether these technological advances will finally fulfill gene therapy's potential to improve the lives of millions of patients who rely on injections or infusions of protein drugs.



Related Posts :

[Light-activated nanoparticles could avoid painful eye injections for 'wet' macular degeneration](#)

[Reviving fetal hemoglobin in sickle cell disease: First patient is symptom-free](#)

[A tissue engineered heart ventricle for studying rhythm disorders, cardiomyopathy](#)

[Putting patients first in the translational research pipeline](#)

[A bold strategy to enhance CAR T-cell therapies, capable of targeting DIPG and other tough-to-treat cancers](#)



About Boston Children's Hospital

[About Us](#)
[Research + Innovation](#)
[Newsroom](#)
[Public Policy](#)
[Boston Children's Video](#)
[Giving to Boston Children's](#)

How Can We Help You?

[Find a Doctor](#)
[Clinical Services](#)
[Conditions + Treatments](#)
[Locations](#)
[Career Opportunities](#)
[Contact Us](#)

Legal

[Privacy Practices](#)
[Patient + Family Rights](#)
[Terms of Use](#)
© 2005-2019 All Rights Reserved

Boston Children's Hospital 300 Longwood Avenue, Boston,
MA 02115 617-355-6000 | 800-355-7944

