Q&A: Scientist partners with colleagues around the globe to make gene therapies more effective and widely available

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Members of the Adair Lab at Fred Hutch Cancer Center. Dr. Jen Adair, center in tan blazer, is working with patients to make gene therapy accessible to all. Credit: Robert Hood / Fred Hutch News Service

Fred Hutch Cancer Center scientist Jennifer E. Adair, Ph.D., is on a mission to foster worldwide collaboration on potentially curative gene therapies.

Holder of the Fleischauer Family Endowed Chair in Gene Therapy Translation, Adair just co-authored two articles published today in *Science Translational Medicine* as part of a special series on global access

to these therapies that she curated.

In a Q&A, Adair discusses the promise of gene therapies to cure an array of diseases, as well as the need for stakeholders around the world to join forces to develop the best possible approaches and get them to the people who need them most.

Read on for Adair's take on the breakthroughs happening in this exciting, but expensive, new field of therapy.

What exactly are gene therapies, and what diseases are they being used to treat?

A gene therapy is anything that is using genetics to drive therapeutic value of the treatment. These therapies are a big paradigm shifter because they're not managing symptoms; they are actually treating the underlying biology that causes a disease or that causes a disease to be severe, and so in most diseases they're curative.

Broadly, they are being used to treat inherited diseases, including sickle cell disease; malignant diseases, or cancer; and some infectious diseases. They're very broadly applicable.

If we understand the biology of the disease, and there is a change we could make to the DNA or some type of genetic element we could add that could undo that biology, there will be a gene therapy for that disease at some point. So far, there are 32 gene therapies authorized globally, most in the U.S.

Being able to change the underlying biology rather than manage symptoms is an important advantage. What are the potential disadvantages of gene

therapies?

In terms of health drawbacks, the field is still young. We don't yet know exactly how durable these therapies are. What it takes to actually modify the underlying biology of cells inside the human body, in the case of in vivo therapies, or outside the human body, in the case of ex vivo therapies—where we remove cells from a patient, alter them and then return them to the patient—is not trivial.

Also, these therapies are very expensive, and the health care systems in which they're being administered were not designed for one-time treatments meant to elicit lifetime cures. There's a lot of work to be done on how we actually settle the economics of these therapies so that companies who make them can still make money, but it's not costing $2 million or $3 million per treatment.

We also need to think carefully about the risk-to-benefit ratio. The first diseases for which gene therapies were developed were diseases with no treatments or cures, and they tended to be fatal. For those patients, the risk-to-benefit ratio is in favor of finding something that extends life or improves the quality of life, even if it also carries some risk. As gene therapies become more prevalent, we will have to reassess the risk-to-benefit ratio.

For example, for HIV, we have highly effective antiretroviral therapy combinations that, if patients have access and they maintain adherence, they can live a normal lifespan, and as long as their virus stays undetectable, they won't transmit it to anyone else.

At the same time, we've not been able to get antiretroviral therapy to the number of people required to control the virus globally, and so we do need a cure. Gene therapy might be that cure, but we would need to demonstrate the ability to control the virus without increasing patients'

risk of cancer in the future.

What was your role in the development of this special series of articles, and what prompted you to be involved?

I am the curator, meaning I came up with the what the series was going to look like, what key pieces we needed, and then solicited the authors. Over the last two years, I have been helping to assemble the articles and working with the editorial team to decide how to organize them—everything down to selecting the cover art for the May 8 issue, where the first two articles will appear.

The artwork really explains why I am involved. It's a painting by Ugandan artists of a bus with a small number of riders, plenty of empty seats and a large queue of people who would love to get on the bus but for some reason can't.

The concept is by Moses Supercharger, and the artists are John Mary Kyambadde, Vanessa Nannyonjo and Moses Katabira. This represents what HIV means to Ugandans. The bus represents freedom from disease for people who've received therapies that put their HIV into remission, but it's not accessible to most people. That is true for gene therapy right now.

There are 39 million people with HIV, and 85% of them live in sub-Saharan Africa. We may be able to cure HIV with gene therapy one day, but we will need to be able to deliver that cure to people in parts of the world that are most affected, which means we need people from those countries involved now in creating and implementing gene therapies.

People on the ground locally need to be enabled to develop these

treatments in the right way for their own people. Unfortunately, there are so many barriers to their participation—systemic, economic, social and geographic.

How does this relate to the Global Gene Therapy Initiative?

In 2020, with my collaborator Dr. Cissy Kityo, at the Joint Clinical Research Centre in Uganda, I co-founded the Global Gene Therapy Initiative, or GGTI, to support implementation of gene therapies in low- and middle-income countries. It's a virtual network of international colleagues who represent every stakeholder group—from patients and caregivers to researchers, clinicians, regulators, government policymakers, investors and companies—who come together to learn from each other.

We have met nearly every week for three-and-a-half years to go over something about the state of the field of gene therapy. We now have hundreds of members representing more than 30 countries on five continents.

What's been the focus of your research on gene therapy?

When I first came to Fred Hutch, I worked with Dr. Hans-Peter Kiem [holder of the Stephanus Family Endowed Chair for Cell and Gene Therapy], on a trial of gene therapy in brain tumor patients. That led to a gene therapy trial for patients living with HIV who also had cancer and eventually, along with other experiences, to a deeper understanding on my part that we are all gatekeepers in our own way, and we have to decide how we're going to gatekeep in ways that are antiracist.

I had worked on this cool technology, "gene therapy in a box," a way to offer gene therapy in places without the multimillion-dollar infrastructure of an institution like Fred Hutch. And that was a great. It was enough of an innovation to get this capability into India, Brazil and South Africa.

But when I actually started to visit the places where I thought it was going to work, I realized very quickly that was me trying to solve the problem, thinking I understood the local needs and knew the answers, but I didn't. However, it got me in the door with a couple of clinics where I could then have conversations.

We learned pretty early that people wanted the convenience of something like vaccination. So, we started thinking about how we could deliver gene therapy inside the body, which led to our research on using gold nanoparticles to deliver gene-editing instructions to cells.

One thing I do now is invite people from low- and middle-income countries who are interested in gene therapy into my lab, and we work on ways to make the processes easier to implement in other settings. Our first post-doctoral research fellow who was part of this effort, Dr. Lois Bayigga worked on ways to shorten the gene therapy process so that it's not weeks long but rather just a couple of days so we can treat more people.

How do you hope the gene therapy field moves forward from here?

There are so many groups right now in the U.S. and Europe who seem to think, "I have the latest and greatest technology that's going to transform the field by being able to deliver gene therapy inside the body to this cell," and they're not talking to the people in Africa who they say are

going to be the beneficiaries of this particular therapeutic.

The patients absolutely need to be considered. As they say, "Nothing about us without us." The advocacy element in the special series of articles is so important.

We're also not thinking enough about genetic diversity. Africa is the most genetically diverse continent on the planet, with 54 different countries represented. It is an ancestral population for all of us.

Does it make sense for scientists in the U.S. and Europe to develop gene therapies in young genomes that are not very diverse, thinking these therapies will go to the rest of the world and work, or should they be developed in the ancestral genome to apply more broadly? Genetic therapies would greatly benefit from genetic diversity being included in the development at the outset.

You mentioned the idea "Nothing about us without us," which is the title of one of the articles you co-authored. Can you explain more about the importance of involving patients in gene therapy development?

It's so important to actually consider patients from the outset as co-creators in genetic medicine because I, as a researcher, might create a therapy that I think is addressing a primary need, but patients might think otherwise.

I remember a presenter at the American Society of Gene and Cell Therapy annual meeting two years ago describing how researchers had spent years developing a gene therapy to protect the heart muscle and diaphragm in people with a degenerative muscle disorder because the failure of these muscles is what ultimately causes death in these patients.

But someone in the first group of patients for their clinical trial said they'd rather die tomorrow than live another 10 years with a colostomy bag so couldn't the researchers make a gene therapy that gives them back continence?

There's been an outcry from some patients who've participated in clinical trials of gene therapy for sickle cell disease that the world is not paying enough attention to fertility loss. The treatment involves having chemotherapy that is likely to make recipients sterile, so patients in the clinical trial were afforded reproductive supportive care.

But that's not something patients will necessarily have after the treatment is authorized unless they have good enough insurance and they know to ask for it. We're not always thinking enough about how we can create a therapy that will be much more amenable to adoption later.

Also, patients sometimes feel taken advantage of. I was at a meeting of the International AIDS Society where a young main from Brazil protested a presentation about a long-acting antiretroviral therapy given by injection for HIV.

He essentially said, "You came to our country, and you asked us to participate in your clinical trials, and we did. You gave us a taste of what life with long-acting antiretroviral therapy could look like. But as soon as you used our data to get your authorization in the U.S., you never made an attempt to negotiate with our government to actually bring this treatment to us."

This is why the people affected by a disease need to be part of this—speaking up, asking questions, saying what they don't like about the current trajectory of their disease and its treatment course or what's not available to them. The sooner we learn how to have these conversations earlier in the development process, the more streamlined it

will become.

The other article you co-authored for the series includes case studies of the state of gene therapy in several low- and middle-income countries. What was your goal for that article?

There are lots of different low- or middle-resource settings that are interested in and actively pursuing gene therapy at different levels. We focused on these six case studies because each is a country that has one of the highest burdens of disease globally for which a gene therapy has already received or is about to receive authorization in the U.S. and Europe. We have a moral obligation for those therapies to be accessible to the places in the world where the majority of the patients live, whatever it takes to get there.

The article is a call to action to say, "These countries have self-nominated, they want to be in the same place as the U.S. and Europe right now in terms of offering gene therapies, so can we fairly identify where they are in this trajectory and what support they could use? Here are the differences in their health care systems and how patients access that care. Here are the differences in the governance infrastructure. Here's what has been done in terms of research and development of gene therapy locally. Here's what has been done in terms of implementation of authorized therapies from high-income countries."

We're also looking at, "Where are the difficulties?" This is what we call the translational gap.

We know that in the places where implementation has been successful, there's been government buy-in. So, how do we get governments on board with supporting research in this space? How do we ensure educational programs can train for capacity?

Going to low- and middle-income countries where this work might be the hardest to do will actually lead to solutions that will provide scalability and sustainability in ways we could never imagine otherwise. All of our brains together are smarter than each of our brains individually. We have the potential to move a lot farther in partnership.

That's what GGTI does. It creates a place where people who are interested in gene therapy can talk to each other. Everything the group has accomplished is really just because we started talking to each other.

My partner is originally from Nigeria, and he refers to this phrase he learned growing up: "If you want to go fast, go alone. But if you want to go far, go together."

More information: Olabimpe Olayiwola et al, Nothing about us without us: Advocacy and engagement in genetic medicine, *Science Translational Medicine* (2024). DOI: 10.1126/scitranslmed.adn2401

Kevin W. Doxzen et al, The translational gap for gene therapies in low- and middle-income countries, *Science Translational Medicine* (2024). DOI: 10.1126/scitranslmed.adn1902

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