

Surprising Findings About Blood Cell Mutations Bode Well for Transplant Recipients

Fred Hutch researchers compared blood samples from 16 recipient-donor pairs, some more than 45 years after transplant.

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After an allogeneic [stem cell transplant](#), a recipient's body faces a daunting task: rebuilding the person's blood-forming and immune systems from the ground up from a relatively small number of "seed" cells obtained from their donor.

To achieve this, the donated cells must replicate again and again — and again.

It's a cycle that might put recipients at risk if a new, potentially harmful mutation arises or if a mutation present in the donated cells is reproduced many times over. Researchers from Fred Hutch Cancer Center set out to determine how common such issues are. The results, published in [Science Translational Medicine](#), surprised them.

In this Q&A, lead author [Masumi Ueda Oshima, MD, MA](#), explains the study and its implications. Ueda Oshima is an associate professor in Fred Hutch's [Clinical Research Division](#).

What question were you trying to answer with this study, and why?

When we do an allogeneic stem cell transplant, we are putting only a very small proportion of the donor's stem cells into the recipient, and that small number of cells has to recreate an entirely new blood-forming system and immune system for the recipient. This means the cells have to divide much more frequently in the recipient than in the donor, who goes on with their life normally.

Our basic question was: Does the increased replication of the stem cells in the recipient cause more changes in the DNA, more mutations, than in the donor, especially after many years or even decades?

Why would an increase in mutations be of interest?

If the transplanted stem cells acquire new mutations over time, there's a chance some of the mutations could predispose a recipient to blood diseases, like [myelodysplastic syndrome](#) (MDS) or [leukemia](#). We already knew the incidence of donor-derived leukemias after transplant is very low. But we still wanted to see whether there are potentially dangerous mutations that could happen in transplant recipients, especially after a long time has passed.

How did you go about investigating this?

We are fortunate at Fred Hutch to have a very robust [Long-Term Follow-Up Program](#) for transplant recipients. So, we have contact information for people who were transplanted at Fred Hutch as far back as the 1970s. We reached out to survivors from this list about participating in the study and asked if it would also be OK to contact their donors.

For the study, we enrolled 16 recipient-donor pairs who were between about 6 and 46 years out from transplant. Each sent us a blood sample through the mail. Then we worked with [TwinStrand Biosciences](#) to do genetic sequencing studies looking with great sensitivity at how mutations in the recipients compared with mutations in their donors.

We also checked the research cell bank at Fred Hutch for any archived DNA or cells from the donors taken at the time of transplant, and we found samples for 11 of the 16. This provided a really unique opportunity to look at mutations that existed in the donor back then and how these mutations may have changed in both the donor and the recipient during the years since the transplant. In other words, it gave us a way to directly compare how these blood cells were aging in the donor versus the recipient.

This study, in addition to being very scientifically intriguing, really speaks to the legacy of transplant being developed and advanced here at Fred Hutch. I don't think there's any other institution in the world that could have done this type of research because of the long-term follow-up that we have here and also the access to historical samples.

What were your main findings?

Our findings were actually not what we expected. As I said, our hypothesis was that the high number of cell replications required in the recipient compared to the donor would result in more mutations and higher mutation frequency in the recipient. But we really didn't find a significant difference in the mutation rate, including in genes that are potentially linked to things like MDS and leukemia.

In the 11 pairs where we had a donor sample from the time of transplant, the average mutation rate — change in mutation frequency per year — was largely similar between donors and recipients. It was 2% per year in donors versus 2.6% per year in recipients. This is a way to directly compare the aging of the blood cells over time in terms of DNA in these two groups of people. The fact that there wasn't a major difference can offer some comfort to physicians and patients by showing that transplantation does not result in higher acquisition of mutations.

You also found that, in the vast majority of cases, mutations passed from donors to recipients did not expand greatly in recipients. Can you explain this aspect of the research?

We identified mutations that are currently present in both the recipient and their donor, which implies the donor already carried the mutation at the time of transplant and the recipient received it via the donated cells. Our task was to see if, many years post-transplant, the mutation existed at the same level in both people or if cells with the mutation had a growth advantage and became more proliferative, or overgrew, in the recipient.

Across the 16 recipient-donor pairs, there were 393 mutations shared by a recipient and their donor. Only 5.6% of the mutations showed a greater-than-10-fold growth advantage in the recipient. Importantly, only 2 of the 393 mutations showed a variant allele frequency greater than 2% in the recipient. This is a way of assessing the mutation burden in the recipient — meaning, in this case, that the mutations from the donor did not expand substantially in the recipients we studied.

What are the implications of this work for who can donate stem cells?

One of the concerns with using older donors for allogeneic stem cell transplants is that we know people have more mutations as they age. The question has been, if you use older donors and they have more mutations in their stem cells and those cells are given to recipients, will there be a higher incidence of donor-derived leukemia?

Our results show that mutations passed from a donor don't expand significantly in the recipient, which gives us more comfort in using older donors. We have to be cautious drawing conclusions from our study because it involved only a small number of participants. And there are probably advantages in other respects to using younger donors, so when a younger donor is available, we would still prefer that. But if there is no younger donor for a patient, this study gives us some peace of mind about using an older donor and the concern that mutations present in the donor will proliferate in the recipient.

Are there also implications for gene therapies, which involve removing and altering a patient's stem cells and then returning them to the patient?

Yes, there are implications for gene therapies, which are now being used more and more for diseases like [sickle cell disease](#) and [thalassemias](#). Although these therapies are not the same as an allogeneic stem cell transplant, there are similarities. For gene therapies, we take stem cells from a patient and later transplant them back into the patient, where they have to divide for many decades, especially if the patient is younger when they receive the treatment. Our study tells us that the replication of the transplanted stem cells over many, many years does not seem to result in the expansion of mutations that existed in the cells.

Where do you see this line of inquiry going next?

Our cohort is a very select group of people who are doing well so many years after transplant. We

did not look at the entire population of transplant recipients, some of whom may go on to develop new cancers or other complications post-transplantation.

It would be interesting to do a similar study in a more prospective and longitudinal fashion, following transplant recipients at the one-year, five-year and 10-year marks after transplant to see how these mutations change overtime. If we study a larger number of patients, we will actually be able to correlate changes in the DNA with clinical outcomes, like [graft-versus-host-disease](#) risk or even some late effects after transplant.

We also want to know how donor cells behave over time in the current era of giving cyclophosphamide, a chemotherapy agent, after transplantation as a way to prevent graft-versus-host-disease.

We have more and more transplant recipients who are living a long time, and we want to know more about how changes in their blood cells may impact their health and longevity.

Also, we are already talking about potential collaborations with other researchers at Fred Hutch looking at not only the hematopoietic, or blood-forming, cells but how the donor's and recipient's immune systems compare many decades after transplant, looking at immune cell repertoires and immune function of these paired samples.

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