New Technologies Hold Promise for TRANSFUSION MEDICINE

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Scalable Platelet Supply CD34+ Pers

More than 100 years ago, Ludwig Hoekten first suggested that blood transfusion might be made safer by crossmatching the newly discovered blood types between donors.[1] This suggestion led to an avalanche of discoveries related to transfusion medicine that would ultimately result in the establishment of the world's first blood banks.

Then in 1950, Carl Walter and W.P. Murphy, Jr., introduced the plastic bag for blood collection, which was "one of the single most influential technical developments in blood banking".[1]

Seventy years later, the technologies being developed to aid in transfusion and cellular therapies are leaps and bounds beyond plastic bags and include such innovations as machine learning, microfluidics devices and robotics. *AABB News* recently spoke with several researchers and scientists about some of these recent advances.

Personalized Donor Intervals

Imagine if a computer could be used to identify the precise amount of time that each individual blood donor should wait before returning to donate again. That is exactly what Alton Russell, a PhD student in the department of management science and engineering at Stanford University, and colleagues did.

"Internationally, there is a lot of disparity in how frequently countries let blood donors give blood," Russell told *AABB News*. "The U.S. allows people to give blood once every 8 weeks, but that is the shortest inter-donation interval of any country."

In Canada, although men can return every 8 weeks, women are required to wait 12 weeks between donations. In the United Kingdom, men must wait 12 weeks and women, 16 weeks.[2]

"There is mounting evidence from the last 30 years that the interval may be too short for some blood donors, and they don't fully recover their iron stores during that time," Russell said. With an increasing reliance on repeat donors, blood bankers must balance the need for a robust blood supply with the probability of deferrals made for iron-deficient donors.

In their study, Russell and colleagues wanted to see if they could use machine learning to identify personalized inter-donation intervals that would balance risk to donors versus risk to blood supply.[2] They used about 2 years of data from the REDS-II RISE dataset looking at 3,162 donations for 1,025 U.S. donors.

"We took those data and trained a machine learning model using characteristics like ferritin level, hemoglobin level, how frequently they had given blood in the past, and questionnaire responses on things like diet and iron supplementation," Russell said. "We wanted to predict — based on how long they wait to come back — the likelihood of hemoglobin deferral, having a completed donation with low iron, a completed donation with absent iron or no problems."

Using the model, they were able to estimate how the risk of adverse outcomes changed in terms of inter-donation intervals and to establish a level of risk they were comfortable with.

"Some donors had very low risk even if they came back only 8 weeks later, and others remained likely to have hemoglobin deferral or absent iron even if they waited a whole year," Russell said. "There was a huge variation in underlying iron status and how long people took to recover."

Using data from REDS-II RISE, the use of personalized inter-donation intervals would have decreased blood collections by 30%, but it would also have reduced hemoglobin deferral by 45%, low-iron donations by 12% and absent iron donations by 73%.

"In principle, a blood center could implement this and, whenever someone comes to give blood, use questionnaire answers and physiologic measurements to personalize inter-donation intervals to each donor," Russell said. "Certain donors, based on their profile, could be told to come back 8 weeks later, and others would be told that they need to wait longer until the risk is low enough."

High-Quality Donors

In addition to identifying how long each donor must wait between donations, new technology may also aid in the identification of "high-quality" blood donors, according to recent research by Hongshen Ma, PhD, a professor of mechanical engineering and biomedical engineering at the University of British Columbia.

"Right now, when we get a red cell unit for transfusion, we do not distinguish them; we consider them to all be the same," Ma said. "The transfusion scientists have known anecdotally that some units seem to be able to last longer in recipients than other units."

Knowing which units can last longer could be particularly important for people who have chronic diseases that require multiple transfusions.

Ma and colleagues have developed a device that could potentially help identify these high-quality donors. In a recent study, they tested the microfluidics device to assess how the deformability of stored red blood cells from eight different donors was maintained during storage. Deformability, which enables these cells to move though the microvasculature of the body,

is often lost during cold storage.

They found that the aging curve of red blood cell deformability varied significantly across the tested donors but was consistent for each donor over multiple donations. Two donors provided blood that stored better than that from the other donors.

"If we can identify donors that can give high-quality blood that lasts longer in circulation, then we can potentially reserve units from those individuals for chronic transfusion recipients," Ma said. "If the transfused blood lasts longer in those recipients, fewer transfusions will be needed —meaning there will be more blood available for everyone."

Simplifying Blood Draws

Now imagine that technology could increase the accuracy of—and decrease the pain associated with—venipuncture for blood donation and other blood draws. Venipuncture is the world's most common clinical procedure, with more than 1.4 billion performed in the U.S. each year.[4]

According to researchers at Rutgers University, previous studies have shown that clinicians fail at venipuncture in 27% of patients without visible veins, 40% of patients without palpable veins and 60% of emaciated patients.[4]

"Some people have very difficult veins to stick, and that results in lost time and money, as well as pain and discomfort," said Josh Leipheimer, a biomedical engineering doctoral student in the Yarmush lab in the biomedical engineering department in the School of Engineering at Rutgers University-New Brunswick. "We thought that with the use of ultrasound and robotics, we could develop much more accurate placement of the needle and obtain overall better results."

The resulting device is an ultrasound image-guided robot that draws blood from veins. Leipheimer called it a "supervised automated device," meaning it is still operated by a human user.

"Essentially, the way it works is that an operator would take the device, load the needle and place it over the general area of insertion," Leipheimer said. "The device would use ultrasound to identify a vessel and then align and insert the needle."

Once the device was removed, the operator would hook up a line.

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>
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Leipheimer and colleagues conducted a human pilot study of the device to assess its feasibility and safety when drawing a small sample of blood from the upper forearm.[5] The device had an overall success rate of 87% for the 31 volunteers whose blood was drawn. Among the 25 people whose veins were easy to access, the success rate was 97%.

"Overall, in terms of success, these results were comparable to or exceeded that of clinical standards when it comes to success rate and average procedure time," Leipheimer said. "The benefits of a device like this would be providing the ability to draw blood reliably every time and reducing how much training that you would typically need to perform a venipuncture on a difficult venous access patient."

More widely, a device like this could potentially be used at bedside in a general hospital or clinical area, Leipheimer said. The device could also potentially be used in places with high throughput for blood draws, such as blood diagnostic centers.

"We want to have a device that assures a successful first stick without patients having to go through unnecessary pain and wasted time," Leipheimer said.

Scalable Platelet Supply

Finally, consider how much the need for blood donors might be reduced if it were possible to produce in vitro generated platelets on a large scale basis.

"Platelets have a limited 5-day shelf life, sometimes resulting in discard," explained Teresa M. DesRochers, PhD, Chief Scientific Officer of KIYATEC, Inc., of Greenville, S.C. "There are more people out there who need platelets than there are willing, available donors, and people with type-specific needs have an even harder time finding platelets."

Last fall, DesRochers and colleagues from KIYATEC presented information on scalable in vitro platelet production from cord blood derived hematopoietic stem cells at the 2019 AABB Annual Meeting.[6] The ability to produce platelets in the lab would potentially allow for an increased shelf life—making the platelets more useful clinically—and also allow for the production of specialty platelets for people with rare blood types.

In the study, DesRochers and colleagues isolated CD34+ stem cells from cryopreserved cord blood

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mononuclear cells and expanded them for 7 days. The CD34+ cells were then quantified again. The researchers performed this experiment 67 times using cells from 18 donors.

"We then go through multiple differentiation steps to make megakaryocytes, which are the cells that make platelets, within an enclosed perfusion bioreactor system," DesRochers said. "The benefit being that because it is enclosed, not only can we scale up the size of the bioreactor or the amount of product running through the bioreactor, but we can also look toward the future of moving into a scaled manufacturing system so that we can make a laboratory produced platelet product available in the clinic."

The platelets produced in vitro were shown to express activation markers similar to donor platelets and contained both activated and non-activated platelets, as demonstrated by scanning electron micrograph.

"When we say scalable now, it is with one single bioreactor with a limited volume, but the goal is to scale it up even more," DesRochers said. "If we continue to do that, we could foresee a future where — similar to drug manufacturing — there are gigantic tanks full of platelets being produced." ■

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