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Tailoring blood cells in the laboratory

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For some blood transfusion patients, it is particularly difficult to find a compatible blood donor. Growing matching blood cells in the laboratory has long been an overarching goal of scientists for these patients. Research from Ashley Toye and colleagues at the University of Bristol, UK, and NHS Blood and Transplant has brought this vision one step closer to reality. The research is published today in *EMBO Molecular Medicine*.

Not everyone has the same blood type: different people have different blood groups, determined by the presence or absence of so-called antigens on the surface of red blood cells. When it comes to blood transfusion, it is very important to take blood groups into account. The immune system can attack any cell presenting an antigen not naturally found on the body's own cells. Receiving a blood transfusion from an incompatible donor leads to an immune response causing destruction of the red blood cells and can be life-threatening.

There are 36 different blood group systems to categorize more than 350 antigens that appear on red blood cells in different combinations. The ABO and Rh blood group systems are the most clinically important as they have the most immunogenic antigens. Before a blood transfusion, donor and receiver are usually matched according to these two systems. Blood from donors who lack the A, B and RhD antigens is tolerated by most immune systems. But there are exceptions. Individuals who require repeated transfusion over longer time periods are more likely to develop an immune response to minor, less common antigens. In addition, people with very rare blood types require donations from an individual with

more closely matched blood type. These cases pose a major challenge to transfusion services.

A more universal source of red blood cells could offer an alternative to donated blood. Toye and his colleagues have now come a step closer to this goal. In previous work, they had already generated a red blood cell precursor cell line, able to be grown indefinitely, that can be induced to generate red blood cells in the laboratory. To meet the needs of transfusion patients at high risk for complication, theresearchers now engineered this cell line to express fewer antigens and thereby, be less immunogenic.

The researchers first conducted a 15-month survey in England to investigate which antigens most commonly caused challenges in identifying a matched donated unit for patients. They identified five blood group proteins with antigens that were responsible for incompatibility in 48 out of 56 cases. Next, Toye and colleagues removed these blood groups from their previously established immortal blood cell by genome editing. They created several new cell lines that lacked individual blood groups before creating a single line in which all five were removed. Red blood cells derived from this line could theoretically serve most of the challenging cases they identified.

Scientists are still a long way from growing blood cells in the laboratory at economically practical and large enough quantities to use them for blood transfusion. However, once the technical hurdles are overcome, the first recipients of such cells will most likely be patients for whom it is difficult or impossible to find a donor. The research of Toye and colleagues shows that it is now possible to tailor the antigenic profile of blood cell lines to the needs of these patients.

More information: Joseph Hawksworth et al. Enhancement of red blood cell transfusion compatibility using CRISPR-mediated

erythroblast gene editing, *EMBO Molecular Medicine* (2018). DOI: 10.15252/emmm.201708454