

## seeing red

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The smallest of things can cause devastation. A word can hurt deeply. Distraction can create an accident. A spark can set off a fire. In the world of molecular biology, “small” rules. Life itself thrives on an intricate and very fragile harmony perpetuated by myriads of tiny molecules. And when something goes wrong, when a molecule changes its habits, it can create havoc. A few examples: cancer, Parkinson’s disease, Alzheimer’s and diabetes, to name but four. Blood transfusion – and even more so its effects – also depends on very small regions which themselves belong to very small molecules on the surface of each of our red blood cells. Pour the wrong kind of blood into someone, and you are in for serious complications. We all belong to a certain blood type, or group. As a consequence, we can only receive certain types of blood. Most of us have relatively common types and finding donors is usually not a problem. However, some people belong to very rare blood types, thus making blood transfusion a particularly delicate task. One of these types is known as Vel-negative. And after 60 years of scientific bafflement, it has finally been pinned down to a protein named SMIM1.



The Wall (2015), by Helmut Findeiß

Courtesy of the artist

Research on blood transfusion began in the 17<sup>th</sup> century with the English physician William Harvey (1578-1657) while carrying out experiments on blood circulation. The very first transfusions were done with animal blood, and were fatal to the receivers. It was only at the very beginning of the 20<sup>th</sup> century that the Austrian physician Karl Landsteiner (1868-1943) discovered that humans belonged to different blood types, which he coined A, B and C – later to become A, B and O. In 1902, his colleagues Alfred Decastello and Adriano Sturli discovered the fourth blood type: AB. Meanwhile, in 1907, the Czech serologist Jan Janský (1873-1921) had also identified the four major blood types – and in one go – but because of poor communication his findings were

shadowed until the 1920s. Today, however, Janský is credited with having been the blood group pioneer. With time it became apparent that everyone’s group is inherited, and that the success of transfusion depends on both the donor’s and the receiver’s blood type. Other major blood types have since been discovered, such as Rh+ or Rh-. But you can also belong to a blood type that is very rare, making it all the more difficult to find a blood donor.

But what exactly is a blood type? To cut a very long and complicated story short, blood types are defined by sugars (or antigens) that are found – or not – on the surface of our red blood cells. So if your blood group is A, this means that you carry the A antigen on the surface of your red blood cells. It also means that your body has produced B antibodies (anti-B) over the years, probably following contact with viruses, bacteria or even plants. If someone makes the mistake of putting type B blood into your body, your B antibodies will react with the foreign B antigens present in the donor’s blood, thus causing it to clot – this is known as a haemolytic transfusion reaction, or HTR, and can be fatal. While it may sound simple, a person’s blood group depends on more than just the presence – or not – of one sugar on the surface of our red blood cells. But you get the picture.

A, B, AB, O, Rh+ or Rh- are the more common blood types. But some people carry blood types that are far less popular. One of these is Vel-negative blood type, so-called because it was found, in 1952, in Mrs Vel's serum after she had suffered an acute HTR following a blood transfusion. Vel is expressed on most people's red blood cells; but it was not expressed on Mrs Vel's. She was Vel-negative, and could only receive blood from Vel-negative people too. This blood type, however, only occurs in 1 out of 4,000 individuals and is consequently not easy to come by. The case is dreaded by doctors because the reaction is known to be particularly aggressive, and despite its clinical implications, the Vel blood group antigen remained a mystery for a further 60 years. It was only in 2013 that its biochemistry and genetics were finally unveiled, paving the way for Vel DNA tests.

People who belong to the Vel-negative blood group lack a specific sugar on a protein known as SMIM1. SMIMs are a collection of small integral membrane proteins of which there are about 25: they are unrelated and most are uncharacterized. SMIM1 is 78 amino acids long. It seems to have only one transmembrane domain, is able to form multimers, and its C-terminus juts out on the extracellular side of red blood cells. The Vel antigen is a sugar, and is docked to this short extracellular domain. In Vel-negative individuals, the sugar is not detected. This is because SMIM1 has been mutated, causing a single amino acid change.

How exactly the mutation affects SMIM1 is not yet known. Does it prevent SMIM1 from being correctly targeted to the cell membrane? Is

SMIM1 targeted in such a way that Vel is not presented properly? Or is the Vel antigen simply not attached to SMIM1? Whatever the answer, Vel goes undetected on the cell's surface thus causing the Vel-negative phenotype. This said, although blood transfusion for Vel-negative carriers is problematic, until now the mutation has otherwise shown no clinical signs of abnormal development or physiology. Carbohydrate entities on the surface of red blood cells are known to have roles in cell membrane integrity and cell adhesion, for example, and can also act as receptors for extracellular ligands and enzymes. The precise role of SMIM1 has not yet been identified, but it does seem to be involved in the regulation of red blood cell formation.

The identification of the major blood groups at the turn of the 20<sup>th</sup> century has helped to save millions of lives. Its fine-tuning with the discovery of Rhesus and the more rare blood types – such as Vel-negative – have hugely improved transfusion on the whole, not to mention the field of obstetrics where differences in the mother's blood type and that of the baby she is carrying can sometimes have dramatic outcomes. Across the globe, we now know that blood types are distributed differently among populations – sometimes even within populations – and these characteristics are widely used by evolutionary biologists to understand early human population migrations for instance. Certainly, little did scientists know a century ago, that such small sugars on the surface of our cells had such long stories to tell.

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