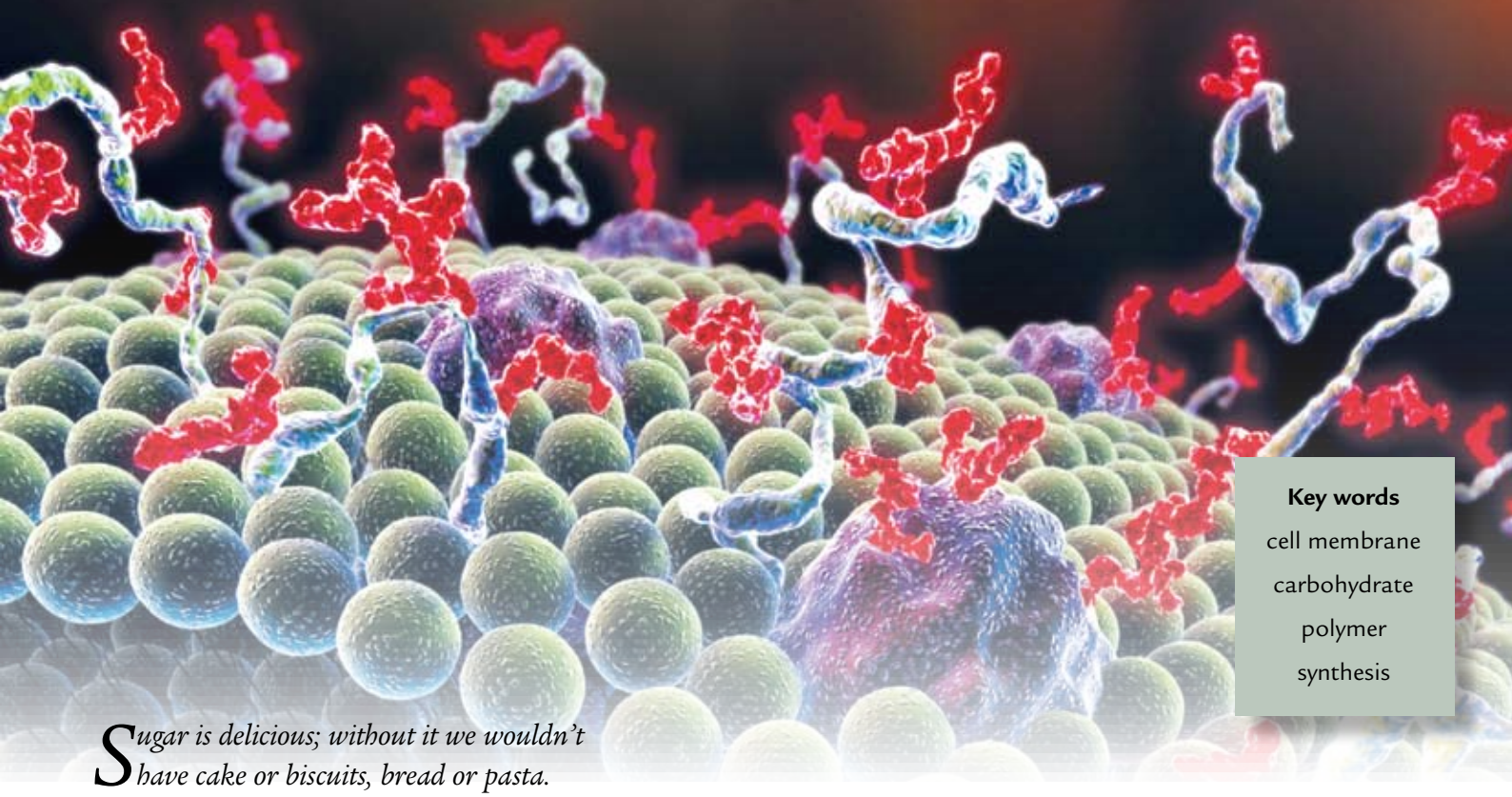
Blocking viruses with synthetic receptors

Joshua Howgego



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synthesis

Sugar is delicious; without it we wouldn't have cake or biscuits, bread or pasta. But to scientists, sugar is much more than a food; sugar molecules can also form polymers which act as 'molecular bar codes' to help cells recognise each other, as Josh Howgego explains.

A few decades ago carbohydrates were seen as the least important of the three types of molecule in biochemistry. Lipids (fats) make up our cell membranes and insulate the neurones which carry our brain waves. Proteins are the building blocks of life, forming enzymes which control all our cellular processes and the structural components of our hair, nails, skin. As for carbohydrates, we knew we needed a decent amount of them to burn up as fuel, but that was about where our interest ended.

Well, we were wrong to be bored with carbohydrates. It's now clear that every human cell is covered in a layer of molecules known as glycolipids; molecules which are part carbohydrate, part lipid (Figure 1). The glycolipids protrude from the surfaces of our cells as identifying markers to the rest of the body. It's vital that cells can tell each other apart, otherwise **phagocyte** cells might begin gobbling up bits of lung or heart, rather than concentrating on bacteria and other foreign material – which could be problematic, to say the least! These identifying glycolipid markers help to ensure this kind of tragedy doesn't happen.

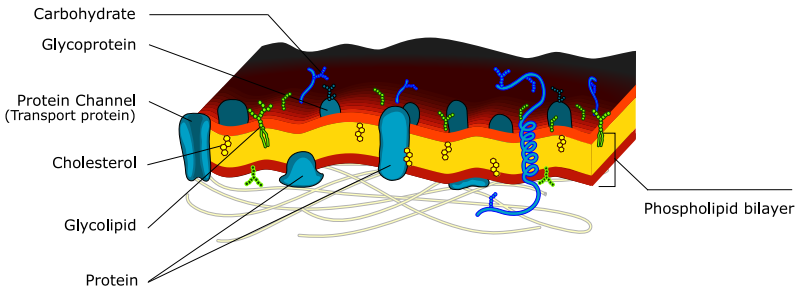


Figure 1 *Glycolipids (green branching molecules) on the surface of a cell.*

For these molecular bar codes to work, the glycolipids need to be complicated enough such that each type of cell can have its own unique identifying molecule. Although sugars themselves are quite simple molecules, they can join together to form polymers. Unlike conventional polymers (such as Nylon) where the **monomers** can join together in just one way, sugar polymers, or **oligosaccharides**, can be much more complicated. This is because sugars have several different hydroxyl (-OH) groups which may react. The bonds formed can also be different in space (see Box) so the resulting polymer can vary in lots of different ways – they're very complicated!

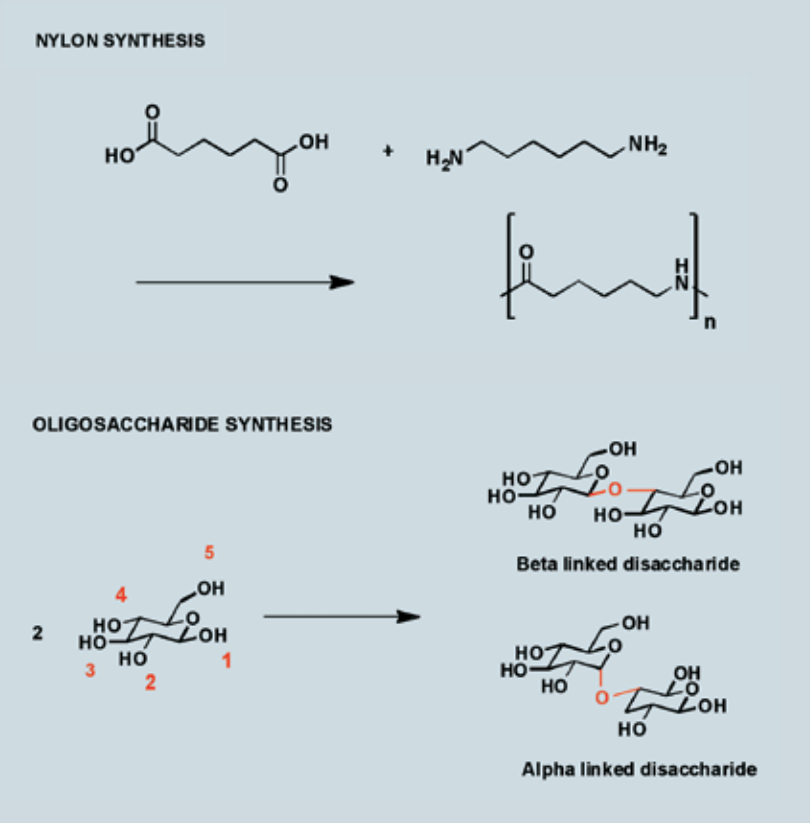
Monomers Small molecules which join together to form the repeating unit of a polymer.

Oligosaccharide A short polymer composed of a few sugar molecules joined together.

Phagocyte A type of white blood cell. These ingest and break down foreign cells and detritus in the body.

Polymerisation of sugars

The monomers which make simple polymers like Nylon can only react in one way, producing a long-chain structure. With sugars it's different though. Any of the 5 hydroxyl groups can react with another sugar and these linkages can also be different in space (alpha or beta). The diagram shows how just two sugar monomers join together; imagine how complicated the structures get when there are more!



'Lock and key' recognition theory

So we can see that by joining up lots of sugar monomer units we can generate a diverse range of complicated 3D structures – enough such that each type of cell in our bodies can have its own unique identifying molecule. But how can our cells 'read' these sugar patterns?

The process of recognition involves complex protein receptors; very large molecules which have a cavity of a specific size and shape (Figure 2). Only sugar markers which have exactly the right shape can bind inside the cleft, like a key into a lock. Since cells have these protein receptors as well as the glycoproteins built into their cell membranes (look back to Figure 1), they are able to recognise each other.

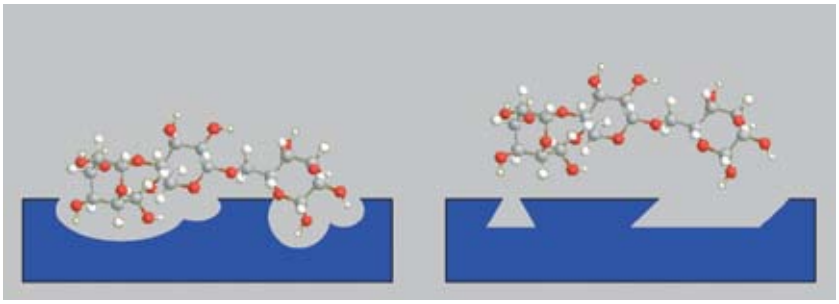


Figure 2 *Only an oligosaccharide (shown as a molecular model) and a receptor (blue) which have exactly complimentary 3D shapes can recognise each other (left). If the 'lock' and 'key' don't fit, then no recognition occurs (right).*

Alien invasion

Unfortunately, the glycoproteins also provide viruses and bacteria – not just the friendly cells from our own bodies - with an identifying handle to grab on to. This is precisely how many viruses (including HIV and influenza) identify their host cells; by using their surface receptor proteins to recognise and latch on to their unique 'bar codes'.

All this knowledge has led to a lot of scratching of heads among scientists. If only we could make something in our laboratories which could bind to specific cell markers it might be possible to block the recognition events which allow viruses to identify the host cells they are seeking to invade. It could be a way to cure lots of terrible diseases, such as HIV.

We are a long way from this goal, but chemists at the University of Bristol have now come up with a logical yet novel way of tackling this problem and have now reported the first artificial receptors for carbohydrates.

Professor Anthony Davis took another look at sugar molecules and recognised that have a cyclic core with just two main features emanating from it, as shown in Figure 3. These are –OH hydroxyl groups (blue) and C-H bonds (red), and they can lie either in the plane of the molecule (equatorial) or stick up from it (axial), depending on the type of sugar. Hydroxyl groups are hydrophilic – they prefer to dissolve in water – whereas C-H groups are hydrophobic and avoid water.

It ought to be possible, he thought, to build a molecule large enough to surround the sugar in a cavity and organise an array of polar hydrogen bonding groups and non-polar panels within it which would present complimentary surfaces to a sugar molecule in the cavity.

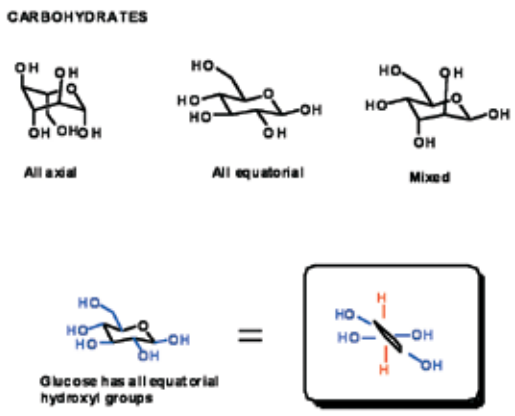


Figure 3 *Carbohydrate molecules have –OH hydroxyl groups which are polar (red) whereas their C-H bonds are non-polar (blue).*

To start with the chemists decided to target sugars which have all their hydroxyl groups pointing outwards to make things a little less complicated. They came up with a complementary scaffold for this and dubbed it a 'temple', due to its hydrophilic 'pillars' and hydrophobic 'roof' and 'floor' (Figure 4). The design also has outwardly directed polar groups which help make sure this large, otherwise non-polar structure can dissolve in water.

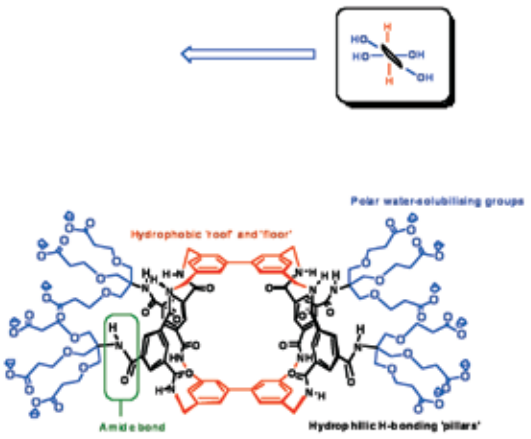


Figure 4 *A trap for a sugar molecule – the synthetic receptor designed by the Bristol team.*

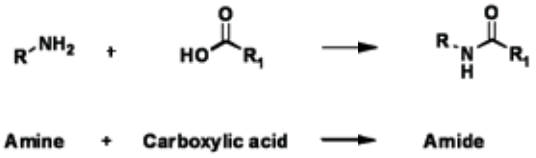


Figure 5 *Chemists use simple reactions such as the formation of amide binds to stitch larger molecules together, piece by piece.*

A chemist working in one of the research labs at Bristol University.

Building molecules

The chemists made the receptor using chemical reactions to build up the structure piece by piece. Although the structure may look frighteningly complicated, chemists use simple reactions to stitch the fragments together – in this case the formation of amide bonds, as shown in Figure 5.

Professor Davis' design worked well and the synthetic receptor was able to bind simple sugars with a strength approaching that of natural proteins. Figure 6 shows a sugar molecule trapped inside the receptor. There's a long way to go before we are truly able to put a cap on viruses – not least being able to bind sugar polymers, rather than just the monomer units. At last, though, the first step on the journey has been taken.

Josh Howgego *is a PhD student at the University of Bristol studying the design and synthesis of carbohydrate receptors.*

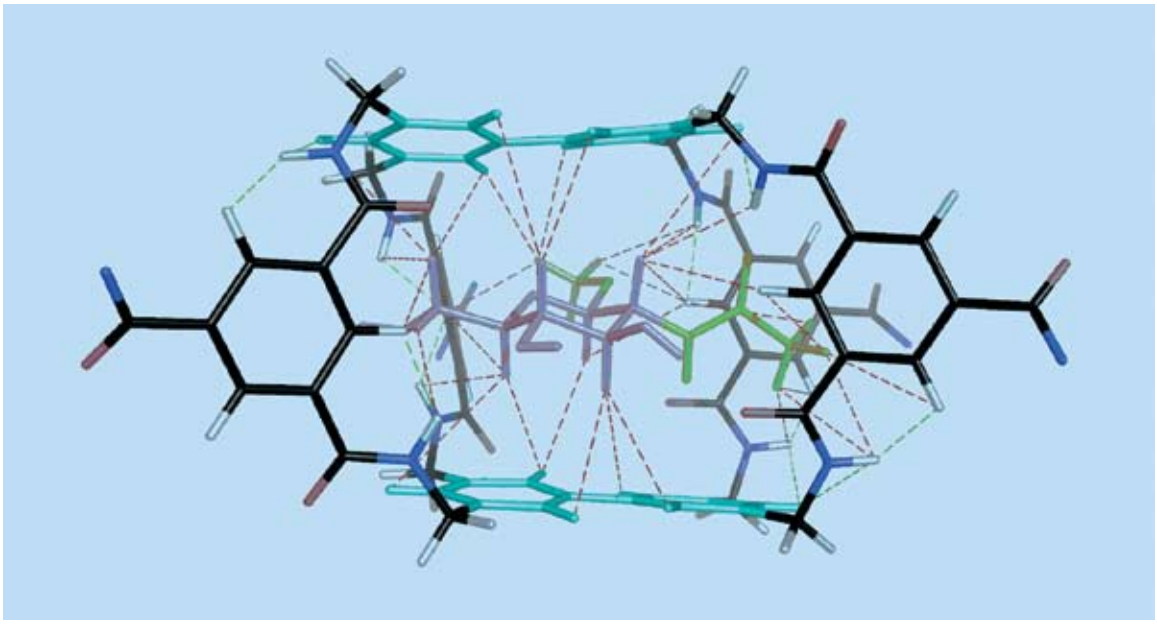


Figure 6 *A molecular model showing how the receptor can trap a single sugar molecule – (the purple and green structure in the centre).*