Programming self-destructing protein nanorobots – a recipe for health?

Diseases are getting harder to treat. It's not that the diseases themselves are changing (though that is also true in some cases) but rather that we have defeated the ones that were the easiest targets. In developed nations at least those that remain are lifestyle -and particularly age-related, cancer being the most notable example. These diseases are multicomponent and complex; they often are due to malfunctioning of the body's own cells which turn against their host. This makes treatments difficult; killing some of your own diseased cells while sparing other, very similar healthy cells is tricky and often healthy cells are caught in the crossfire, leading to unpleasant side effects and limiting treatment efficacy.

So why can't we target our drugs more effectively so they only reach the cells where they are needed? Traditionally drugs are small dumb molecules that once in the body enter the blood steam and are passively distributed throughout the body to those places where they are needed and crucially, to those that they are not. Because the molecules are simple and "naked" they can potentially act anywhere in the body, resulting in side effects. Another problem is that more complex "smarter" drugs such as enzymes tend to be more fragile and can be easily destroyed before they reach their target.

These problems could be overcome if we could design a tiny container into which drugs could be placed before being put into the body. The container would protect the drug from the body, stopping sensitive drugs from being destroyed. If the container could be modified to be taken up only by diseased cells and only then open up to release their drug cargo then it would result in a great improvement for treatment. This is not a new idea in fact it is billions of years old: It is essentially how a virus works. The simplest viruses are nothing more than a DNA (or RNA) instruction code (the genome) inside a spherical protein shell made of many copies of a protein building block and just 10s of nanometres in diameter (a nanometre is a billionth of a metre). Viruses act like tiny robots; structures on the outside of the shell target it to specific cells, and only once inside does the shell break down to release the cargo.

If viruses are so great then why not just remove their genome and replace it with our desired rugs? This has been attempted but is not without its difficulties: Some viruses have unwanted effects – they may not naturally a target the same cells you wish to treat, and them may not naturally be able to carry the desired cargo. Furthermore, the protein building blocks that make up the virus shell are connected by a network of many bonds which stick them tightly together. This means that they are typically very stable, so much so in fact that it is difficult to break them apart on demand (so called "triggerable disassembly") would be a highly desirable property for our hypothesized drug carrier.

Ideally a designed spherical protein (a so-called "protein-cage") could overcome these problems. An artificial system would allow us to design-in all the properties we desire while leaving out the undesirable ones. Until now nobody has been able to produce an artificial protein cage where the disassembly of the cage could be triggered on demand. Recently though we managed to achieve this, producing a cage called *TRAP-cage* where the protein building blocks that make up the cage are held together by atoms of gold. This cage is extremely stable and robust and very difficult to break apart under normal circumstances. But it can be disassembled in certain conditions like those in our cells (known as reducing conditions). In our new work we propose to both understand more about how this novel structure is formed and then use this knowledge to increase its "smartness". The first thing we will do is replace the gold "glue" that holds TRAP-cage together as gold could potentially toxic for as well as being expensive. By replacing the gold with chemical bridges we hope to achieve two things: one is increasing the size of the cages so that they can carry more cargo; the second is to use cross-linkers with different characteristics to actually program the conditions in which the cage breaks down such that not just reducing conditions but other triggers can be used. This "disassemble on demand" will give our system wider applicability. Finally, we will develop methods to put useful cargoes inside our cages and show that they can be released in cells on triggering.

In summary, an understanding the fundamentals of the TRAP-cage system will allow us to build programmable cages that can be filled with useful cargoes. In the future we may be able to use these novel cages as smart nanorobots to fight disease.