



## The search for a prostate cancer magic bullet

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For decades, cancer researchers have been trying to develop *magic bullets* that will target a toxin to a tumour. This task has proved difficult, but some cancers are now being treated by this class of drug. This week's research blog describes progress in creating a magic bullet style of drug for prostate cancer.

### The cancer magic bullet

It's been over 100 years since the term *magic bullet* was first used. German Nobel prize-winner Paul Ehrlich coined the term in 1900. He envisaged a medicine that would specifically target tumours, bringing a toxic payload only to the tumour cells. Although this concept is fairly simple, to date only a handful of such medicines have been approved for treating cancer. Given that it's 120 years since the idea was first announced, it's safe to say that progress has been slow.

An example of a magic bullet is the breast cancer drug Kadcyla. Kadcyla targets breast cancer cells via receptors on the surface of breast cancer cells. It carries a toxin that kills these cells.

### Antibodies for targeting magic bullets

The magic bullet imagined by Paul Ehrlich has two components. The first is a targeting molecule that directs it to cancer cells. The second is a toxin; a poisonous component that will kill the cancer cell.

The discovery of [antibodies](#) has provided very useful targeting components. Antibodies are large proteins produced by the immune system. They act as watchdogs for the body, recognising and sticking to invading foreign organisms. In the past 15 years, many different antibodies have become part of successful cancer therapies. These antibodies are designed to recognise cancer cells by binding to biomarkers on the cell surface.

A useful cancer-fighting antibody will recognise cancer cells but not normal cells. An essential requirement of antibody targeting is a good target (i.e. a "biomarker" molecule). We need to find a biomarker that is only present on the surface of cancer cells. If too many other cells have these



biomarkers, then the new drug will kill these normal cells as well. This can lead to toxic side effects. A lack of good target biomarkers has held up the development of magic bullets.

### **Antibody-drug conjugates – a type of magic bullet**

An *antibody-drug conjugate* is a type of magic bullet. It consists of an antibody, which targets the cancer cells, and a toxic drug that kills the cancer cells. A small number of these magic bullets, such as Kadcyca, are currently being used to treat cancers.

Fortunately prostate cancer has some good biomarkers. One is the protein called PSMA (prostate-specific membrane antigen). PSMA is found on the surface of prostate cells. High levels are found if the cell is cancerous. We only expect to see prostate cells in the prostate gland. So finding cells containing PSMA around the body can show tumours that have spread. This is the basis for PSMA-PET scans. Targeting toxins to the PSMA protein is a promising avenue for drug development.

Unfortunately low amounts of PSMA are also found in the nervous system, small intestines, and salivary glands. This means the drugs targeted through PSMA could affect these organs, leading to difficult side effects. These side effects can be minimised by using lower doses of the PSMA-targeting drug. But lower doses means the drug may not be as effective.

STEAP1 is another promising biomarker for prostate cancer. It's a protein found on the outside of cells that's involved in transporting molecules in and out. STEAP1 is found on the outside of prostate cancer cells but not on most other cell types. The study described below targets a toxin to prostate cancer via STEAP1.

### **A new magic bullet for prostate cancer passes a phase 1 trial**

Researchers from the Memorial Sloan Kettering Institute in the US have [recently published](#) a “first in humans” trial of a magic bullet drug targeting prostate cancer through STEAP1. The research group were led by eminent oncologist and researcher Prof Howard Scher.

Their experimental drug has been made to target prostate cancer through STEAP1 proteins. The drug uses an antibody that recognises STEAP1. This antibody is attached to a toxin to kill the cancer cells. They have helpfully labelled the new drug as DSTP3086S.



The toxin used in this drug, called monomethyl auristatin E, is like a natural chemotherapy. It was first isolated from a sea creature called the [Wedge Sea Hare](#). By itself, it's too toxic for use in humans. But when properly targeted, it makes a useful treatment for some types of cancer.

The aim of the phase 1 trial was to ask whether the new drug could be safely used in humans. Phase 1 trials are usually the first time that the drug has been taken by people, so safety is a major concern. Phase 1 trials start at low doses for the first few volunteers. Once the drug can be safely taken at a low dose, new volunteers will receive increasing doses. Researchers will carefully assess any side effects before increasing the dose for the next volunteers. The dosing will stop once side effects become apparent, before they become unacceptable.

Volunteers joining this trial were men with late-stage prostate cancer, whose cancer had spread despite hormone therapy. This is called metastatic castration resistant prostate cancer. The researchers first confirmed that these men had tumours that carried the STEAP1 protein. They received treatment once every 3 weeks.

Results from this trial determined the recommended dose for a phase 2 trial – where the benefits of the drug will be assessed. The researchers concluded that DSTP3086S had an acceptable safety record at a dose that is worth testing in a phase 2 trial, which is good news.

The bad news is that the new drug brought considerable side effects. These included fatigue (tiredness), nausea, constipation, diarrhoea, vomiting and peripheral neuropathy (pain in the hands and feet). Most of the men in the trial had more than one of these issues.

During a phase 1 trial, researchers usually look for signs that the drug is working. For DST3086S there were some promising signs. 18% of the men had their PSA levels drop under 50%. Other makers of disease such as circulating tumours cells showed positive signs. As this is a short-term trial and many of the men received a low dose, these numbers are probably underestimating the benefits.

Despite many side effects, this new magic bullet looks like progressing to phase 2 clinical trials. Unfortunately, the drug development process takes many years to complete. But it's pleasing to see that there are promising new drugs for prostate cancer that are in the pipeline.