

# Developing a treatment for ovarian cancer

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## Abstract

Ovarian cancer is a really nasty disease. Although, like most cancers, it is curable if caught early enough, in practice it is not usually diagnosed until it is too late for curative treatment. It initially responds well to treatment and patients can go into remission for months or even years, but it usually returns and ultimately proves fatal. In this article, I describe a project I have been working on designing clinical trials with a high-tech immunological product, Cvac™, which uses modified autologous dendritic cells to prime the patient's immune system to attack ovarian cancer cells. We hope that Cvac™ will prolong the period of time in which women can remain in remission from ovarian cancer, but we will have to wait for the results of the clinical trials to know whether it does.

**Keywords:** Cancer, Immunology, Clinical trials, Outcome measures

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There are many reasons why I love my job, but one of them is that I sometimes get to work on projects which are not only interesting, but also have the potential to make a real difference to human health. In this article, I would like to tell you about a project I have been working on recently which fits firmly into that category.

One of the reasons why I originally wanted to become a scientist was that I had this crazy idea that I might make important discoveries that would make the world a better place, like finding a cure for cancer or something like that. Well, I am never going to do that in the way I originally imagined, as my career as a lab scientist was over long before I ever got to do anything useful. Those of you who have sat within earshot of me in the bar at an EMWA conference will doubtless have heard the story of the little phosgene gas incident that was partly responsible for cutting my lab career short.

But of course 'finding a cure for cancer' is not as simple as just making a discovery in a lab one day.

It is a hugely complex multidisciplinary process, involving lab scientists for sure, but also doctors, statisticians, medical writers, clinical project managers, etc. Potential cures must not only be discovered, but also investigated thoroughly in a series of laboratory experiments, animal studies, and of course clinical trials in humans. Every part of that complex process is necessary if a discovery is ever going to make it from the lab to clinical use.

So even though I never got to discover anything of interest in my lab career, I now find myself contributing to the process of improved cancer treatments in my work as a clinical trials statistician, helping to design trials that may show a potential new treatment really does have clinical benefit. I will settle for that. Although I got there by an extremely roundabout route, it is remarkably close to what I thought as a child that I'd do when I grew up.

I should point out at this point, although I am sure you already knew, that there is no such thing as a 'cure' for cancer. Cancer is not just one disease, but a generic term for a whole series of different pathological conditions. So a treatment that may have huge benefits for one particular cancer may be useless for other types of cancer. Think of tamoxifen, for example, which has been a great advance in the treatment of breast cancer, but is not much use for anything else. And it is pretty rare for any of the treatments currently at our disposal, with the exception of surgery, to be anything like a 'cure'. Although genuine cures may come one day, the best we can hope for at the moment for those patients unlucky enough not to have been cured by surgery is to prolong the time in which they can enjoy a reasonable quality of life before the cancer finally gets them. But even that, of course, is a thoroughly worthwhile aim.

So what is this exciting project I have been working on recently? It's a pleasingly hi-tech treatment called Cvac™, produced by the Australian biotech company Prima BioMed

(<http://www.primabiomed.com.au/>), which we are trialling for patients with epithelial ovarian cancer.

Ovarian cancer is a really nasty disease. Like most cancers, it can be cured with surgery if caught early enough, but becomes metastatic and ultimately fatal if it is not. But unlike many other cancers, it is rare for it to be caught early enough. As the tumour is on an internal organ, it is not obviously noticeable, and as initial symptoms are non-specific, such as abdominal pain or irregular periods, they are often not identified as being due to cancer. So usually, by the time the symptoms have become severe enough that the diagnosis is made, it is already too late for surgery to have a good chance of being curative.

Now, the good news is that ovarian cancer often responds well to chemotherapy (a combination of platinum-based drugs and a taxane is usually the treatment of choice), and patients can often go into remission and be quite healthy after initial chemotherapy. But this happy state of affairs does not usually persist, as the disease usually recurs after a period of months or at best a few years. The recurrence may also respond well to chemotherapy, but by that stage future recurrences at ever-decreasing intervals are more or less guaranteed. One large trial that reported in 2009 found a median progression-free survival (time until either disease recurrence or death) of 16 months and a median overall survival (time to death) of 44 months in patients with stage III or IV ovarian cancer after initial surgery.<sup>1</sup>

Cvac™ is unusual in that it is designed to treat patients while they are in remission, with the hope that remission will be prolonged. The way it does this is really quite cunning. Cvac™ is an immunotherapeutic product, which is designed to stimulate the patient's own immune system to fight the cancer. The idea is that once the immune system is primed to attack the cancer cells, then any recurrences will be destroyed by the immune system before they grow to the point where they cause trouble.

So how does it work, exactly? Well, it relies on the fact that many ovarian cancer cells over-express a surface protein called mucin 1. Normal mucin 1 appears in some healthy cells, but a modified form is expressed in cancer cells. The main difference is that mucin 1 is normally extensively glycosylated in healthy cells, but much less so in ovarian cancer cells. The more exposed mucin 1 in the cancer cells is therefore an easier target for immunological attack.

And how is the immune system primed to attack mucin 1? Well, this is where it gets quite tricky,

because Cvac™ is an autologous cellular product, which has to be individually prepared for each patient. The patient has to undergo leukapheresis, during which her mononuclear cells are harvested, which are subsequently differentiated into dendritic cells. The dendritic cells are then cultured, together with a fusion protein of mannan (which acts as an adjuvant) and modified mucin 1. Thus Cvac™ is autologous dendritic cells primed with modified mucin 1. It must, of course, be injected back into the same patient from whom the cells were harvested in the first place.

The modified dendritic cells are now in a position to activate the T cells of the immune system to recognize the modified mucin 1, and kill any cells that are expressing it in any quantity, which hopefully includes ovarian cancer cells. That is probably a hideously simplified explanation of how it really works, as I do get a bit hazy on some of the details of complex immunology, but I dare say that it will do as an overview.

I have had the pleasure to work on two clinical trials with Cvac™. They are still at an early stage, so we do not yet know whether the product works as well as we hope it will (or even at all). We have recently finished recruitment into a phase II study in about 60 patients, although it will be another year or two before the study is complete. We probably will not learn very much about efficacy from such a small study, but we might see some hint that the product works if it works well. We should, however, learn about the safety of the product, and initial results seem to be very promising, with no sign so far of the sort of toxicity that might be expected from conventional cancer chemotherapies. This is the great advantage of using such a precisely targeted therapy, as opposed to the sledgehammer approach of cytotoxic chemotherapy.

We will soon be starting a phase III study, and being involved (as the project statistician) in the design of that study has been fascinating. We have thought about the design very carefully, and have received advice from both the European Medicines Agency and the American Food and Drugs Administration on the study. One of the most important questions we have had to grapple with is the choice of primary endpoint. Phase III studies in cancer typically use either progression-free survival or overall survival as their primary endpoint, and the choice is not straightforward. Overall survival has the benefit of being a thoroughly objective and clinically relevant measure, and is preferred by regulators. In contrast, using progression-free survival means that you have results sooner,

which is advantageous not only commercially but also ethically, in that a treatment that may have significant benefits can be brought to patients sooner. Furthermore, you could make a strong argument than when patients are in remission and enjoying a good quality of life, the time they spend in remission before the disease returns is highly clinically relevant, perhaps even more so than overall survival. The time spent between when incurable cancer returns and death is not much fun, as anyone who has lost a friend or relative to cancer will be aware. One could argue (and I absolutely would) that there is little benefit to prolonging that period of time, whereas prolonging the time spent in good health until the disease returns is self evidently of great benefit.

In the end, that last argument won, and progression-free survival will be the primary endpoint of the trial. The trial will be starting very soon (and perhaps will have started already by the time you are reading this), but will take a few years before we see the results. If the results are as we hope they will be, then this could transform the outlook for patients with ovarian cancer. Being a part of that is the sort of thing that makes going to work seem all worthwhile.

## Reference

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**Adam Jacobs** is the director of Dianthus Medical Limited, a company providing medical writing, statistical consultancy, and data management services. He has a PhD in chemistry, an MSc in medical statistics, and is currently studying part time for a degree in economics. He was president of EMWA in 2004–2005.