

Australasian Science

Calling Time on Cancer

Tailoring Treatment to the Immune Cycle

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Window of Opportunity

MARTIN ASHDOWN & BRENDON COVENTRY

By targeting cancer treatments to specific phases of the immune cycle, researchers believe they can dramatically improve the chances of complete remission.

It is just over 100 years since Charles Mayo, of Mayo Clinic fame, was exchanging letters with William Coley, a New York surgeon who was using “bacterial toxin” vaccines to successfully treat patients with advanced cancer – even causing complete remission of all cancer in 5–10% of patients. These historical letters from the 1890s are truly instructive.

Fast-forward to 2014 and we find that cancer immunotherapy is again topical as a result of occasional promising new responses. But how do we make cancer immunotherapy work for all patients? Are we truly on the precipice of major advancement?

A cancer drug that has been used for more than 20 years and can cure advanced cancer patients is providing new information about how to achieve complete remission from cancer. This drug, interleukin-2, is providing something analogous to how the “Rosetta Stone” unlocked historical script.

In the late 1790s, during the Napoleonic expedition into Egypt, a French soldier found a metre-high stone tablet that enabled Jean-Francois Champollion to decode hieroglyphics, which had remained unfathomable for about 2000 years. The Rosetta Stone had the same information in three different languages: Ancient Greek, Demotic Greek and Egyptian hieroglyphics. The Greek components were understood so, by a relatively simple process of comparison and substitution, the meaning, syntax and content of the hieroglyphs were translated. Consequently, as a result of this deciphering and years of extensive archaeological investigation, we have a detailed understanding of the day-to-day life, literature and history of the Egyptian civilisation over four millennia.

The word “translation” is often used in cancer science too, referring to the process of translating experimental discoveries into clinical use, and vice versa. However, translation of many laboratory findings into clinically effective therapies has been tediously slow and marked with many failures. The whole field has lacked its own version of a Rosetta Stone.

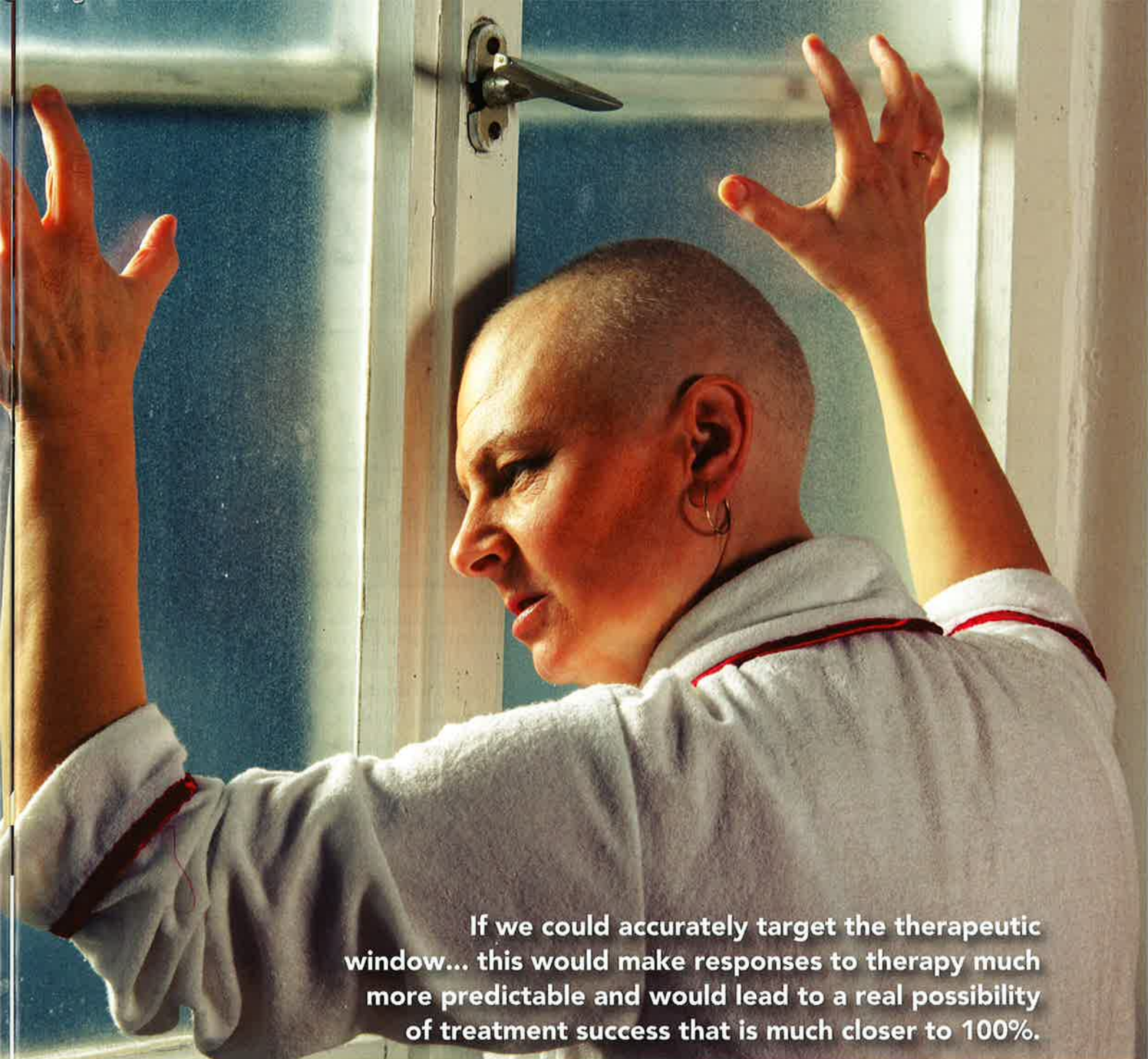
Despite billions of dollars of research expenditure, the mortality rates for advanced cancer have not changed appreciably over the past 50 years. More than 150,000 people die of cancer each week, so what’s gone wrong? A senior US oncologist, Dr Laurence Baker, stated in the *Journal of the National Cancer Institute*: “I am trying to get people to stop saying how successful the cancer research enterprise is. It is not true. It is just not true.”

However, the Rosetta Stone for cancer may be much closer than we think. Interleukin-2, together with a new understanding of its mode of action, is providing important clues suggesting it might be made to work in most, if not all, cancer patients. Recently, Los Angeles oncologist Dr Omid Hamid wrote of immunotherapy in the journal *Oncology*: “We find ourselves at the precipice of major discovery”.

Interleukin-2 is an immune hormone, or cytokine, that was originally thought to switch the immune response “on”. It was



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If we could accurately target the therapeutic window... this would make responses to therapy much more predictable and would lead to a real possibility of treatment success that is much closer to 100%.

used to treat late-stage cancer, particularly kidney cancer and malignant melanoma, and achieved complete responses (where all cancer disappears) in some patients. These cancers have very different origins yet interleukin-2 strangely delivers complete remissions in 7% of patients on average. This rate has been unchanged for more than 20 years.

The conundrum is that when 100 patients are treated with interleukin-2, no one knows which seven or so patients will achieve complete remissions. Even more remarkable is the observation that these complete remissions typically happen within two cycles of treatment, and many of these are “cures”. So why doesn’t interleukin-2 therapy work as well in the remaining 93% of patients?

This is where the story gets more interesting. About 10 years ago it became apparent that interleukin-2 is not only responsible for initiating the immune response, much like pushing a

car’s accelerator pedal, but paradoxically it also terminates that same response – like pushing the brake pedal. How do we explain this paradox of opposing effects?

If the accelerator or brake were applied separately we would see either acceleration or braking. But what if both were applied together at the same time, or sequentially? We must turn to physiology for an explanation.

The immune response is a time-dependent sequential process. We know this from our experience with vaccines, as it takes about 10–14 days to develop protective immunity after a vaccination. Once stimulated, immune hormones like interleukin-2 and their cell receptors interact over time and a response then occurs.

Interleukin-2 receptors are present on activating and suppressing immune cells that either stimulate or inhibit the immune response, respectively. Therefore, the immune response

can be switched either “on” or “off” by interleukin-2 depending on whether activating or suppressing immune cells have interleukin-2 receptors. However, interleukin-2 receptors are only present on the immune cells for 8–12 hours before declining.

The missing piece of information – perhaps the “Rosetta Stone” of this dilemma – is that interleukin-2 receptors are not expressed all at once on all of the cells, but are expressed sequentially, first on activating immune cells and then on suppressing cells. But another piece of information is needed to translate our immunological Rosetta Stone, and again we need to examine known physiology.

Most physiological processes show regular fluctuations or cycles. Examples are the monthly menstrual cycle and the diurnal temperature and cortisol cycles. These cycles are determined by underlying hormonal fluctuations. The immune response to cancer also appears to fluctuate in a repetitive manner to form an immune cycle that is unique to each patient.

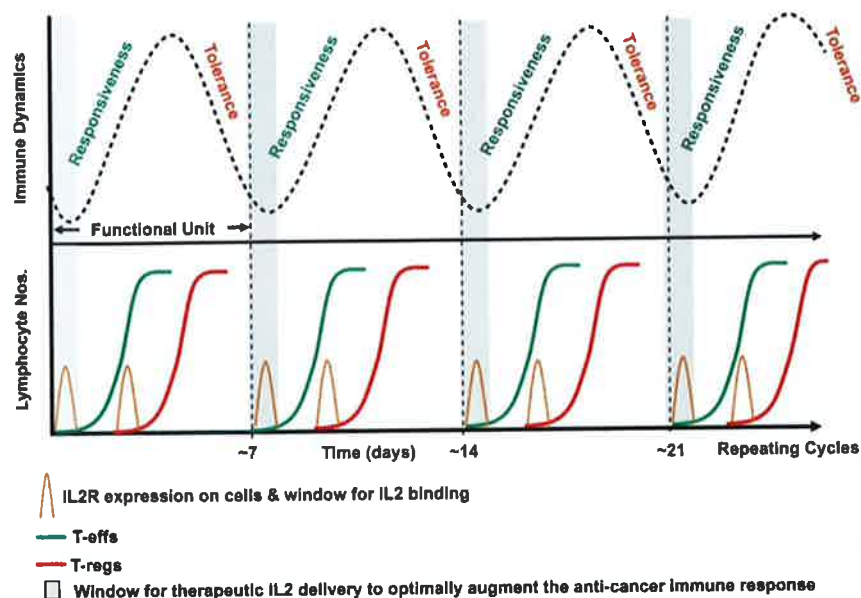
With this knowledge we can understand that naturally produced interleukin-2 receptors are expressed alternately on the activating and then the inhibiting cells, and that the interleukin-2 released drives each group of cells into “waves” of cell division, thus turning the immune response on and off in immune cycles.

Our work is clearly showing that the timing of therapeutic intervention is crucial for dictating the outcome, with random administration giving random responses. Historically, the repeated findings of a 7% chance of achieving a complete response, where all tumour is removed by the patient’s immune system, strongly suggests that mathematical probability is at play and is limiting the chance of a successful response.

Indeed, we have derived a simple equation that explains why the random administration of interleukin-2 therapy provides a complete response rate of about 7% due to a 12-hour window in an approximate 7-day immune cycle (168 hours). Thus the chance of hitting that window is one in 14, or 7%.

This explains that the 7% success rate for interleukin-2 therapy is not random at all. Rather, success occurs when interleukin-2 has been given at the correct time in the immune cycle to accelerate and drive the immune response forward.

Now that we understand this principle, how can we deliver interleukin-2 at the correct time to generate a complete remission? The fact that only about 7% of patients treated with interleukin-2 achieve successful complete remission, while 93% of patients do not, implies that correct administration of inter-



Interleukin-2 therapy will achieve a complete response when it is administered during a 12-hour window in the 7-day immune cycle. Credit: Cancer Management and Research

leukin-2 occurs in about 7% of cases and that the immune response is stopped or turned off in the 93% of non-responding patients. How does this occur and why has this realisation taken so long?

Failure to factor physiological fluctuations over time into experimental designs has been a major oversight by cancer researchers. The transient nature of receptor–cytokine interactions on immune cells, and the bimodal actions of interleukin-2 and many other cytokines, have not been adequately appreciated.

Experiments with cancer in mice have not properly examined the detailed changes in the immune response using daily serial measurements for 2–3 weeks. Insufficient frequency of measurements and monitoring has stopped researchers from observing the underlying cyclical nature of the immune response to cancer in either animals or humans. Measurements of biomarkers taken once or twice a week may not show the cyclical immune fluctuation pattern necessary to understand the effects of treatments administered, so the dynamics of the immune response have not been noticed.

Fourteen years ago we recognised this as a major oversight, and did some mouse experiments that showed how the immune response in a chronic infection oscillates on and off continuously over an approximate 7-day cycle. This cyclical immune phenomenon has been consistently shown in human cancer patients, indicating that the immune response switches on and off in this situation with a periodicity of about 7 days.

Using the physiological principles outlined above we have deduced that narrow therapeutic windows in the ~7-day cycle must exist. These windows could be accidentally hit about 7% of the time when interleukin-2 doses are given. If we could

accurately target the therapeutic window at the correct time-point in each patient's immune cycle, this would make responses to therapy much more predictable and would lead to a real possibility of treatment success that is much closer to 100%.

The recent marketing of immunotherapeutic agents has renewed the prospect of manipulating the immune system to treat or cure cancer. These agents cost more than \$80,000 per course yet they do not produce more complete remissions than interleukin-2 therapy. Already researchers are investigating combinations of these agents, hoping for an additive effect, but so far without considering their opposing immune functions. The same mistakes with the use of chemotherapeutic agents could thus be repeated. Moreover, insufficient or infrequent monitoring would lead to the wrong conclusions again.

Interestingly, these newer agents work through cellular receptor targets that are transiently expressed, just like interleukin-2 and interleukin-2 receptors. Many of the newer agents also affect the initiation and termination of the immune response, so they are encountering similar problems to interleukin-2: they randomly generate a few complete remissions but perform poorly in most patients.

The timing effect has been noted by several researchers, but remarkably has not been further investigated. Now our work is confirming that timing is especially important and that serial monitoring with accurate delivery of therapy to coincide with the correct phase of the patient's immune cycle appears to be essential for treatment to be successful.

More importantly, our work is also showing that the drugs are already available for successful and cost-effective treatment of cancer. However, to do this they need to be used more accurately. An appropriate analogy is that of the diabetic patient who must closely and regularly monitor blood glucose levels in order to accurately self-administer insulin injections to achieve blood glucose stability and avert death. Likewise the fertility patient must monitor daily hormone levels to determine the precise time to conceive.

We have now serially monitored patient's blood samples to determine the immune cycle and then used accurate personalised treatment approaches to create successful clinical responses, even after the failure of other therapies. These examples indicate that the techniques we propose are both achievable and effective, but require improvement, testing and wider acceptance.



Only about 7% of patients treated with interleukin-2 achieve complete remission.

The Rosetta Stone of cancer therapy may now indeed be translated. Using daily serial monitoring of immune markers to define the immune cycle in each patient, and then by accurately timing therapy, the immune system appears capable of being focused to achieve either activation or suppression. It can thereby be manipulated in the desired direction for a particular clinical outcome.

In the case of cancer we are now fairly certain that successful immune manipulation can be achieved by relatively simple blood monitoring and correctly timed intervention. Moreover, because there are recurrent therapeutic windows in repeating cycles, failure to respond in one cycle can be overcome in another cycle. Persistence in targeting the window will be the key.

We are actively investigating and refining these techniques further.

Martin Ashdown is a Research Fellow in the University of Melbourne's Faculty of Medicine. Brendon Coventry is Associate Professor of Surgery at the University of Adelaide.