

THE NEW DAWN OF IMMUNOTHERAPY

Steven Rosenberg made headlines around the globe for a breakthrough that could make immunotherapy a frontline cancer treatment.

The idea of immunotherapy, or modifying the body's own defence mechanism to fight diseases such as cancer, dates back to the 1890s and the pioneering work of US surgeon William Coley, who established a link between bacterial infections in cancer patients, their immune response to those infections, and the subsequent remission of their cancer. Coley developed a prototype treatment, known as Coley's toxins, but this was soon outpaced by new surgical techniques and the emerging technology of radiotherapy.

The promise of immunotherapy lay dormant for decades, but as biomedical science advanced during the 20th

century, it began to reawaken. A key breakthrough came in 1976 with the discovery of how to produce *in vitro* cultures of T lymphocytes – otherwise known as T cells, or the white blood cells that adapt the body's immune response to specific threats.

Miraculous event

Steven Rosenberg, then a young surgeon, now Chief of Surgery at the US National Cancer Institute (NCI) Center for Cancer Research, was involved in the work that built on this discovery. His interest in immunotherapy had started early in his career, when he met a young cancer patient whose tumours had disappeared without treatment. "All aspects of his cancer had gone," says Steven. "He had

undergone one of the most rare events in medicine – a spontaneous regression."

Steven felt the explanation for this had to be buried somewhere in the patient's immune system. "The body has hundreds of billions of lymphocytes," he says, "and somewhere in the body of the patient there had to be lymphocytes that could recognise what was different about the cancer. This led us to identify the cells that were attacking the cancer and then use them to develop a cancer treatment."

Steven and his colleagues subsequently isolated various types of immune cells and, in a series of early trials, injected them into patients. Initially, success eluded them, but in 1984 they gave their 67th patient a far higher dose of T cells. She responded to the treatment and is still alive today.

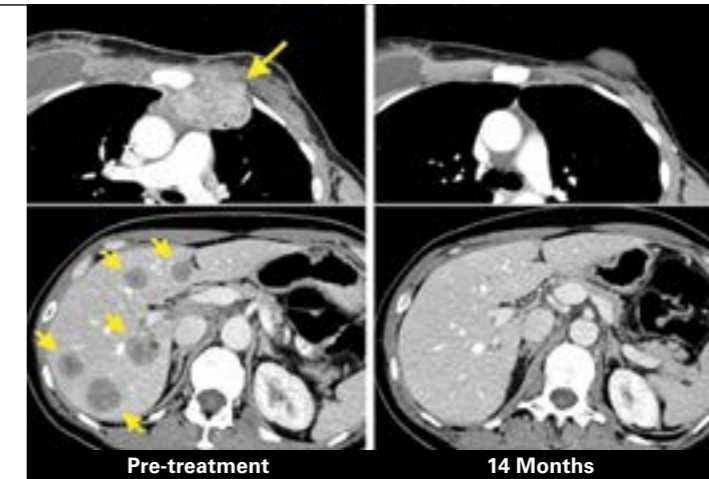
Frontline treatment?

The key was to perfect the technique of extracting T cells from a patient's body and growing them by the billions in the lab. This has yielded increasingly positive results, but it's the outcome of their latest clinical trial, published in *Nature Medicine*, that suggests a breakthrough that could see immunotherapy become a frontline treatment for cancer.

Their subject was a patient with metastatic breast cancer who had failed to

STEVEN ROSENBERG

- ✓ Chief of surgery at the National Cancer Institute in Bethesda, Maryland
- ✓ BA and MD degrees at Johns Hopkins University, PhD in Biophysics at Harvard University
- ✓ Residency training in surgery at the Peter Bent Brigham Hospital in Boston, Massachusetts
- ✓ Developed the first effective immunotherapies and gene therapies for patients with advanced cancer
- ✓ Studies of cell transfer immunotherapy have resulted in complete remissions in patients with metastatic melanoma
- ✓ Recent studies have seen regressions of metastatic cancer in patients with sarcomas and lymphomas.



Left. ACT using autologous lymphocytes targeting somatic mutations

respond to all previous chemotherapy and hormonal treatment.

Steven describes his new technique as "a high-throughput method to identify mutations present in a cancer that are recognised by the immune system. But because this new approach to immunotherapy is dependent on mutations, not on cancer type, it is in a sense a blueprint we can use for the treatment of many types of cancer".

It amounts to a modified form of adoptive cell transfer. This has successfully treated cancers with high levels of mutations, such as melanoma, lung and bladder cancers, but has been less effective with cancers that start in the lining of organs, such as stomach, ovarian, and breast cancers, and have lower levels of mutations.

Targeting tumours

Steven and his team used tumour-infiltrating lymphocytes (TILs) from the patient, which, as their name suggests, specifically target tumour cell mutations.

Their first step was to identify the patient's unique cell mutations by sequencing DNA and RNA from her normal tissue and her tumours. They found 62 different mutations. Next, they tested the TILs to pick out those that recognised one or more of her mutated proteins. The job was then to grow these TILs in sufficient numbers in the lab and inject them back into the patient in order to create a much more powerful immune response against her individual tumours. Her cancer is now in full regression.

"For multiple cancer types that are refractory to all known chemotherapies and immunotherapies, attacking the

unique mutations in a patient's cancer can result in dramatic durable regressions," says Steven. "This breast cancer patient is now cancer-free based on all available studies two-and-a-half years after treatment."

Way forward

It's an outcome that he hopes will point the way forward for immunotherapy: "This approach holds the best opportunities for finding effective immunotherapies for patients with the solid cancers. I have showed the slides (pictured) at two American Association of Cancer Research meetings, and have shown that about 80% of patients with common epithelial cancers have T lymphocytes reactive against their own cancer, and that of the 197 immunogenic recognised mutations 196 were unique to the patient's cancer and not shared by any other patient."

Steven feels this insight should change the way cancer is treated: "We need a new paradigm for cancer therapy. Highly personalised treatments are likely to be necessary to make progress in treating common cancers. A unique drug for each patient may be needed. Many oncologists think this is not practical. I think a drastic change is needed and I now know of at least three companies that are working to try to develop this commercially."

Almost 130 years after William Coley first suggested the idea of immunotherapy, Steven and his team have shown that its inherent biological complexities can be overcome, and in the process have taken a giant leap towards a personalised treatment for a personalised disease. 