

Plastic Fantastic! Biopolymers Efficiently Boost T-Cell Therapy

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Solid tumors can be difficult to remove completely through standard surgery, depending on their location and invasive characteristics. This forces physicians and scientists to explore other therapies in order to reduce the risk of relapse by eliminating as many malignant cells as possible. One such alternative treatment under development is called adoptive cell therapy, and uses tumor-reactive immune cells (T cells) to specifically locate and kill diseased cells. Although promising, the technique is in many cases hampered by inefficient tumor homing and poor survival of injected T cells. This concern prompted Drs. Sirkka and Matthias Stephan in the Clinical Research Division to investigate established surgical protocols in search of "a simple tool" that could increase the clinical efficacy of T cell therapy. What they found was biodegradable polymer implants, currently in use for local delivery of chemotherapeutic agents to brain cancer patients. The drawback of this technique is the *passive* release of drugs from the polymer, making it hard for the chemotherapeutics to reach tumor cells that are more than a few millimeters away from the implant. Consequently, the resulting overall survival among treated patients has only been improved to a limited degree.

Nevertheless, the Stephan Lab saw potential in these polymers as vehicles for T cell delivery and generated customized macroporous scaffolds from the US Food and Drug Administration (FDA)-approved polysaccharide polymerized alginate. To test their effectiveness, the investigators used an *in vivo* mouse breast cancer resection model that mimics tumor recurrence after surgery, and embedded the developed T cell-containing scaffolds directly into the cavities from which tumors had been incompletely removed. The results were clear: neither intravenous nor intracavitary injection of tumor-reactive T cells in solution produced any substantial survival advantages; similarly, prestimulation of immune cells with various antibodies and interleukin 15 superagonist improved the outcome only modestly. Biopolymer-delivered T cells, on the other hand, effectively reduced the relapse rate to zero.

"Once implanted, T cells *actively* emigrate deep into the surrounding tumor, where they robustly expand (up to 400-fold in our studies), and even infiltrate tumor-draining lymph nodes," explained Dr. Matthias Stephan, whose results are hot off the press in the highly ranked scientific journal *Nature*

Biotechnology. The key to the Stephan Lab's success lay in making the scaffolds bioactive, which means providing an adhesive coating to support cell egress and stimulatory signals to trigger proliferation. This was achieved through integration of collagen-mimetic peptides and porous antibody-coated microparticles infused with T cell growth factors, called interleukins.

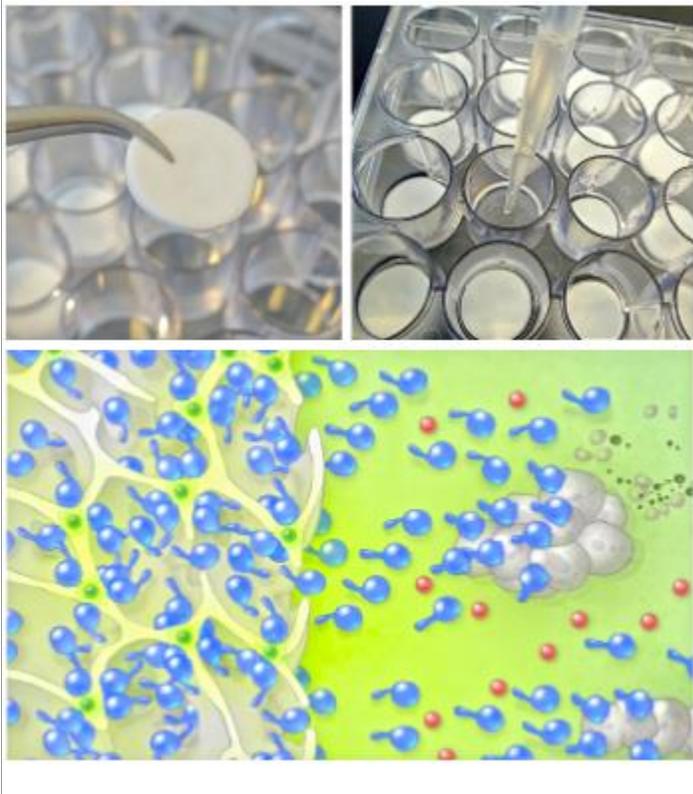
The striking effectiveness of the new technique was further studied through bioluminescence imaging, showing equally impressive improvements in targeting of tumor sites and proliferation *in vivo* compared with directly injected T cells. Lastly, significant increases in overall survival and time to relapse were also demonstrated in a mouse model of late-stage ovarian cancer.

"We demonstrate for the first time that launching cancer-fighting immune cells from polymeric devices can safely and effectively prevent relapse and provide an effective treatment option for inoperable tumors," Dr. Stephan said, adding that "implemented in the clinic, biomaterial-supported T cell implants could maximize the success of tumor surgery, and spare patients from repetitive operations, extended hospital stays, and rounds of radiation or chemotherapy."

The novel approach shows great potential for resolving two issues that have restricted the clinical use of T cell therapy against solid tumors: efficiency and practicality. Compared with adoptive cell therapy, which demands time-consuming and expensive procedures for isolation and *in vitro* expansion of the infused T cells, in addition to irradiation and/or immunosuppressing pretreatment regimens, the biodegradable scaffolds incorporate all key activation and proliferation factors. The released T cells can attack malignant target cells directly, without requiring impairment of the patient's own immune system before therapy.

Encouraged by these advances, the investigators are now continuing their research to include delivery of genetically reengineered T cells and other tumor-fighting immune cells, such as natural killer cells or invariant natural killer T cells, or even combinations of cell types. "We are also developing various injectable polymeric compositions for the minimally invasive implantation of active depots of anticancer T cells into poorly accessible or inoperable tumors (e.g., under ultrasound guidance)," Dr. Stephan said, adding that their ultimate goal is to implement biomaterial-supported T cell implants in the clinic, in collaboration with clinical investigators at Fred Hutch.

[Stephan SB, Taber AM, Jileeva I, Pegues EP, Sentman CL, Stephan MT.](#) 2015. Biopolymer implants enhance the efficacy of adoptive T-cell therapy. *Nat Biotechnol* 33(1):97-101.



Images provided by Dr. Matthias Stephan

The photographs show biopolymer scaffolds being hydrated and loaded with tumor-targeting T cells. The schematic diagram demonstrates the action of a T cell-containing scaffold implanted at a tumor site; green dots represent stimulatory microspheres incorporated into the polymer framework, which trigger proliferation and migration of the T cells (shown in blue) into the surrounding tissue as the scaffolding material biodegrades.