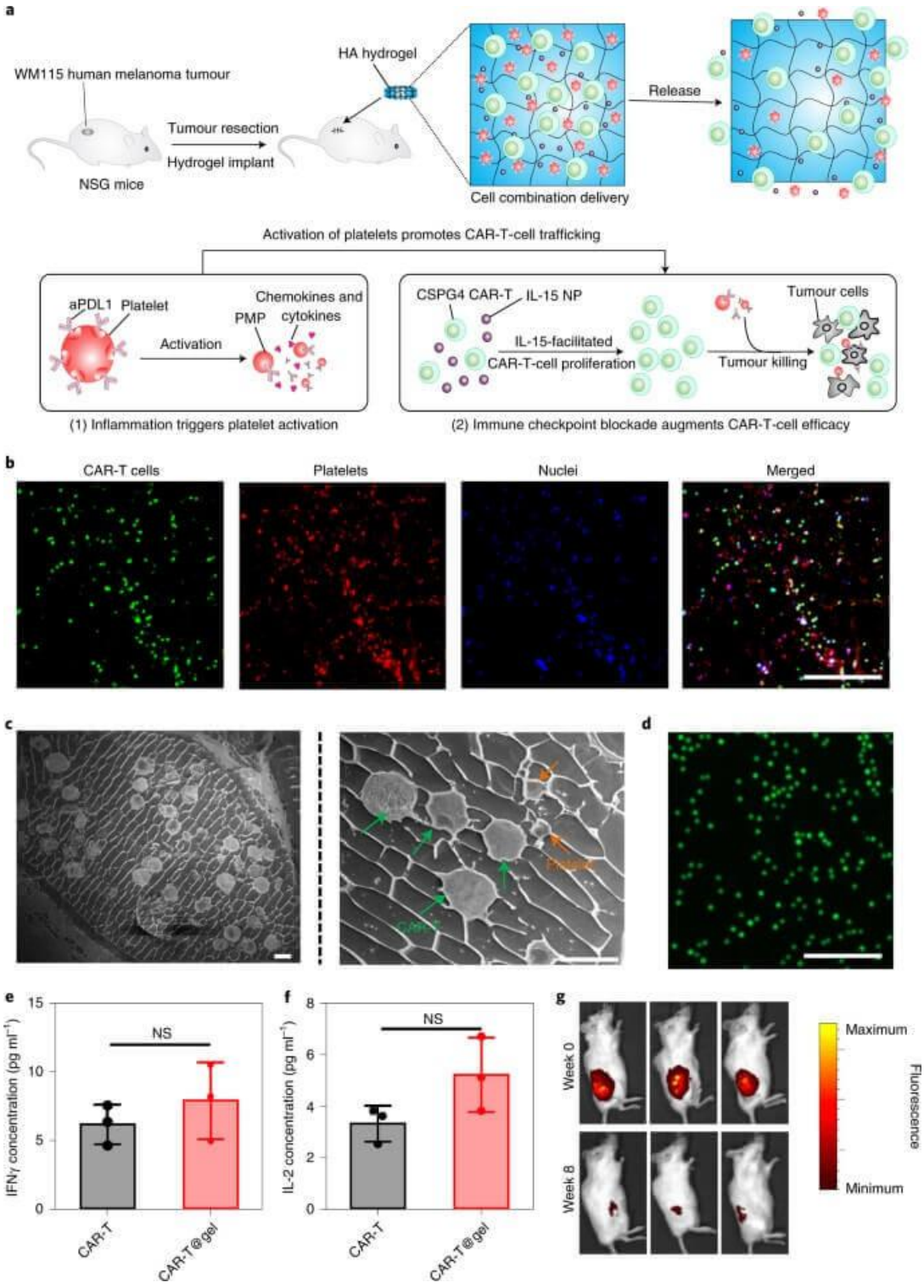
Hydrogels Deliver CAR-T cells For Solid Tumor Treatment

The full name of CAR-T gene therapy is Chimeric Antigen Receptor (CAR) T-cell Therapy**.** Chimeric antigen receptor (CAR) T cell therapy is a form of immunotherapy in which T cells are taken from a patient's blood and placed in a laboratory setting to be modified so that they can recognize and destroy specific cancer cells. The modified T cells are then delivered back to the patient. Once back in the patient, the modified T cells can detect cancer cells and destroy the cancer by harnessing the body's own immune response. Since 2017, **several CAR-T therapies approved for marketing are related to the treatment of hematological tumors. In the treatment of solid tumors, CAR-T has not yet achieved substantial breakthroughs.**

3D hydrogel is a star carrier in the field of drug delivery. Through tunable material and structure design, it can not only mimic the native extracellular matrix (ECM) of immune tissues to maintain cell viability, but also deliver to the defense sites in the body in real time to prolong the residence time of carrying cells, thus improving the effect of immunotherapy. Could hydrogel-loaded CAT-T cells bring CAR-T therapy one step closer to solid tumors?

1. Nature Biomedical Engineering (IF=29.234) : Local controlled release of immune cells based on "cell warehouse" for CAR-T therapy of solid tumors; 2021.4.26

CAR-T cell therapy has encountered many setbacks in the treatment of solid tumors, largely due to the physiological barrier of solid tumors and the immunosuppressive nature of the tumor microenvironment, which inhibit the activity and survival of CAR-T cells. Using methacrylylated hyaluronic acid (HAMA) hydrogel as a carrier, the researchers combined CAR-T cells targeting CSPG4 antigen (melanoma-specific antigen) and anti-PDL1 blocking antibody-bound human platelets (P- aPDL1) loaded into the hydrogel. To support the viability and proliferation of CAR-T cells in the hydrogel, PLGA nanoparticle-packaged cytokine IL-15 was also incorporated. This method can be used in combination with other therapies (such as chemotherapy and radiotherapy) to better inhibit tumor recurrence and metastasis. At the same time, the novel cell delivery strategy also provides new ideas for the treatment of other cell therapies and related diseases.



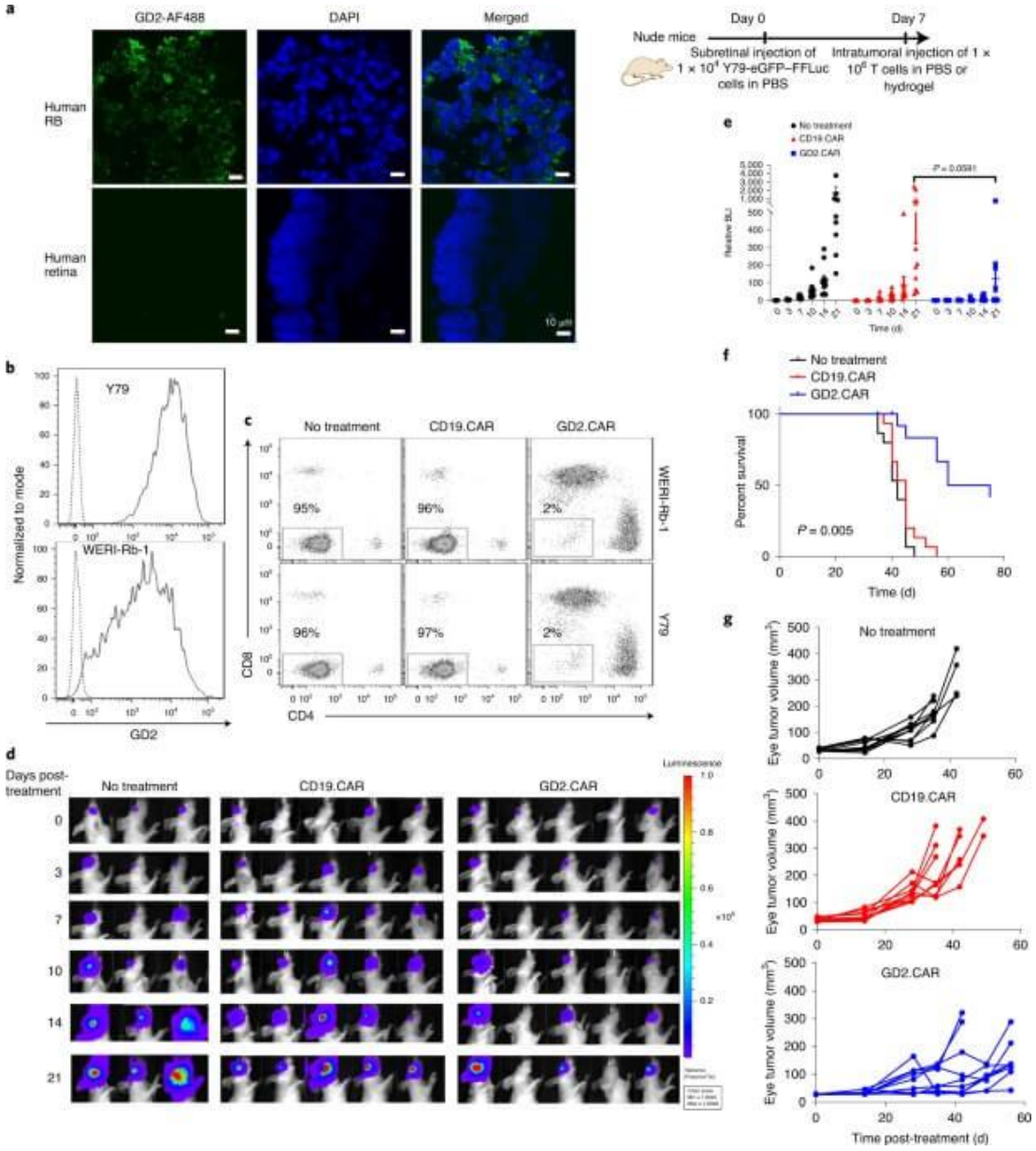
Original article:

Inhibition of post-surgery tumour recurrence via a hydrogel releasing CAR-T cells and anti-PDL1-conjugated platelets

https:/ / doi.org/10.1038/ s41551-021-00712-1

2. Nature cancer (IF=23.177): Hydrogel assists CAR-T therapy with significant curative effect in the treatment of eye cancer; 2020.8.12

Retinoblastoma (RB) is a pediatric retinal tumor that overexpresses the ganglioside GD2. Although early diagnosis can be treated, patients may lose one or two eyes. The researchers selected chitosan-polyethylene glycol (PEG) thermosensitive hydrogel as the best injectable hydrogel for intraocular delivery of CAR-T (GD2-specific chimeric antigen receptor T lymphocytes). Most of the T cells encapsulated in the hydrogel remained viable and were released from the gel to the outside within 1 week. The experiments found that when combined with locally released interleukin-15 and injected hydrogel GD2, CAR-T successfully eliminated RB tumor cells without compromising vision in mice.



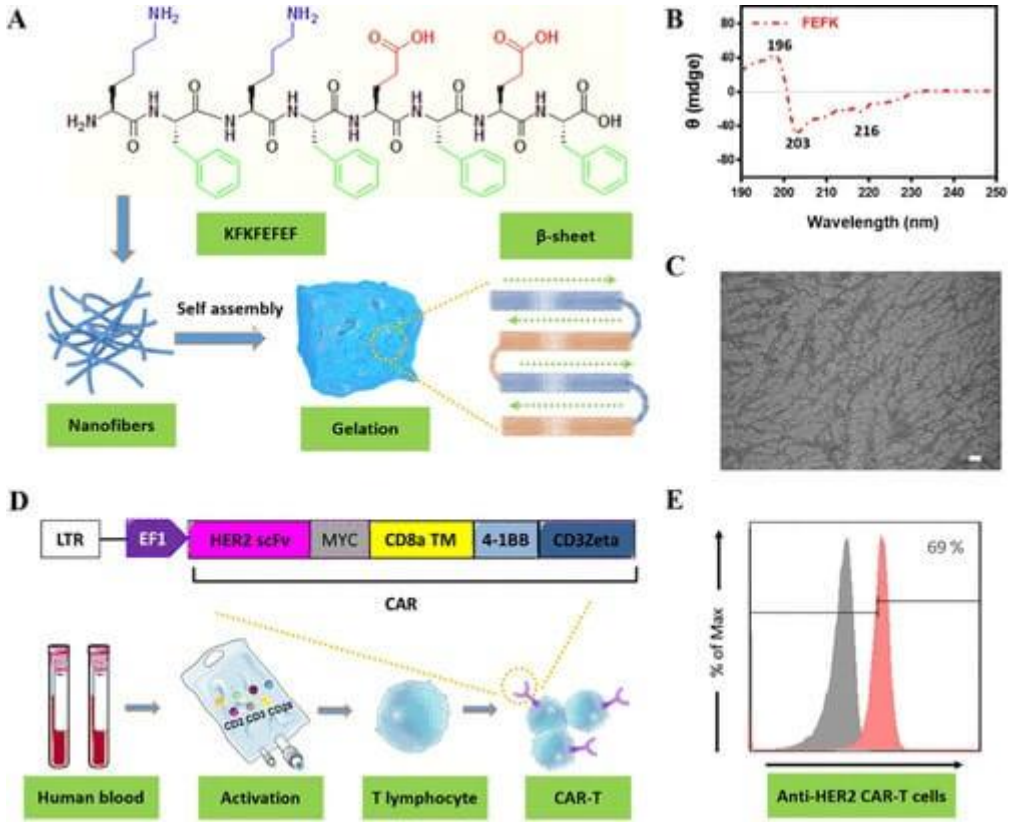
Original article:

GD2-specific CAR T cells encapsulated in an injectable hydrogel control retinoblastoma and preserve vision

https:/ / doi.org/10.1038/ s43018-020-00119-y

3. ACS Applied Materials & Interfaces (IF=10.383): Polypeptide hydrogels for CAR-T proliferation and solid tumor immunotherapy; 2022.8.9

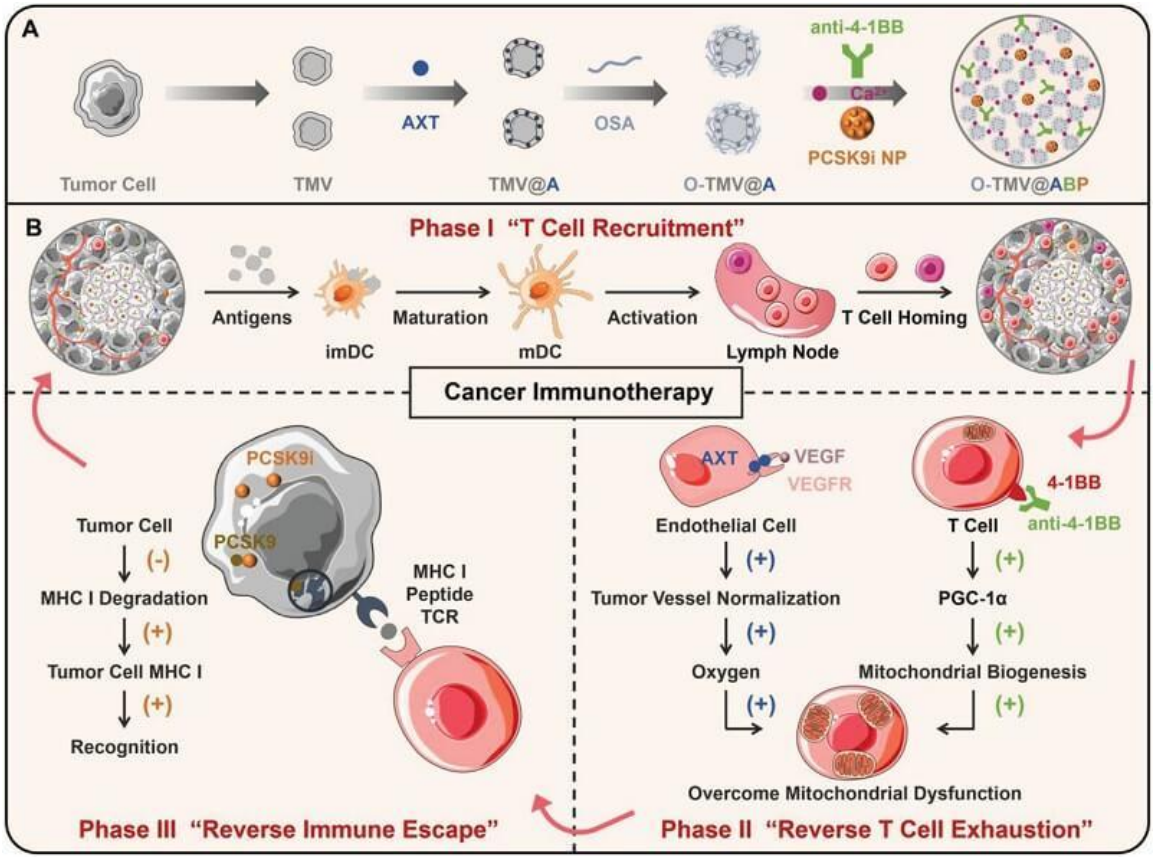
In order to obtain better clinical efficacy of CAR-T therapy, it is necessary to rapidly expand in a short time to generate a large number of functional T cells, and the current technology cannot solve this problem. Longer operating times result in the loss or alteration of the function and phenotype of CAR-T cells, which can also lead to patients losing optimal treatment time. Using FEFK (F is phenylalanine, E is glutamic acid, and K is lysine) polypeptide hydrogel as carrier, the researchers designed a microenvironment with similar lymphoid organs to activate and expand immune cells. Mimicking matrix hydrogels showed optimal stiffness and adhesion ligand density, which accelerated the proliferation of CAR-T cells. Meanwhile, the intrinsic PD-1 blocking single chain variable fragment (scFv) secreted by engineered CAR-T further enhanced cell proliferation and cytotoxicity. Compared with traditional CAR-T therapy, localized delivery of CAR-T cells from scaffolds can achieve long-term retention, significantly inhibit tumor growth, and increase infiltration of effector T cells. With the continuous in-depth research of bioengineering and genetic engineering methods, CAR-T based cell therapies are expected to achieve rapid expansion, maintain and enhance functional activity, and solve the problems of great clinical demand and time urgency.



Original article:
Customized Multifunctional Peptide Hydrogel Scaffolds for CAR-T-Cell Rapid Proliferation and Solid Tumor Immunotherapy
https://doi.org/10.1021/acsami.2c10727

4. Small (IF=15,153): Injectable hydrogel regulatory T cells for cancer immunotherapy; 2022.6.17

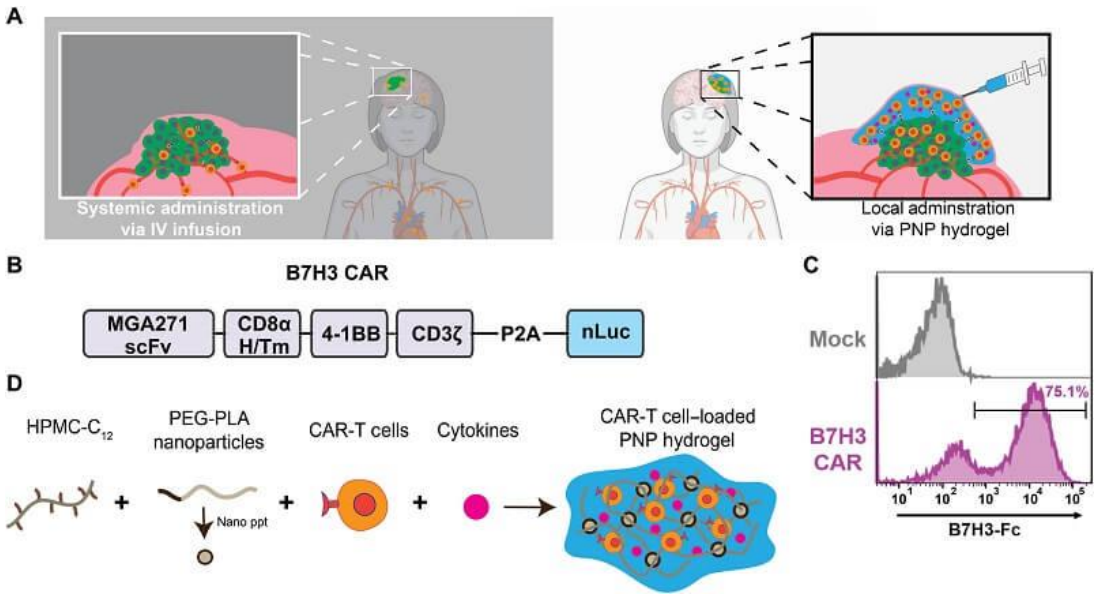
Mitochondrial dysfunction-induced T cell exhaustion is a major obstacle to T cell-based cancer immunotherapy. In addition, the deficiency of major histocompatibility complex I (MHC I) on tumor cells limits the efficiency of T cell recognition of tumor cells and affects their therapeutic efficacy. These two factors are the main barriers to cancer immunotherapy. Based on this, the researchers used oxidized sodium alginate(OSA)-modified tumor cell membrane vesicles (O-TMV) as a gelator, and axitinib is encapsulated in the lipid bilayer of O-TMV, 4-1BB antibody and proprotein convertase subtilisin/kexin type 9 inhibitor PF-06446846 nanoparticles encapsulated in the cavities of hydrogels to develop an injectable hydrogel to simultaneously modulate T cell exhaustion and MHC I Expression, amplifies cancer immunotherapy.



Original article:
An Injectable Hydrogel to Modulate T Cells for Cancer Immunotherapy
https://doi.org/10.1002/smll.202202663

5. Science Advances (IF=14.957): "Coating" CAR-T cells on tumors to enhance efficacy; 2022.4.2

For blood cancers such as leukemia and lymphoma, approved CAR-T therapies have benefited many patients. However, for solid tumors, the role of CAR-T therapy has been limited. Brain tumors, liver tumors, stomach cancers, etc., are generally solid tumors that are located in specific locations and form dense tumors that are not easily recognized by immune cells. And it is difficult for CAR-T cells to penetrate and attack cancer cells. The researchers used hydroxypropyl methylcellulose and PEG-b-PLA copolymer as an injectable hydrogel carrier to temporarily "package" CAR-T cells and stimulatory cytokines together. Using a syringe, the gel is "applied" near the tumor, where T cells can grow and proliferate, and are continuously released from the gel to encircle the cancer cells.



Original article:
Delivery of CAR-T cells in a transient injectable stimulatory hydrogel niche improves treatment of solid tumors
https://www.science.org/doi/10.1126/sciadv.abn8264

6. Journal of the American Chemical Society (IF=7.571): T lymphocyte capture DNA network for local immunotherapy; 2021.11.15

Efficient isolation of immune cells with high purity and low cellular damage is an important part of immunotherapy, but it remains a high challenge. The

researchers designed a cell-trapping DNA network hydrogel containing a multivalent multiphantom for the specific isolation and in situ culture of T lymphocytes (T cells). Two ultralong DNA chains synthesized by an enzymatic amplification process were rationally designed to include functional multimodules as cellular anchors and immune adjuvants. Complementary sequences facilitate DNA network formation and T cell encapsulation, and provide restriction endonuclease cleavage sites for reactive release of T cells and immune adjuvants. The purity of the captured tumor infiltrating T cells was 98%, and the survival rate was about 90%. T cell-containing DNA networks are further used for local immunotherapy of tumor lesions. The research work provides a powerful nanobiotechnology for the efficient isolation of immune cells and other biological particles.

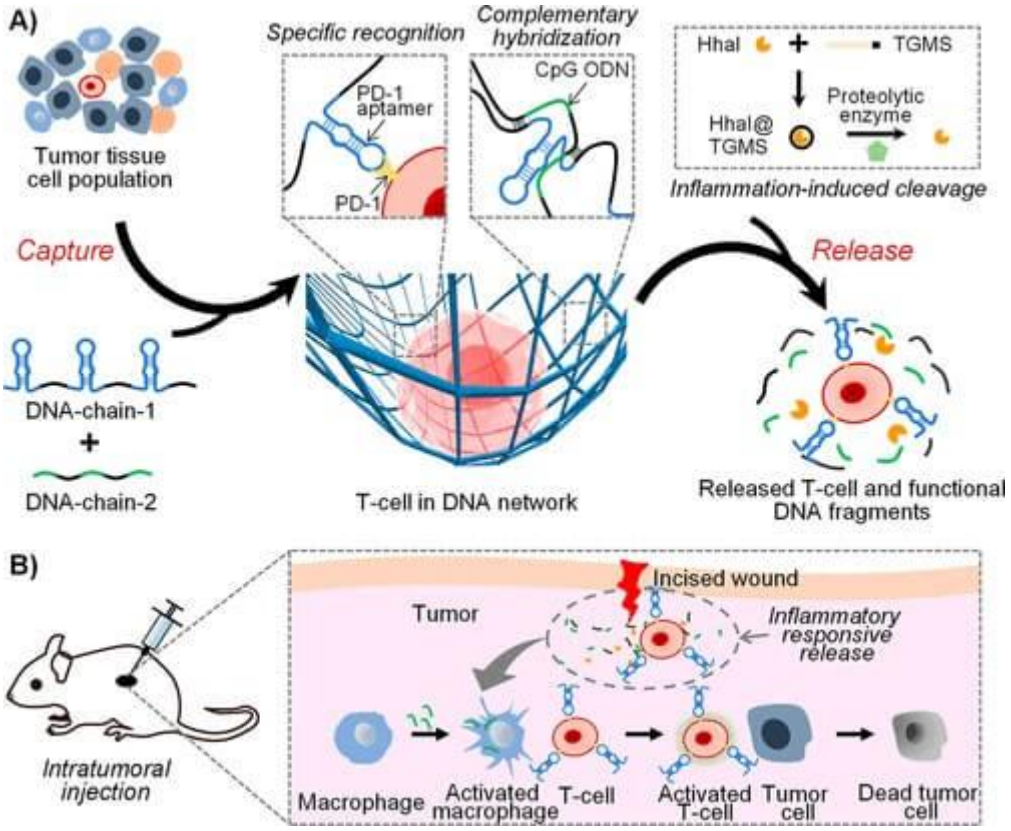
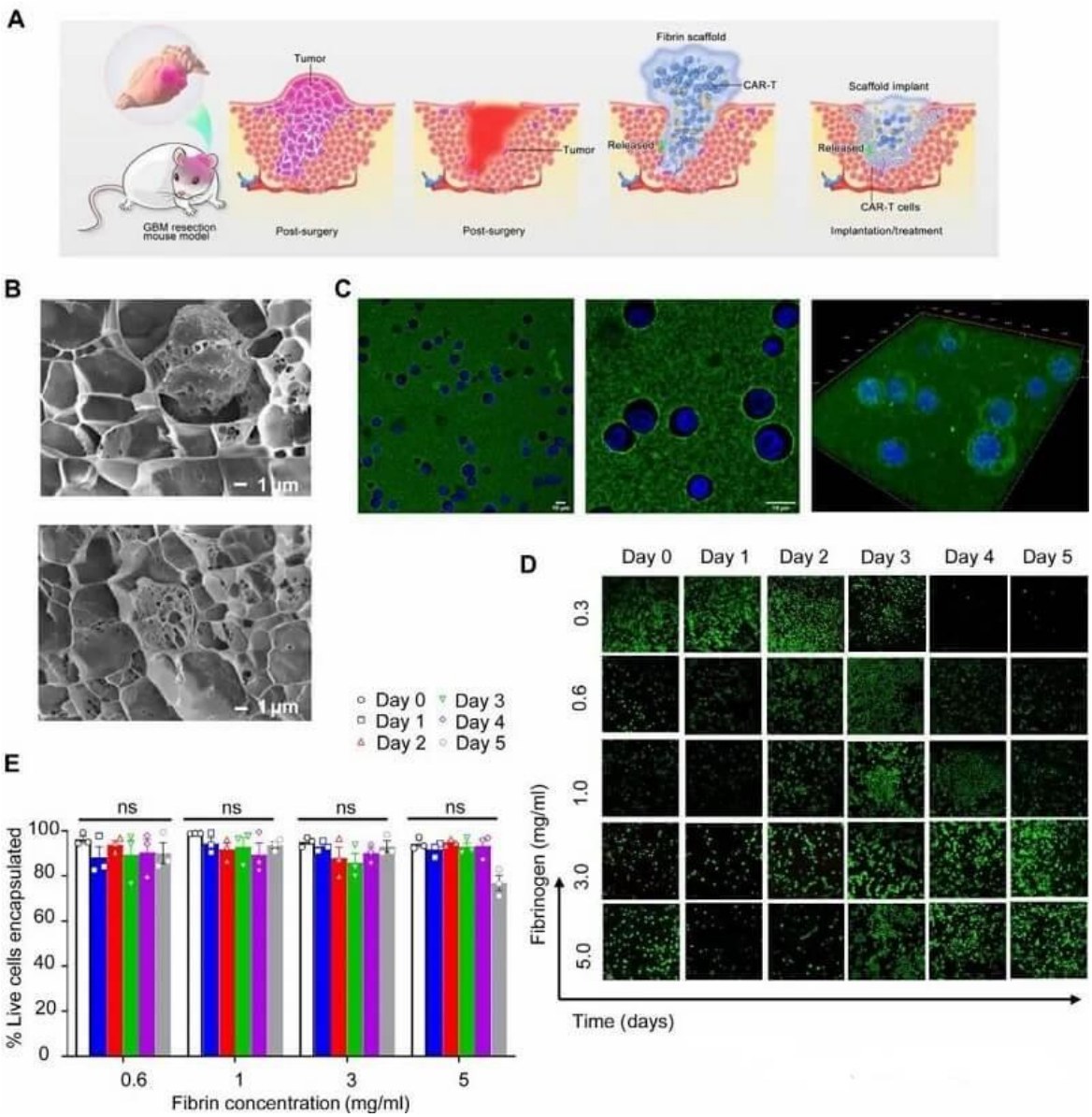


Figure 6
Original article:
T Lymphocyte-Captured DNA Network for Localized Immunotherapy
https://doi.org/10.1021/jacs.1c07036

7. Science Advances (IF=14.957): Fibrin glue enhances the antitumor effect of CAR-T cells in glioblastoma; 2021.8.6

CAR-T cell administration represents a plausible therapeutic approach in glioblastoma as an alternative to intravenous administration to avoid blood-brain barrier barriers. Here, the researchers combined a newly

developed fibrin gel with immunotherapy to exert synergistic effects, demonstrating that the use of a fibrin-based gel to deliver CAR-T cells in the surgical cavity is superior to direct inoculation. CAR-T cells delivered to the tumor resection cavity have better antitumor activity.



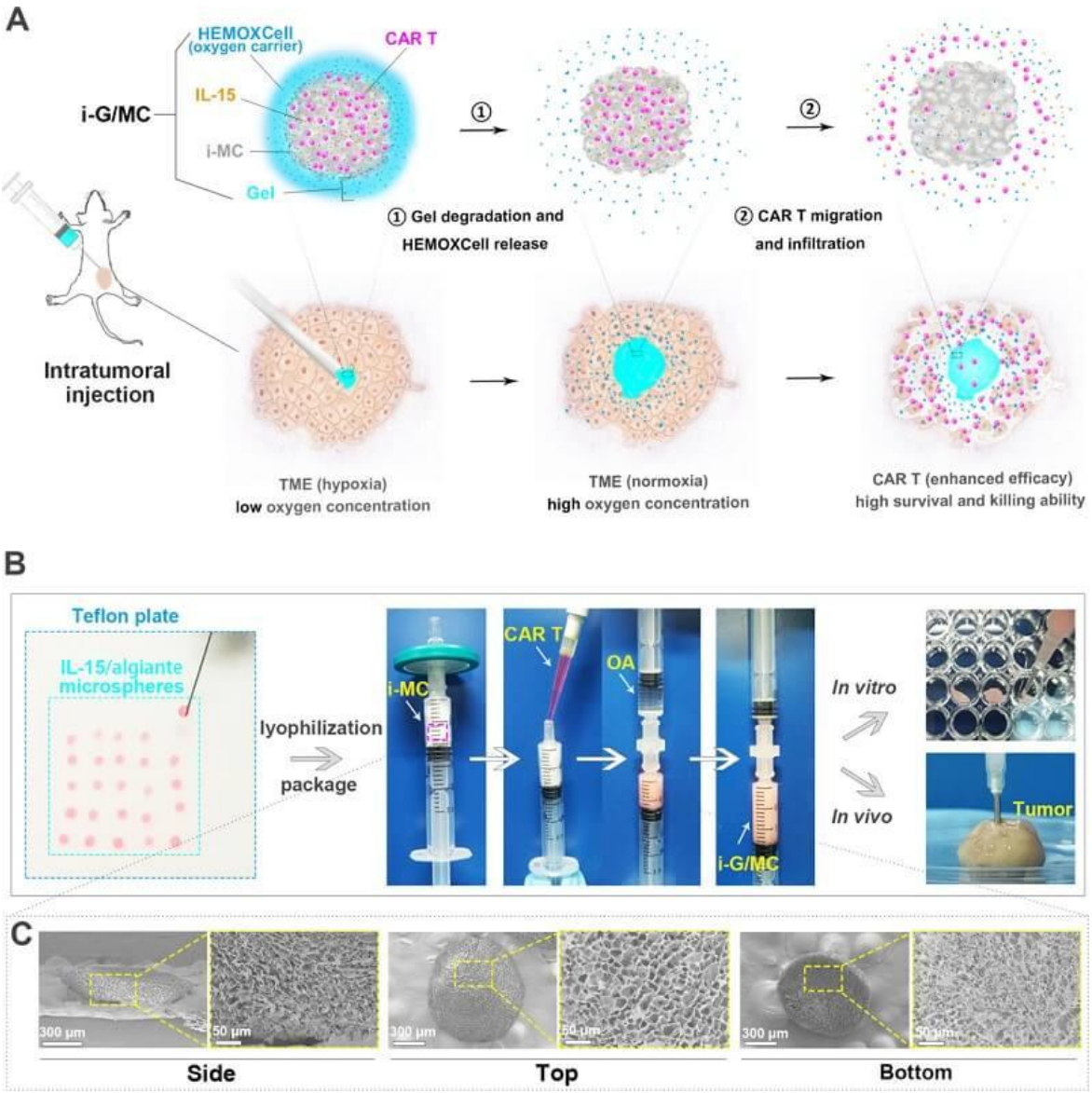
Original article:

Fibrin gel enhances the antitumor effects of chimeric antigen receptor T cells in glioblastoma

https://doi.org/10.1126/sciadv.abg5841

8. ACS Applied Materials & Interfaces (IF=10.383): Injectable immune microchips enhance the efficacy of CAR-T cells; 2020.12.11

The role of CAR-T cells in the treatment of solid tumors is limited due to poor transport of CAR-T cells injected into the tumor site and the limited infiltration and survival of the cells in the immunosuppressed and hypoxic tumor microenvironment (TME). This study proposes a sodium alginate gel-based injectable immune-microchip (i-G/MC) system that delivers CAR-T cells within tumors and improves their therapeutic efficacy in solid tumors. The results showed that oxygen carrier and IL-15 synergistically enhanced the survival and expansion of CAR-T cells under hypoxia, and improved the efficacy of CAR-T cells.



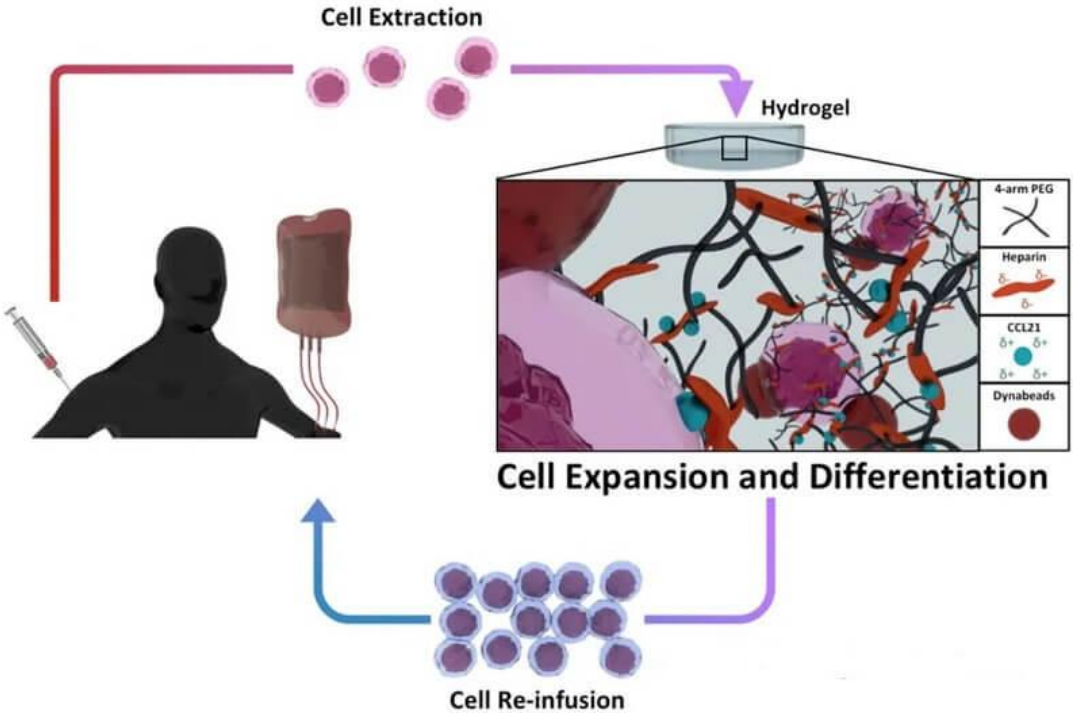
Original article:

Injectable Porous Microchips with Oxygen Reservoirs and an Immune-Niche Enhance the Efficacy of CAR T Cell Therapy in Solid Tumors

https://dx.doi.org/10.1021/acsami.0c15239

9. Biomaterials (IF=15.304): 3D hydrogels that promote T cell proliferation; 2020.8.13

There are still many limitations of T cells in the field of immunotherapy, such as the difficulty of producing large quantities of therapeutic T cells in a short period of time in an economical and feasible manner. The researchers designed a three-dimensional (3D) polyethylene glycol (PEG) hydrogel covalently bound to low-molecular-weight heparin, designed to resemble a lymph node where T cells multiply. Among them, PEG provided the desired structural and mechanical properties, while heparin was used to anchor the cytokine CCL21 (CCL21 is present in lymph nodes and can affect cell migration and proliferation). Compared with state-of-the-art expansion systems consisting of artificial antigen-presenting cells, 3D hydrogels have superior loading capacity and the ability to promote CD4+ T cell proliferation.

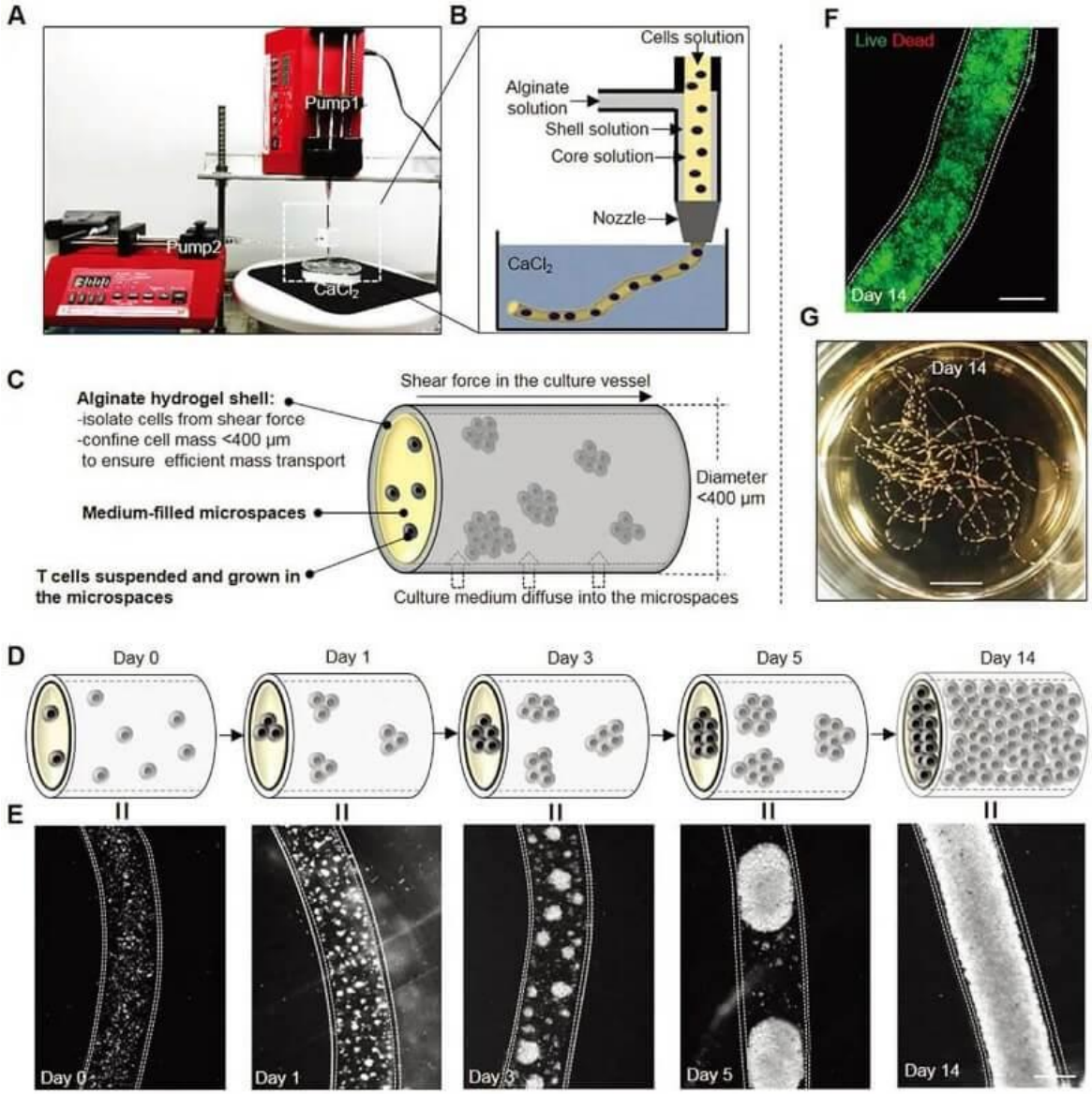


Original article:
CCL21-loaded 3D hydrogels for T cell expansion and differentiation
https://doi.org/10.1016/j.biomaterials.2020.120313

10. Adv Healthcare Materials (IF=11.092): Automatic expansion of primary human T cells in hydrogel microtubules for immunotherapy; 2018.5.11

Immunotherapy is a highly effective strategy for the treatment of many human cancers, and is commonly used in melanoma, cervical cancer, lymphoma, and leukemia. The study cultured T cells suspended in microscale alginate

hydrogel tubes (AlgTubes), which protect cells from hydrodynamic stress and limit cell mass to 400μm(radial diameter) to ensure efficient mass transport and create a cell-friendly microenvironment for T cell growth. Under optimized culture conditions, T cells cultured by AlgTubes have high cell viability, low DNA damage, high growth rate (320-fold expansion in 14 days), high purity (≈98% CD3+) and high yield (3.2×10^8cells/ml). This method has greater application advantages than the current T cell culture method in terms of culture amount, time, cost and yield.



Original article:

Automated Expansion of Primary Human T Cells in Scalable and Cell-Friendly Hydrogel Microtubes for Adoptive Immunotherapy

https://doi.org/10.1002/adhm.201701297

CAR-T gene therapy is a new type of precision targeted therapy for cancer treatment. It is a very promising new tumor immunotherapy method that can be precise, rapid, efficient, and has the potential to cure cancer. CAR-T therapy involves a series of steps such as isolation, modification, amplification and reinfusion. As a functional carrier, hydrogel plays an important role in the two steps of amplification and reinfusion.

In recent years, the application of hydrogels in biomaterials, tissue engineering, drug release and other fields has become a hot spot of scientific research. Among them, polyethylene glycol (PEG) hydrogel has the characteristics of good biocompatibility, non-toxicity and low immunogenicity, and has a good application prospect. Huateng Pharma provides 4-ArmPEG-SS, 4-ArmPEG-SG, 8-ArmPEG-SS and 8-ArmPEG-SG with MW 2k, 5K, 10K, or 20K, which can be used as hydrogels for medical devices. And we can also provide PEG derivatives for 3D bioprinting.

Related article:
Global CAR T-cell Therapy Development Progress