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Chip-based Prognostic Tool for Improved Leukemia Treatment Outcomes

Accurate, inexpensive, and rapid predictive tool to assess patient responsiveness to immunotherapies, such as chimeric antigen receptor (CAR) T-cell therapy

Category

Life Sciences/Platform Technology
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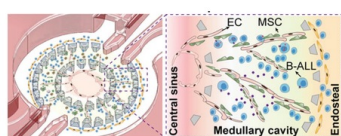


Figure 1: Schematic illustrating the chip's architecture which effectively models human bone marrow. The chip includes three interconnected anatomical regions (central sinus linked to medullary cavity encircled by endosteum) populated with endothelial cells (ECs), perivascular mesenchymal stromal cells (MSCs) and B-ALL cells.

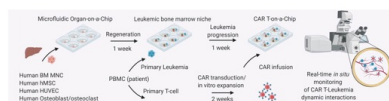


Figure 2: Schematic illustrating the multiweek workflow for measuring a patient's responsiveness to CAR T-cell therapies using prognostic microfluidic biomimetic chips.

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Technology

The [Chen lab](#) has engineered a novel microfluidic chip that accurately replicates the structure of pathological bone marrow for use as a prognostic tool to evaluate B-cell acute lymphoblastic leukemia (B-ALL) patient response to standard-of-care and emerging immunotherapies, specifically CAR T-cell therapy. As described in published work (*Ma et al. Sci. Adv. 2020*), the innovative chip design includes three anatomical regions of the bone marrow (central venous sinus, medullary cavity, and endosteum) constructed from fibrin hydrogel compartments and collectively integrates hematopoietic cells, leukemia blasts, and stromal cells (amongst other bone marrow cell types) to accurately mimic the *in vivo* tissue architecture of B-ALL bone marrow (see Fig. 1). The chip serves as an effective model for evaluating patient response to chemotherapies and CAR T-cell therapy by allowing for direct, real-time visualization of the pharmacodynamics; for example, tumor cell killing and any accompanying cellular or transcriptomic changes in the microenvironment. In the context of CAR T therapy, this chip permits measurement of T cell tumor infiltration, cytokine profiling, and T cell activation and inactivation. The application of the chip is straightforward and rapid. Primary patient samples are loaded onto the chip followed by patient-derived tumor samples (e.g., leukemia blasts) to generate the B-ALL model. Then immunotherapies (such as CAR T cells) are added and monitored for their effectiveness (using fluorescent microscopy or other measurement tools) (See Figure 2). In published proof-of-concept (POC) studies, the Chen Lab assessed the efficacy of three approved chemotherapies (nilotinib, prednisone, and vincristine) against B-ALL cells and used the chip's cell viability readouts to identify combination therapies effective against B-ALL cells with protective niche cells. Additionally, in pre-publication work in the context of CAR T cell therapy, the chip was tested with anti-CD19 CAR T cells, and in line with expectations, showed a near-complete killing of leukemia CD19+ blasts. Further measurements revealed, as

expected, that CAR T-cell treatment significantly enhanced T-cell markers of activation and proliferation (e.g., cytokine secretion). In unpublished proof-of-concept work, the research team screened CAR T-cell therapies on chips from different patients' derived cell products and identified heterogeneous responses where one product outperformed other options. The investigators have also developed a novel functional index to describe the measured screening results.

In summary, this chip allows for accurate *ex-vivo* predictions of B-ALL treatments' efficacy in an inexpensive and rapid format without the typical safety concerns accompanying clinical testing.

Development Status

This chip is currently being standardized for high-throughput manufacturing and further pre-clinical evaluation.

Background

Acute lymphoblastic leukemia (ALL) is a rare form of blood cancer with fewer than 200,000 cases in the US per year, yet is considered the most common pediatric cancer. B-ALL, the most prevalent ALL subtype, carries a high relapse rate after initial treatment and is the leading cause of death for pediatric patients. Individuals with refractory and relapsed B-ALL have a 5-year survival rate of approximately 10%, which is primarily attributable to drug resistance and the lack of available treatment options. CAR T cell immunotherapy is one promising treatment for blood cancers (such as B-ALL), yet its broad application is hindered due to undesired side effects (e.g., cytokine release syndrome) and unsatisfactory clinical responses. An additional drawback is low patient responsiveness; patients administered CAR T cell treatments have ~ 40-60% patient relapse rate within 6 months of treatment. Given the high relapse rate for B-ALL, there is an urgent unmet need for inexpensive and rapid prognostic tools that can accurately predict drug effectiveness *ex vivo* before they are administered to patients.

Applications

- Patient compatibility testing for:
 - B-ALL chemotherapeutics; approved treatments or those in clinical testing
 - B-ALL CAR T-cell therapies; approved treatments or those in clinical testing
 - Non-cancer bone marrow diseases, including anemia, infection, poisoning, and physical injuries
- Use in pre-clinical or clinical development of new B-ALL therapies
- Research tool to investigate the B-ALL microenvironment, tumor heterogeneity, CAR T-cell dynamics, and chemoresistance mechanisms

Advantages

- **Improves treatment response rate:** predicts treatment response *ex vivo* prior to therapy administration
- **Facilitates inexpensive personalized treatments:** medicines are tested *ex vivo* on patient-derived samples to predict compatibility
- **Recapitulates B-ALL tumor microenvironment:** replicates the *in vivo* spatial architecture and cellular composition of the bone marrow microenvironment
- **Rapid and tunable testing platform:** chips are ready for evaluation within 3 weeks and can be used with different therapies and patient-derived samples
- **Long-term monitoring of efficacy:** Multi-week evaluation of CAR T-cell therapy responses
- **High-resolution, real-time monitoring of B-ALL treatment responses:** provides multiplexed readouts about pharmacodynamics (e.g., tumor cell viability, T cell infiltration, etc.)

Intellectual Property

NYU has filed non-provisional utility patent applications in the U.S. and Europe covering the design of the device and its method of use for predicting patient responses to chemotherapies and CAR T therapies in the context of cancer.

References

1. Ma C, Witkowski MT, Harris J, Dolgalev I, Sreeram S, Qian W, Tong J, Chen X, Aifantis I, Chen W(2020) , <https://pubmed.ncbi.nlm.nih.gov/33127669/>
2. Ma C, Wang H, Liu L, Tong J, Witkowski MT, Aifantis I, Ghassemi S, Chen W(2023) , <https://pubmed.ncbi.nlm.nih.gov/37131801/>