Insights and proven strategies from researchers and practitioners in the field

Mastering TIL therapy manufacturing

cytiva

Introduction

How can manufacturers develop workflows to deliver highly individualized cell therapy products, while developing processes that can deliver treatments for many?

To address this challenge, we've connected with individuals well versed in TIL therapy manufacturing. From their extensive knowledge and experiences, we've gathered valuable tips, insights, and recommendations that will help empower and guide you on your cell therapy manufacturing journey.

Article 01

Tumor infiltrating lymphocytes as cell therapies

ARTICLE 1:

Tumor infiltrating lymphocytes as cell therapies

Understanding the potential of TIL therapies in advancing cancer care

Introduction

Nature is incredibly smart, creative, and efficient in so many ways, and the human immune system is a testament to that (1). As we've begun to slowly understand and unlock the complexities of immune mechanisms through technology, we've found better ways to fight disease. Immunotherapy of cancer is a prime example — it's based on natural immune defenses that can be optimized to target specific cancers. Here, we focus on an important player in such targeted, highly personalized cancer therapies called tumor-infiltrating lymphocytes (TILs).

Two modes of immunotherapy for cancer have garnered much attention in the past decade: immune checkpoint inhibitors and adoptive cell transfer (ACT). TILs belong to the latter, along with chimeric antigen receptor (CAR) T cells, and are used to treat late-stage patients, including those patients who don't respond to checkpoint inhibitor drugs. CAR T cell therapy is perhaps the better-known ACT modality, but TILs have proved more promising in treating certain solid tumors. This article will look at the tapped and untapped potential of TILs in cancer care, as well as the limitations of their use and some challenges in therapy development.

What are tumor-infiltrating lymphocytes?

In adoptive cell transfer or ACT, immune cells are removed from the body, expanded in the lab, and then returned to the patient. The ACT approach uses one of two strategies to destroy tumors: naturally occurring TILs from solid tumor masses or genetically modified T cells that recognize specific tumor cells (i.e., CAR T cells and TCR modified T cells; see Fig 1) (2).

TILs are a naturally occurring, heterogeneous population of lymphocytes (white blood cells) that migrate into a tumor, and they may be the most relevant immune cells in the body for fighting that cancer. TILs mostly comprise T cells that actively engage in tumor destruction. So, how can we harness and target the cytotoxic ability of TILs to fight cancer?

"TILs enter into the tumor to eradicate it, but for some reason their activity has been stopped; maybe because there's too few of them, maybe due to some immunosuppressive mechanism within the tumor microenvironment — we know this has a huge impact on the infiltrating lymphocytes," responds Dr. Özcan Met, Associate Professor and Head of Cell Manufacturing at the National Center for Cancer Immune Therapy, University Hospital

Herlev in Denmark. "So, the idea with TIL therapy is to extract these cells from the tumor, activate them, increase them in number, and reintroduce them to the patient to generate a robust immune-mediated anti-tumor response."

Why are TILs important in immunotherapy for cancer?

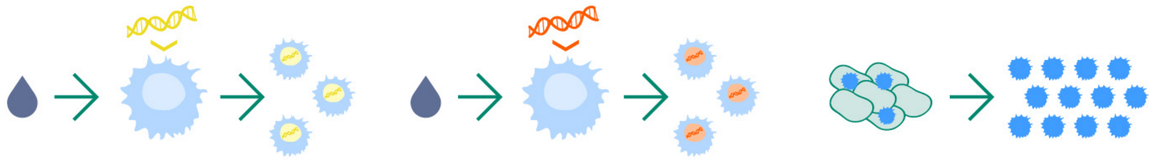
The clinical benefit of TILs was observed as early as 1972, many years before they were developed into the kind of therapy used today (3). It is now believed that TILs may very well be present in many solid cancers, and their presence is often associated with a favorable prognosis, according to Dr. Met. But how do TILs compare to CAR T cells? The key fact to understand here is that both these therapy forms are effective and have their own merits, but for different indications. "It's not one or the other," says Dr. Met.

While TIL therapy takes advantage of the natural, tumor-specific T cells that exist in the patient, CAR T cells are genetically modified to obtain specificity to a certain antigen. Another difference is the source of the cells: TILs are extracted from solid tumors, while T cells later modified with a CAR are extracted from peripheral blood. In terms of clinical response, TILs have shown clear efficacy in one solid cancer type — melanoma (4), and there's more research now into other solid cancer types, such as breast, cervical, and ovarian cancer (5,7). CAR T cells have been very effective in hematological malignancies that present CD19, an antigen exclusively expressed on the surface of B cells (another type of immune cell), both normal and cancerous. Particularly in acute lymphoblastic leukemia (ALL), CAR T therapy has demonstrated complete response rates of 70% to 90%, as reported by multiple institutions (2).

Because CAR T therapy can affect normal B cells, there is a major side effect termed 'on-target off-tumor toxicity'. But this is a manageable problem, according to Dr. Met. The patient can be given immunoglobins before and after the therapy to manage B cell depletion (B cell aplasia). However, this type of side effect could be fatal if the antigen was expressed on cells in essential organs, such as the liver or heart. Hence, there is a considerable barrier for the use of CAR T therapy to treat solid cancers.

"When it comes to TILs, it's very important to stress that the major focus has so far been on melanoma. We are starting to slowly investigate the use of TILs in other cancer forms, but most of the proof-of-concept has been done in melanoma, particularly by Dr. Steven Rosenberg's group at the National Cancer Institute (NCI)," notes Dr. Met. "On the other hand, the proof-of-concept for CAR T cells has been in cancers like B cell lymphomas and lymphocytic leukemia." Essentially, the applications have fallen into different buckets so far.

Types of adoptive T-cell therapy



CAR T cell therapy
T cells are isolated from the patient's blood and genetically modified to encode the CAR protein, then expanded and infused into the patient.
The CAR modification triggers T cells to attack the specific cancer.

T cell receptor (TCR) cell therapy
T cells are isolated from the patient's blood and genetically modified to encode the TCR protein, then expanded and infused into the patient.
The TCR modification triggers T cells to attack the specific cancer.

Tumor-infiltrating lymphocyte (TIL) therapy
T cells are isolated from the patient's tumor, activated and expanded, and infused back into the patient.
These T cells actively engage in destroying the specific tumor.

Fig 1. Types of adoptive cell transfer.

An interesting feature of TILs that also points to their significance in cancer therapy is antigen recognition. TILs contain T cell receptors (TCR) that recognize various intracellular proteins and shared antigens expressed in many different organs as well as cancer tissue. Thus, antigen selection is difficult with TILs, compounded by the fact that the tumor microenvironment is much more immunosuppressive in solid cancers than in cancers formed in blood or blood-based

organs. But the silver lining here is that TILs can also recognize neoantigens — antigens that are very specific for each patient, because these antigens result from unique mutations acquired during cancer development. As such, it's possible to optimize TILs to target them to a certain neoantigen. According to Dr. Met, this type of optimization towards neoantigen recognition is at the leading edge of TIL therapy research currently.

How TIL therapies are developed and the associated challenges

Developing a TIL therapy starts with collecting a tumor tissue sample and extracting the lymphocytes from it. Because these cells are present in very low numbers, they must be carefully handled and expanded. Dr. Met explains that you can obtain T cells from a resected tumor in two ways: "You can either take the tumor and do a tissue digest to get a single-cell suspension, or you can cut the tumor into fragments that you can grow in plates."

During TIL culture, high doses of interleukin-2 (IL-2), a growth factor, is given to activate the TILs and promote their growth. Then the TILs are expanded using a rapid expansion protocol pioneered by Dr. Steven Rosenberg and his colleagues at the Surgery Branch of the NCI. "It's a 2-week expansion," says Dr. Met. "The first week is a static phase, and the second week is a dynamic phase. We initiate the cell expansion on day 0 using anti-CD3 antibody, allogeneic feeder cells, and a high dose of IL-2. In our case, we typically go from 20 million TILs to an average of 100 billion TILs. This is a 5000-fold expansion within two weeks."

Before the TILs are returned to the patient, the patient is given a high dose of chemotherapy to remove some nonspecific immune cells and 'make room' for the infusion of TILs — this is called lymphodepletion and it's followed by another dose of IL-2 (8). "The lymphodepletion is crucial for getting a significant effect," Dr. Met says. "Without preconditioning the patient with lymphodepletion, some groups have failed to show high clinical response." Figure 2 provides an overview of TIL therapy development.

The intensive nature of this treatment and the fact that it's highly specialized are some of the main limitations of TIL therapy. Trained personnel are required to handle the TILs,

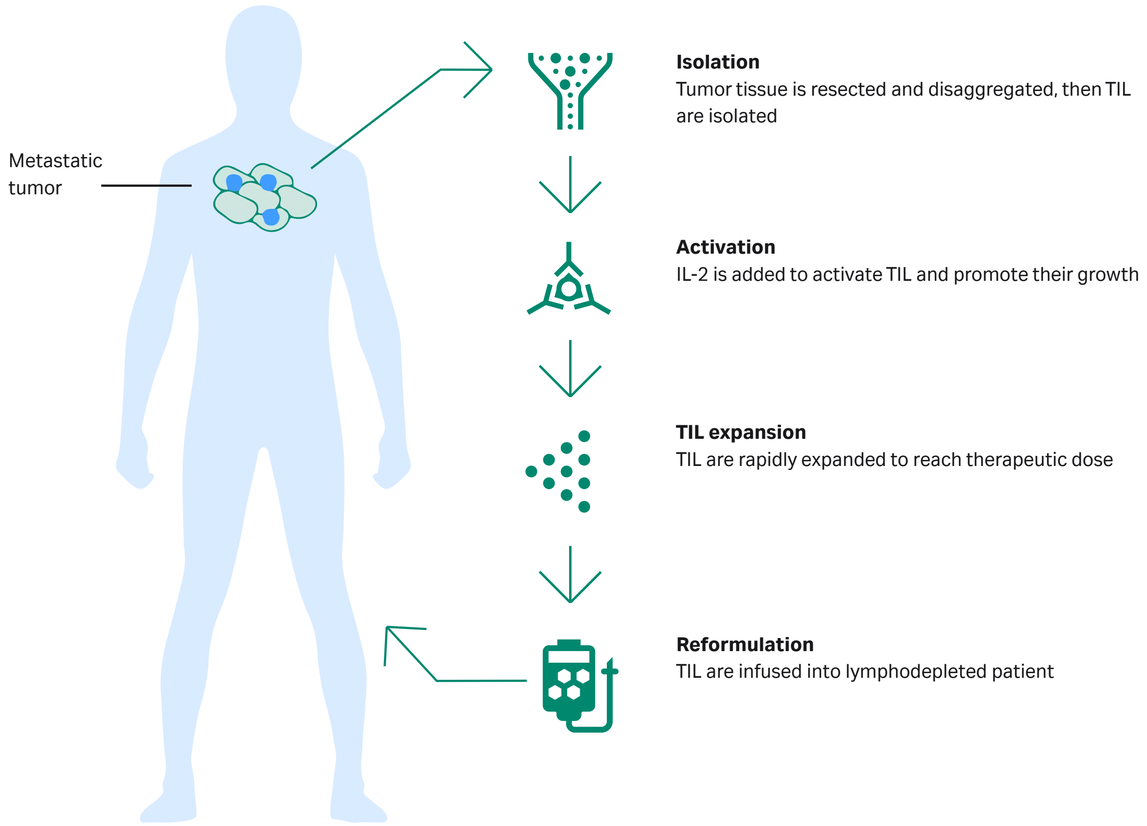


Fig 2. How TIL therapy is developed.

ensure cell growth, and successfully turn around a product. Also, production requires a good manufacturing practices (GMP) grade facility, and the clinic must be tailored specifically for patients receiving this therapy. Dr. Met explains that it's difficult to establish these facilities in a normal hospital setting, "there's only one dedicated center in Denmark for this."

Then there are the time and cost factors — developing the TIL therapy takes four to eight weeks. But some late-stage patients don't have that long, and most of the 'cost' of TIL therapy comes from the time it takes to produce the cells. Dr. Met believes there are opportunities to bring down the time, and consequently the cost, by exploiting technology to optimize things like sample processing.

However, compared to CAR T therapies, producing TIL therapies may actually be cheaper, at least in an academic setting. "Currently, making CAR T cells is more expensive because of the viral vector that you put into the cells," Dr. Met reflects. "With TILs, there is no genetically modified component and no use of viral vectors. What you need are some antibodies and allogeneic feeder cells, which are not as expensive, comparatively."

Advancing TIL therapy: what the future looks like

As mentioned earlier, TIL therapy has shown significant, durable success in treating melanoma, in multiple studies (2). Dr. Met's team in Denmark has explored TIL therapy for melanoma in combination with other treatment options like checkpoint inhibitors. "We have seen that patients previously given checkpoint inhibitors are still responding to TIL treatment, and responding better than just the checkpoint inhibitor monotherapies," he notes. Now, the focus is on expanding this success to other cancer types. Dr. Met and colleagues are testing TILs on ovarian cancer, using the same expansion method but pretreating and priming the patients with checkpoint inhibitors. They are also researching ways to make TILs more potent, cytotoxic, and specific, particularly for cancers that can see benefit from neoantigen-specific TILs.

"We are working on having two targeting modalities with TILs: on the one hand you have those TILs that recognize shared antigens broadly, and then on the other hand you have TILs that specifically recognize certain mutations unique to a patient — and that's our research focus going forward," explains Dr. Met. "We may have a hundred billion cells after TIL expansion, but the number of cells that actually do recognize and attack the tumor are much less. So, the trend is towards developing more specific TILs."

Right now, TILs are being used as a salvage treatment for late-stage cancers, after first- and second-line treatment with checkpoint inhibitors (2). Dr. Met points out that, "if we can move TIL therapy to an earlier stage, we might derive even more benefit from it." At the rate medical technology is progressing, it wouldn't be a stretch to say we'll see such developments in the near future.

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Article 02

Sample collection and processing in TIL therapy development

ARTICLE 2:

Sample collection and processing in TIL therapy development

Addressing challenges in collecting, handling, and processing tumor tissue

Introduction

Adoptive cell transfer, in which a patient's own immune defenses are boosted or rewired to kill cancer cells, is one of the most effective forms of personalized cancer care to ever reach patients. There are two types of adoptive cell transfer. In one type, immune cells called T cells are isolated, genetically modified, expanded, and returned to patients (e.g., CAR T cell therapy, TCR-modified T cell therapy). In the second type, the cells are expanded and infused back without genetic modification. The latter involves tumor-infiltrating lymphocytes or TILs — a naturally occurring, heterogeneous population of white blood cells that migrate into a tumor. TILs are known to be the most suitable immune cells to attack and destroy the cancer they homed in on. (For an introductory overview of the status and desirable evolution of TIL therapies, please refer to our previous article here.)

"Back in 1988, we published our first work showing that TILs isolated from patients with metastatic melanoma could be expanded in the lab and returned to the patient, where they mediated cancer regression," stated Dr. Steven Rosenberg, chief of surgery at the U.S. National Cancer Institute, in a report by the American Association of Cancer Research (AACR) in 2018 (1). His decades-long research into TILs, along with multiple studies by other groups, have proven that TIL therapy shows significant, durable success in treating melanoma (2, 3). TIL therapy is now being explored for precision treatment of other types of solid cancers.

While it has been advanced over many years, the process of developing TIL therapies still suffers from certain challenges, particularly in the collection and processing of tumor samples used to extract TILs. This article attempts to lay bare some of these challenges and discuss how novel technological solutions can help overcome them.

Collecting tumor tissue for TIL therapies

TILs are typically not present in high numbers within a tumor. Thus, they must be carefully extracted and handled to ensure that cell viability and yield is maintained. The first step in preparing TILs for therapeutics purposes is the collection of a sample of the solid tumor tissue. Dr. Sophie Papa, a Clinical Reader in immuno-oncology and Consultant Medical Oncologist

at King's College London, is a medical lead heavily involved in various clinical trials on TIL therapies. She says that "one of the greatest factors currently preventing patients from receiving TIL therapy is the difficulty of easily accessing and harvesting their tumors as a sample for processing." The reason, she elaborates, is the labor-intensive protocols that require skilled personnel like surgeons and technicians who can expertly remove enough viable tissue.

After the tissue is taken in the operating room, it is sent to the pathology department. There, a pathologist decides how much of it can be allocated to research while keeping enough material for clinical and diagnostic needs. "Only pathologists can make this decision — they need to make sure that they do not harm the clinical output of the patient," says Dr. Yehudit Cohen, Scientific Director of MIDGAM — the Israel National Biobank for Research, a governmental entity located at the Weizmann Institute for Science in Israel. Once the tissue is released by the pathologist, Dr. Cohen helps direct it to researchers for further research and processing.

Maintaining cell viability for higher yields

According to Dr. Cohen, the time between tissue resection and tissue submersion in the required medium (and the choice of medium itself) plays a significant role in cell viability and yield. "We measure this time length in two portions — the warm and the cold ischemic time," explains Dr. Cohen. "We can only affect the cold ischemic time. The warm ischemic time [the time a tissue remains at the original body temperature after its blood supply has been cut off, but before it is cooled] depends on operation room procedures. For example, we can ask for the tissue to be delivered to us as soon as possible, but if the surgeon is still working and is not able to release the tissue, we can't really change that."

However, once the tissue is out of the operation room on ice, it must quickly arrive at the pathology department, where it is cut up and allocated for research and clinical purposes. There is some control over this 'cold ischemic time' to influence cell viability of the tissue given to a TIL therapy study. "The quality and viability of the tissue is dependent on how quickly it's cut up, how well its temperature is controlled, and how rapidly it's put into the medium that

TIL processing steps and challenges:
From tumor collection to tissue disaggregation

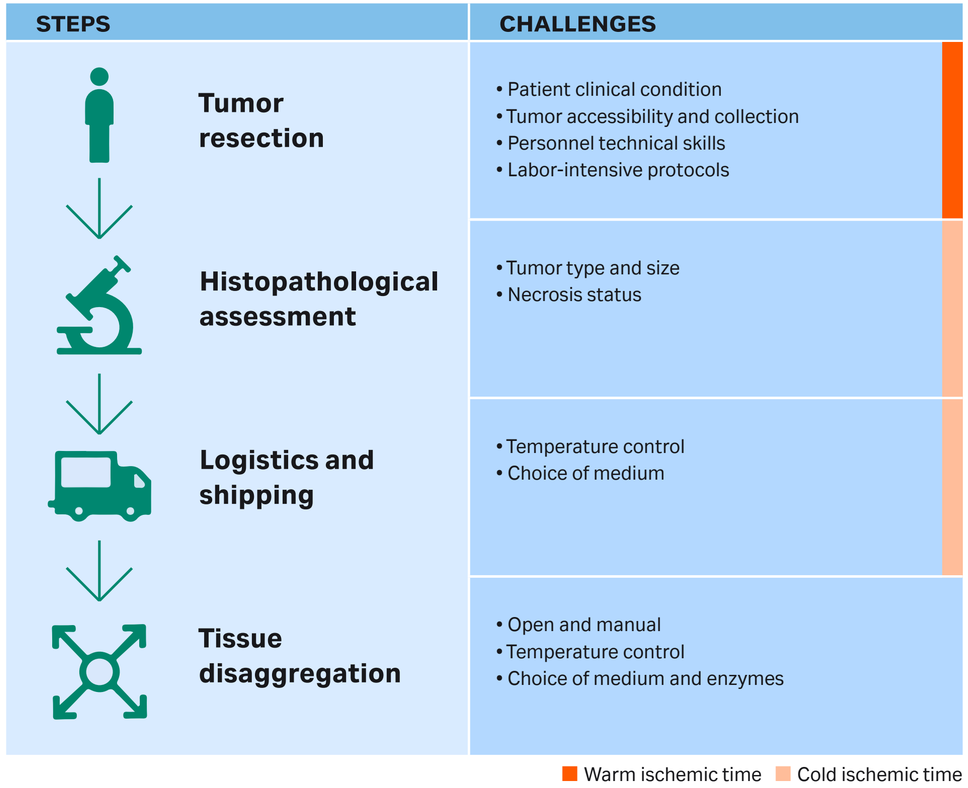

Fig 1.
A schematic diagram showing the different steps in the process of developing a TIL therapy: from tumor collection to disaggregation. Critical aspects highlighted.

it's transported or disaggregated in," Dr. Papa confirms. All of these steps introduce variability to the quality of the starting material, and, in the end, to the TIL therapy.

The viability of cells in the tissue sample is also affected by the donor's clinical condition. For instance, following chemo or radiotherapy procedures given to the patient, many cells may be necrotic, fibrotic and/or nonviable. Likewise, the type of tumor that is sampled can also impact the cell yield. "If you take colon or lung tumor tissues, you will probably have enough material to work with," Dr. Cohen states. "But in contrast, most tumoral breast tissues are small — so, the potential of having enough tissue to work with is lower. Another example is pancreatic cancer. It's very hard to access the tumor in a procedure like a biopsy — so collecting enough tissue is difficult, on top of the fact that TILs are present in low numbers." Dr. Papa adds that some cancers have more lymphocytes infiltrating them than others, and these differences are inherently part of the biology of the disease.

At the National Center for Cancer Immune Therapy, University Hospital Herlev in Denmark, researchers have access to fresh tissue when isolating TILs for therapeutic purposes. "In our facility, we don't have to get chilled tissue from other parts of Denmark, because we usually have the patients in-house or in a nearby hospital," explains Dr. Özcan Met, Associate Professor and Head of Cell Manufacturing at the center. Dr. Met's team is able to expand TILs from resected tumor in more than 95% of patients with metastatic melanoma. He believes this is, at least, partly due to their rapid access to fresh tissue.

Improving manufacturing — automation, environmental control, and standardization

Experts like Drs. Papa, Cohen, and Met agree that there is a lot of room to improve the efficiency of the TIL therapy development process. Particularly, in the time period between physically removing tissue from a patient and transporting it to the laboratory — whether that's in the same building or on a different continent — several aspects can be optimized to enhance the quality and efficiency of the process.

Anything that involves the patient is hard to standardize. "Harvesting the tissue and treating the patient are two things that you

TIL processing steps and challenges:
From tissue disaggregation to cell therapy delivery

STEPS	CHALLENGES
Tissue disaggregation	• Open and manual • Temperature control • Choice of medium and enzymes
Cell activation and expansion	• Choice of medium and growth factors • Feeder cells • No shared protocols
Cryopreservation and shipping	• Temperature control • Logistics
Therapy delivery	• Patient lymphodepletion protocol • Patient clinical conditions

Fig 2.
A schematic diagram showing the different steps in the process of developing a TIL therapy: from tumor disaggregation to therapy delivery. Critical aspects highlighted.

can't standardize or automate at either end, but everything else in the middle we should be striving to automate and standardize as much as possible," Dr. Papa suggests. Also, she believes that eliminating the need for a surgical procedure, where possible, would be helpful. Interventional radiology and biopsy-based techniques to obtain tissue are much less complex than surgery and would speed up the process. According to Dr. Papa, technologies that could enable rapid tissue disaggregation, maybe directly at the bedside or in the operating theater, would improve the quality of the harvest.

Once the samples are received in the lab, they are taken into a sterile environment where the tumor is disaggregated and the cells grown and expanded in medium supplemented with growth factors, cytokines (e.g., high dose of IL-2), and supporting feeder cells. Throughout this manufacturing process, there are multiple quality checkpoints for the cells, but much of the process is not standardized or temperature controlled.

According to Dr. Papa, there are many different protocols using various reagents and supporting cells for different periods of culture. "Traditionally, and in some current circumstances, a lot of this is done in a manual, open manner," she notes. Such open systems lack effective monitoring of the process temperature, which can result in low yields, contamination, and inconsistencies between samples. Moreover, the tumors used to extract TILs may contain contaminants from the beginning.

Right now, one of the biggest hurdles in trials of TIL therapies is the lack of standardization of protocols, whether it's in sample collection or processing. "If you've got multiple different centers that are recruiting to your trial, the more standardized things are, the more you can compare results, like whether patients respond to treatments or not, and be confident about the quality of the cellular product," Dr. Papa says. Her recommendation to reduce variability is to make the upstream process of getting tumor samples for the therapy manufacturer as simple, automated, standardized, and regulated as possible.

Dr. Met agrees that there should be more standardization and optimization in the upstream steps. He explains that TIL therapy is a very specialized form of therapy, and different countries have different regulations for manufacture. "For instance, in Denmark, we can use allogeneic feeder cells for the expansion of the TILs, but this is not allowed in some other countries and they have to use autologous feeder cells," Dr. Met adds, pointing out that changing manufacturing protocols requires extensive validation, which is both costly and time-consuming. He believes there's more leeway to optimize sample processing before expansion, and industry could help in this regard with collaborations and new technological innovations.

"It would be really helpful to have more sharing of information relevant to sample processing, so that there can be more standardization across protocols," concludes Dr. Papa. "That way, we can draw conclusions more confidently across trials about the efficacy and feasibility of the therapy."

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Article 03

Scalable and automated end-to-end workflow for TIL manufacturing

Background

- Autologous tumor infiltrating lymphocyte (TIL) therapy targeting solid tumors is clinically advancing globally.
- The process starts at tumor resection, followed by TIL isolation from the tissue, GMP cell manufacturing to expand cells, then delivery back to the patient.
- Novel strategies to scale and automate this workflow, however, remain to be fully developed.
- In this study, we aim to develop a TIL workflow that includes end-to-end logistics, electronic standard operating procedures (eSOPs), cellular manufacturing and analytics which is scalable throughout the various clinical environments. The workflow is mainly based on equipment and consumables developed by Cytiva.

Methods

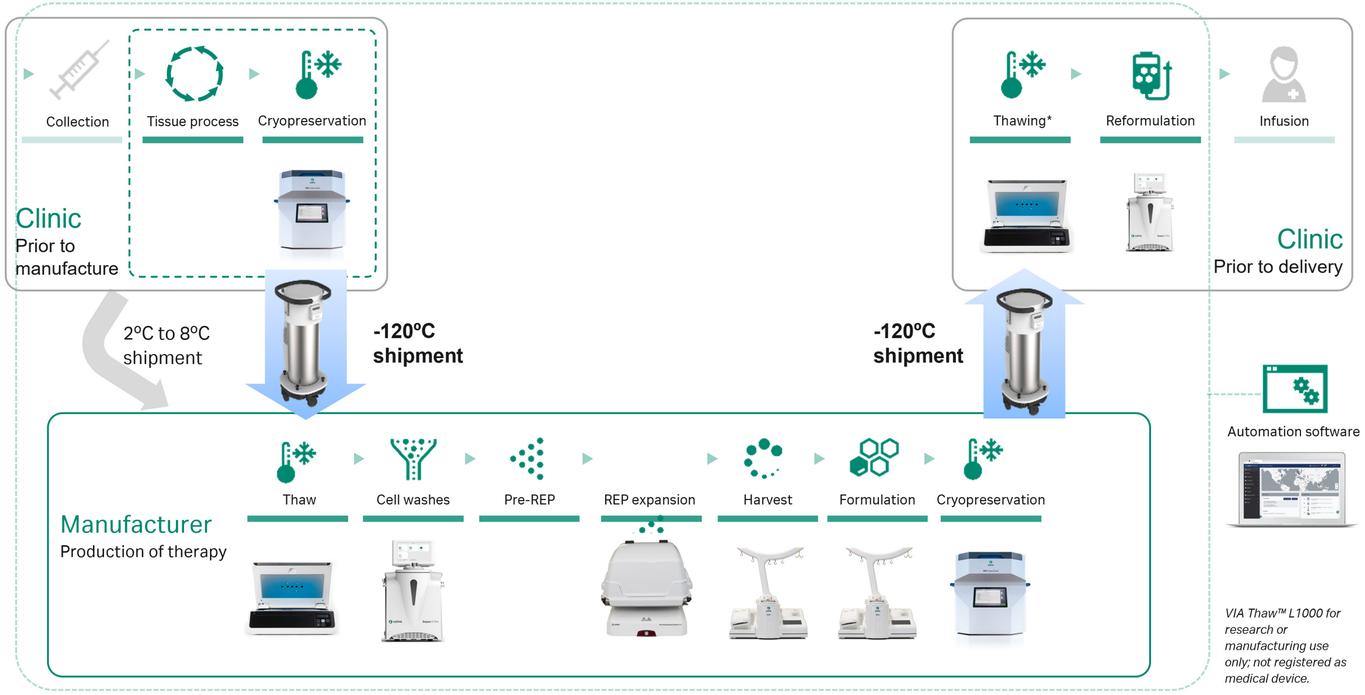


Fig 1. Strategy of Cytiva TIL manufacturing workflow: This workflow consists of the following sequential steps: tumor transportation post-resection, tissue disaggregation and cell isolation, pre-Rapid Expansion Protocol (pre-REP), full-REP, final formulation, cryopreservation, Cryochain shipment logistics and transportation, analytical assays for in process controls and release testing, and a manufacturing automation software.

Results

1. Successful *in vitro* expansion of TILs isolated from tumor biopsies

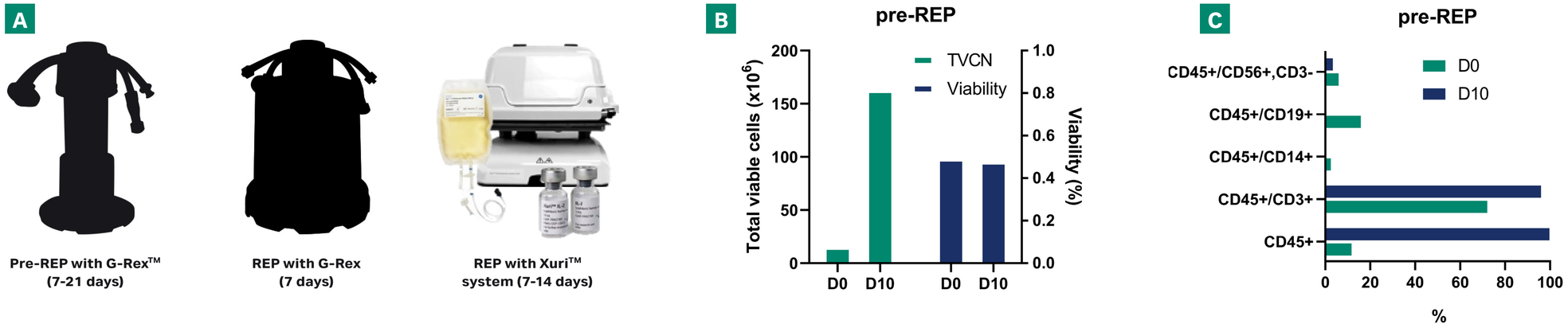


Fig 2. In vitro expansion of the representative TILs isolated from tumors: (A) outline of the cell culture workflow. For TIL culture, tumors were resected from a tumor site at 0.25-0.5g of mass and collected in sterile conditions. The collected tumor tissues then were shipped to Cytiva overnight. After receiving, the tumor tissue was disaggregated and the cells were isolated in a closed, temperature controlled, automated device. The extracted cells were cultured in Xuri EM media with 6,000 IU/mL Xuri IL-2 for 7-21 days to achieve abut 1E7 TILs (pre-REP). Primary TILs were further expanded using a rapid expansion protocol (REP) by stimulation with anti-CD3 antibody and irradiated peripheral blood mononuclear cells (PBMCs) in a GRex100M CS. REP TILs were then transferred to Xuri bioreactor to further expand to ~1E10 viable TILs. **(B)** pre-REP cell expansion. The isolated cells show high viability. Cells were successfully expanded. **(C)** Subpopulation of the cells during pre-REP. TILs were grown out. (D) REP TIL expansion.

Results

2. REP TILs cultured in Xuri cell expansion system display a memory-like phenotype

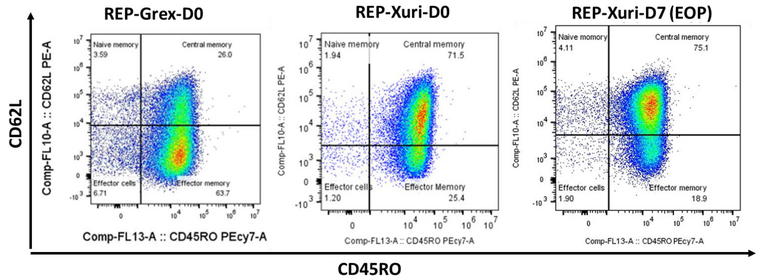


Fig 3. Increase of the memory phenotype during REP in Xuri system: TILs show increased percentage of central memory-like T cells (CD62L+, CD45RO+) in the EOP cells when compared to pre-REP TILs (REP-G-Rex-D0).

Results

3. REP TILs were successfully harvested, washed, and formulated using Sefia™ S-200 cell processing instrument from Cytiva

A

B

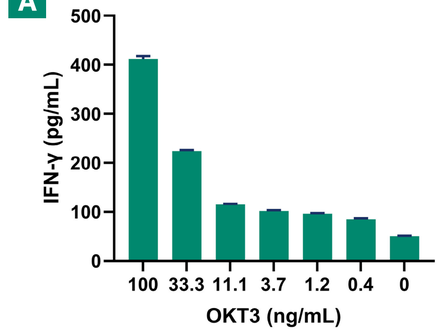
Sample	Viability (0%)	Viable cell density (1e6/mL)	Volume (mL)	Total viable cell number	Recovery rate
Prior wash and formulation	98.53	2.51E+06	5000	1.25E+10	89.52%
Prior wash and formulation	94.10	7.48E+07	150	1.12E+10	

Fig 4. TIL harvest and formulation: (A) Final TILs product post Sefia processing. **(B)** High recovery rate and viability post Sefia processing.

Results

4. REP TILs with Xuri system show effector function in response to CD3 antibody (OKT3) and irradiated PBMCs

A



B

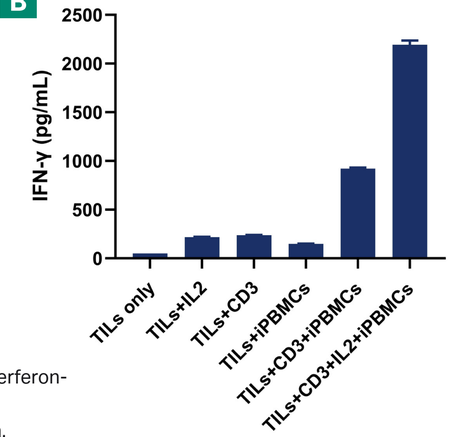


Fig 5. IFN-γsecretion by TILs: (A) TILs show increased interferon-gamma (IFN-γ) secretion in response to OKT 3 stimulation. **(B)** Feeding with irradiated PBMCs increase IFN-γ secretion. Measured by Ella (an instrument performing ELISA analysis).

Results

5. TILs were successfully shipped coast to coast without losing the viability, phenotype, and function antibody (OKT3) and irradiated PBMCs

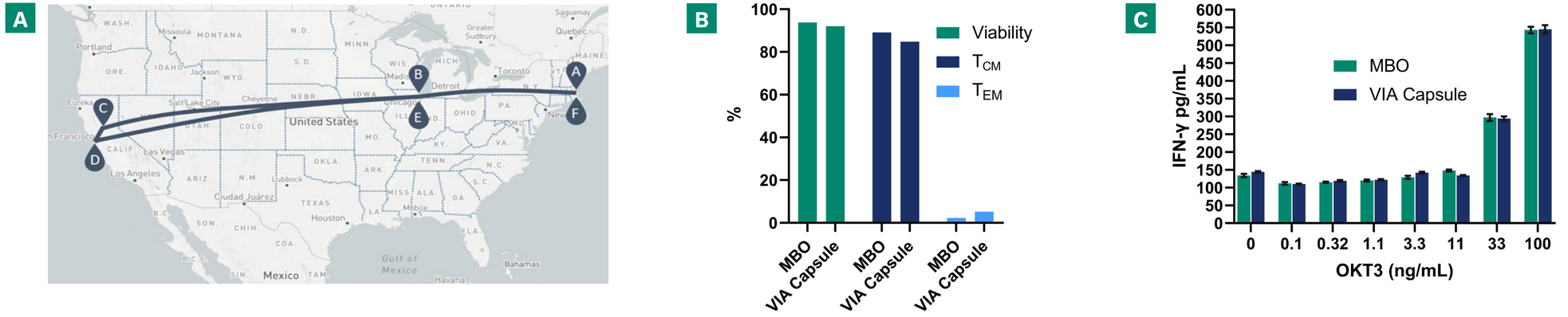


Fig 6. Cryochain shipment: **(A)** TILs were shipped to California and returned to Marlborough (MBO) using the VIA Capsule™ system. The temperature and logistics was monitored on real-time by Chronicle™ automation software. (B) Secretion in response to OKT 3 stimulation. **(B)** Viability and immunophenotype were not altered compared to the retaining sample (MBO). **(C)** TILs remain functionable assessed by IFN-γ secretion.

Conclusions

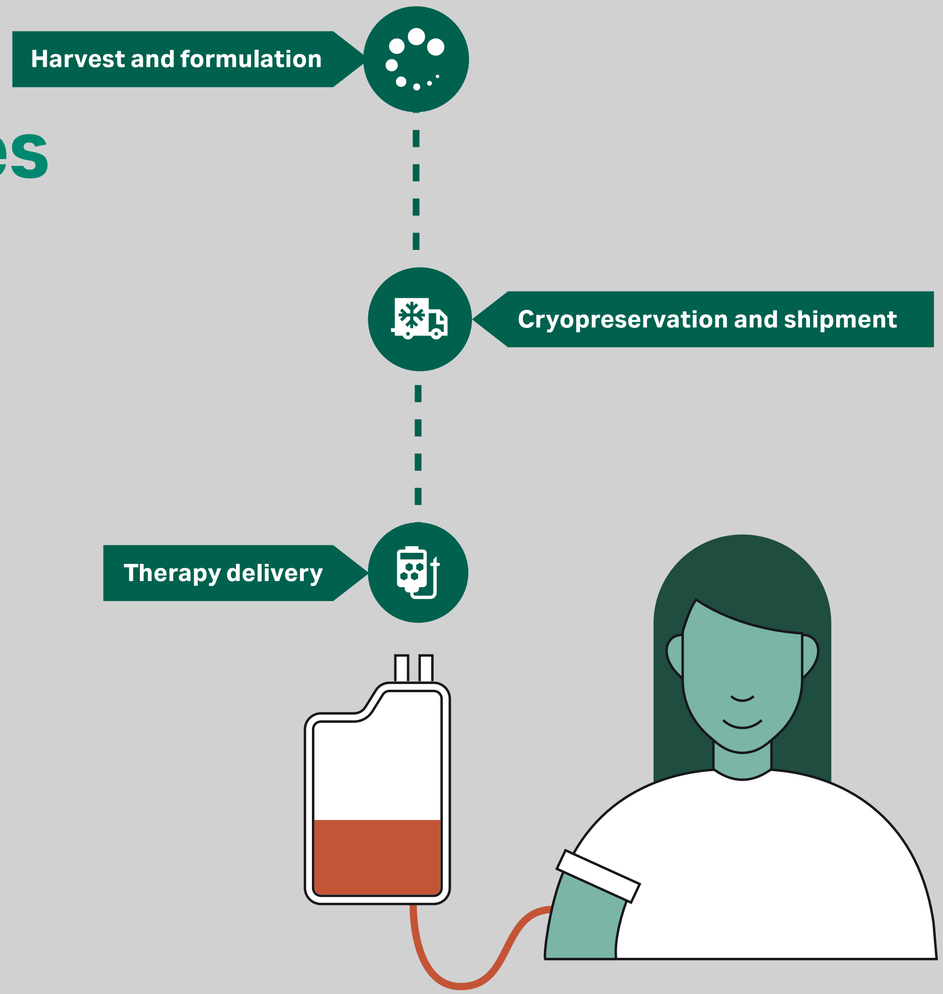
An end-to-end, scalable, functionally-closed TILs manufacturing workflow was developed. It is deployable with reduced requirements in multiple manufacturing sites.

From tumor resection to therapy delivery, there are a number of hurdles at each stage of your TIL therapy manufacturing workflow.

Curious how to address these common challenges?

Our infographic details each step of the TIL therapy manufacturing workflow with key challenges and solutions for every stage.

Download infographic



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