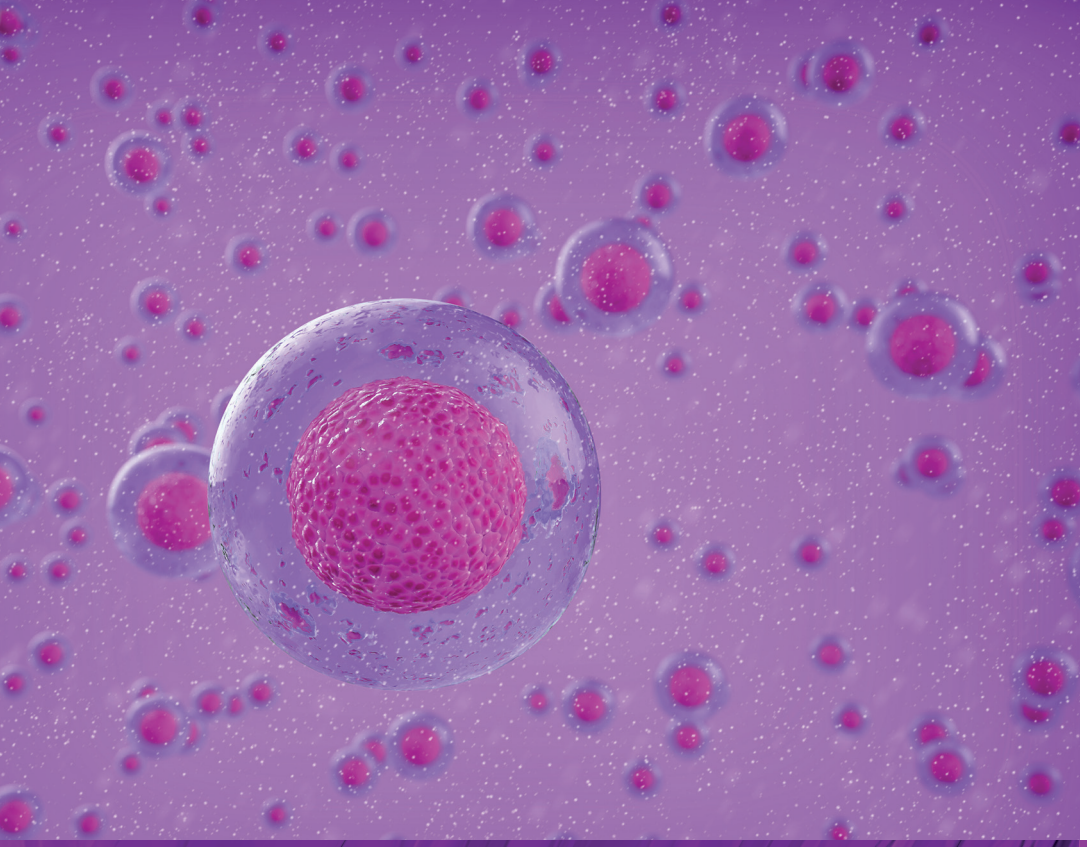


Hitachi Chemical

HITACHI

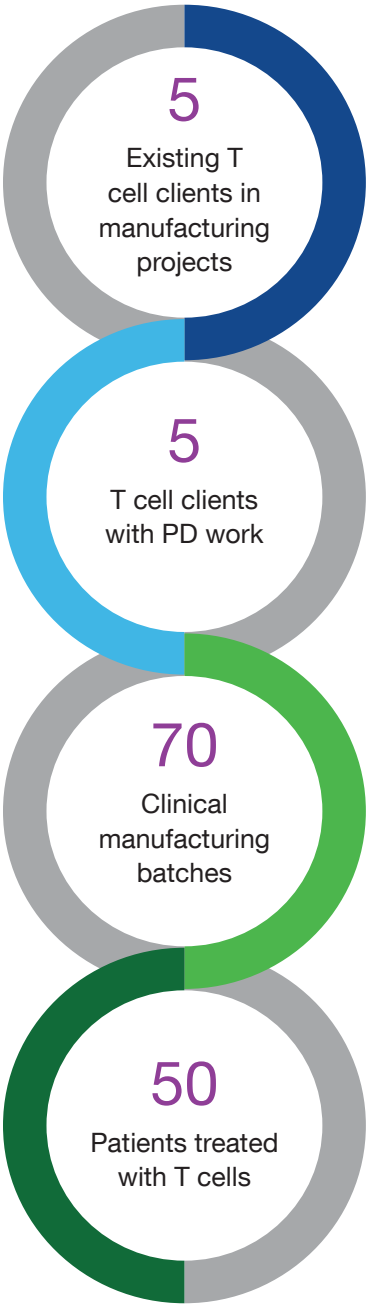
The Expertise to Advance Your T Cell Program

with Commercialization in Mind

Hitachi Chemical Advanced Therapeutics Solutions (or "HCATS", formerly known as PCT) has been an external cell therapy optimization, development and manufacturing partner for more than 16 years. With this background, some of the first developers of CAR-T technologies began to come to HCATS for process development and clinical trial manufacturing support and our clients now include a number of the key players in the industry. We balance our deep knowledge of T cell therapy manufacturing with cuttingedge innovation in bioprocess engineering to deliver unique solutions that accelerate the clinical development of our clients' T cell programs.

pct

Manufacturing Transformation



T Cell Therapy Expertise

Cell Type	Typical Process	Clinical Effects
CAR-T Cells	Isolated from patient apheresis material, activated, transduced with a CAR construct, expanded, and harvested into a cell therapy product for autologous cell therapy against cancer.	• Kill tumor cells • Produce cytokine • Generate memory T cells for durable response
Engineered T Cells	Isolated from patient apheresis material, activated, transduced with an engineered TCR construct, expanded, and harvested into a cell therapy product for autologous cell therapy against cancer.	• Kill tumor cells • Produce cytokine • Generate memory T cells for durable response
Tregs	Isolated from patient apheresis material, purified, selected, expanded, and harvested into a cell therapy product for autologous cell therapy to control autoimmune diseases.	• Suppress autoimmunity • Produce inhibitory cytokines

At HCATS, our T cell-specific experience and expertise means that not only do we understand T cell therapy manufacturing, but that we understand our clients' products technically, allowing us to make significant contributions to the success of clinical trial manufacturing. When it comes to T cells, moving from academic-stage to commercial-ready manufacturing processes that are truly deliverable means that high-quality product must be consistently produced at a reasonable cost of goods to meet demands over the commercial life of the product.

Ines Mende, PhD

Associate Director, Process Development

Dr. Mende is an experienced immunologist with 15 years of hands-on research experience in the biotech industry and at academic institutions. During her academic career, one of her main research interests was studying interactions between dendritic cells and T cells in the context of tumor immunotherapy. Prior to joining HCATS, Dr. Mende was a scientist at Aragen Bioscience. Recent work includes development of flow cytometry characterization assays for CAR T cells and process development/ assay development for a regulatory T cell immunotherapy. [PhD, Technische Universität München (TUM); postdoc, Stanford University]

Academic publications include:

- Standley SM, et al. Incorporation of CpG oligonucleotide ligand into protein-loaded particle vaccines promotes antigen-specific CD8 T-cell immunity. Bioconjug Chem. 2007 Jan-Feb; 18(1):77-83.
- Mende I, et al. Highly efficient antigen targeting to M-DC8+ dendritic cells via FcgammaRIII/CD16-specific antibody conjugates. Int Immunol. 2005 May; 17(5):539-47.
- Karsunky H, et al. High levels of the onco-protein Gfi-1 accelerate T-cell proliferation and inhibit activation induced T-cell death in Jurkat T-cells. Oncogene. 2002 Feb 28; 21(10):1571-9.

David O'Neill, MD

Director, Analytical Development & Medical Director

Dr. O'Neill is board-certified in Anatomic and Clinical Pathology and Blood Banking/ Transfusion Medicine. He has more than 25 years of academic and industry research and development experience in biochemistry, genetics, molecular biology, immunology, and stem cell biology, including 12 years working on human cellular therapies. His recent R&D work involves developing and testing a regulatory T cell immunotherapy for diabetes and exploring novel therapeutic uses of stem cell populations found in human peripheral blood. [BA, Cornell University; MD, Ohio State University]

Academic publications include:

- Adams S, et al. Immunization of malignant melanoma patients with full-length NY-ESO-1 protein using Toll-like receptor 7 agonist imiquimod as vaccine adjuvant. (2008). J. Immunol. 181, 776-84.
- Valmori D, et al. Vaccination with NY-ESO-1 protein and CpG in Montanide induces integrated antibody/Th1 responses and CD8 T cells through cross-priming. (2007). Proc. Natl. Acad. Sci. USA., 104, 8947-8952.
- O'Neill DW. Dendritic cells and T cells in immunotherapy. (2010). J Drugs Dermatol. 9, 1383-92.

Our T cell team includes:

Cenk Sumen, PhD

Senior Manager, Business Development

Dr. Sumen's love of T cells began with his PhD project, where he developed an artificial membrane system for deconstructing the molecular events in T cell antigen recognition. During his postdoc he developed a new molecular tool using quantum dots to track virus antigens in vivo. Since then he has held positions at Biogen, Memorial Sloan Kettering Cancer Center, Life Technologies, STEMCELL Technologies and more. [PhD, Stanford University School of Medicine; postdoc, Harvard University]

Academic publications include:

- Grakoui A, et al. The immunological synapse: a molecular machine controlling T cell activation. Science. 1999; 285:221-227
- Sumen C, et al. T cell receptor antagonism interferes with MHC clustering and integrin patterning during immunological synapse formation. Journal of Cell Biology. 2004; 166:579-90.
- Sumen C, et al. Adoptive T-cell therapies: Unlocking the potential of engineered antigen receptors. Drug Discovery World. 2015; 16(2): 47-54.

The Passion for and Potential of T Cells:
Expert Insights

Why are T cells promising/exciting in cell therapy right now?What potential do you see?

"T cells play a central role in the immune response, as they have the potential to directly kill virus-infected or malignant cells, as well as modulate immune responses. With the development of the CAR T technology, T cells can be engineered to express antigen-specific TCRs (T Cell Receptors) or CARs (Chimeric Antigen Receptors) and thus be directed to kill any cells that express a particular antigen. This has proven to achieve long-lasting clinical effects in case of hematologic malignancies, while more development is needed to successfully apply CAR T cell therapy to solid tumor settings. The attractiveness of the T cell approach is clearly the potential of having complete and durable responses after a single treatment, with long-living T cells providing immune surveillance including across the blood brain barrier. Another exciting area are regulatory T cells, as initial Phase I clinical trials indicated both safety and efficacy in GVHD (Trzonkowski et al, 2009, Brunstein et al., 2010, Di Ianni et al. 2011), as well as type I diabetes (Marek-Tronzkowska et al., 2012, Bluestone et al, 2015). With improved methods to consistently isolate and expand these cells, an area in which HCATS is actively working, regulatory T cells have potential therapeutic use in a large number of chronic autoimmune diseases." – Ines

"T cells direct the immune system, and are potent and specific killers of malignant or virus-infected cells. They can be isolated efficiently from blood and expanded consistently in vitro for cell therapy, typically in oncology (leukemia and other blood cancers) or antiviral clinical indications (such as EBV). In the case of regulatory T cells (Tregs), they can be used to suppress autoimmune conditions such as asthma, diabetes, and inflammatory bowel disease." – Cenk

What do you see as the most significant discoveries or advancements in this field in the past few years? Why?

"The development of engineered TCR or CAR (chimeric antigen receptor) expressing T cells pioneered by Zelig Eshar, Carl June, and others certainly is the most prominent, with previously unknown success rates for treatment of ALL (93% complete remission in CTL019 Phase II clinical trial) and potential applicability for treatment of a variety of tumors. While CARs recognize surface antigen, TCRs can potentially be specific to any expressed protein, irrespective of its cellular localization thus broadening the number of targetable proteins." – Ines

"The development of CAR T cell therapies for B cell malignancies looks to be a major advance in cellular immunotherapy. The development of immune checkpoint inhibitors has been a major advance in the use of biologics to treat cancer." – David

"I think the most significant advances have come from the NCI (Rosenberg et al), U Penn (June, Levine et al) and MSK (Sadelain et al) teams, using CAR and TIL (Tumor Infiltrating Lymphocyte) T cell therapy to achieve (among other spectacular clinical results) up to 90% response rates to blood cancers such as ALL, often in pediatric patients with no other viable option. In my opinion, this work clearly deserves a Nobel prize, and I hope to see one awarded to these investigators

(as well as Zelig Eshhar, "father" of the CAR)." – Cenk

How have your previous work experiences and research impacted T cell work you have done for cell therapy clients since joining HCATS?

"I am an immunologist by training with most of my academic research focused on the interactions between dendritic and T cells. I was always interested in the normal and pathologic biology of T cells, their characterization and function, including tumor-infiltrating lymphocytes. I did my postdoc in the laboratory of Dr. Engleman at Stanford, who is a co-founder of Dendreon, which further stimulated my interest in cell therapies using either dendritic cells or T cells. When clients bring their T cell processes to us, my prior experience and scientific knowledge allows me to quickly understand the client's needs, facilitate the technology transfer and to suggest process optimization geared towards a more robust GMP manufacturing process." – Ines

"My previous academic work on immune monitoring for patients receiving active immunotherapies (vaccines) for cancer has helped me design and develop methods at HCATS for measuring T cell potency and suppressive activity of regulatory T cells." – David

"I have been productively engaged in the T cell field for nearly 20 years, having worked

in graduate school under the leadership of Mark Davis and Mike Dustin to establish the Immunological Synapse paradigm, with over 4,000 citations for my publications to date. I have also been involved in several technology development teams in industry to build tools to better understand, isolate, activate, track, image, and engineer these potent cells for pre-clinical and clinical applications. When clients bring us their T cell technology platforms, we are excited

to leverage our deep understanding of these systems to build a T cell therapy manufacturing process with the best chance of clinical and commercial success." – Cenk