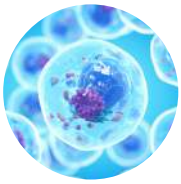
Cell Therapy - TRAcking, Circulation, & Safety (CT-TRACS)



Our Mission

The committee's mission is to facilitate the translation of cell-based therapies to the clinic by driving the development of tools, methods, and knowledge required to evaluate the safety and fate of therapeutic cells by identifying gaps/unmet needs and designing strategies to fill them, aligning "tools required" to available technology, understanding "cell fate" *in vivo*, addressing concerns regarding the potential for tumorigenicity, and developing scientific knowledge needed to help support international standards development.

Chairs

Public Chair
Dr. Tineke van den Hoorn (Medicines Evaluation Board, The Netherlands)

Private Chairs
Dr. Bill Shingleton (Cytiva) [up to May 2022]
Dr. Mick Fellows (AstraZeneca) [as of May 2022]

HESI Staff

Dr. Lucilia Mouriès (lmouries@hesiglobal.org)
Dr. Connie Chen (cchen@hesiglobal.org)

Webpage

https://hesiglobal.org/cell-therapy-tracking-circulation-safety-ct-tracs/

2022 Committee Highlights

Participating Organizations
7 government/regulatory agencies, 20 industry, 11 academic/research institutes, 2 other

Supplemental Funding
HESI EIC awarded $60K to CT-TRACS' Foresight Proposal Type I, to support the second phase of the Advance Sequencing project, for identification of off-target mutations associated with genome editing.

Publications
1 submitted, 1 in progress

Web Tools, Assays and Resources
1 database
- Cell Tracking Database: in development

Scientific Meetings and Trainings
1 meeting
- CT-TRACs 2022 Annual Meeting (virtual; 42 attendees)

Outreach
2 posters, 4 oral presentations, 3 other

International Society for Stem Cell Research (ISSCR) 2022 Annual Meeting

- Poster: Safety of Cell Therapy Products: *In Vitro* Methods to Assess the Tumorigenicity of Human Cell-Based Therapeutic Products.

International Society for Cell and Gene Therapy (ISCT) 2022 Annual Meeting

- Poster: Imaging cellular therapeutics *in vivo* for safety and efficacy: perspectives and a new resource from the multi-stakeholder committee HESI CT-TRACS.

nTRACK Open Day Workshop 2022: "Stem Cell NanoImaging –Advances and Applications Conference"

- *CT-TRACS' Committee perspectives on imaging for cell-based therapies: benefits, gaps, challenges.* Dr. Martha Lundberg (NIH/NHLBI) and Dr. Mya Thu (VisiCell Medical).

Advanced Therapies Congress 2022

- *New approaches for identification of potential off-target mutations associated with genome editing in cell therapies – a collaborative initiative*. Dr. Mick Fellows (AstraZeneca).

HESI Annual Meeting 2022

- *Combining unbiased and targeted approaches to assess tumorigenicity risks for gene edited cell therapies*. Dr. Mick Fellows (AstraZeneca).

American College of Toxicology (ACT) 2022 Annual Meeting

- *Assessment of CRISPR-Cas9 Induced Off-Target Mutagenesis in Gene-Edited Cellular Therapeutics (Induce-Seq + DS): A HESI CT-TRACS Supported Project*. Dr. Mick Fellows (AstraZeneca).

2022 Committee Highlights (continued)

Other presentations highlighing CT-TRACS work were pressented at:
- World Stem Cell Summit
- Korean Society for Stem Cell Research (KSSCR) Annual Meeting
- JSRM-ISCT iPSC Joint Committee Symposium

Collaborations
1 internal, 4 external

- HESI ITC, GTTC - HESI Advisory Core Group for Eng. T cells Safety.
- CAR-T consortium - exchanges on the IL-2 assay practices.
- Standards Coordinating Body (SCB)
- NC3Rs 2022 CRACK-IT challenge "T-ALERT: Animal-free tumorigenicity assessment of CART and other genetically modified T cells".
- UK National Institute of Health Research, Blood and Transplant Research Unit: jointly funding a 3-year PhD studentship project at Newcastle University.

Geographic Representation
Australia, Germany, Japan, Netherlands, Sweden, Switzerland, United Kingdom, United States

Working Groups

- **Point of Administration-Biodistribution (PoA/BD) WG.** This working group aims to identify current approaches, gaps, and needs in monitoring/evaluating the fate and activity of cells after their administration *in vivo*, to assess the safety of cell-based therapies.

NEW Three year PhD studentship project at Newcastle University entitled "Improved understanding of cell fate with multi-visceral normothermic perfusion models", jointly funded by CT-TRACS.

- **Tumorigenicity WG.** This working group aims to address concerns regarding the potential for tumorigenicity of cell therapy products by assessing and/or developing methodologies and approaches that could support tumorigenicity evaluation.

  International Multi-site Study: in vitro methods to assess tumorigenicity in iPSC-derived cell therapy products:

  - ddPCR team completed step-1 of the study (assessing the variance of the ddPCR analytical process at 5 sites by using samples prepared at one site) and step-2 is underway (assessing the variance of the whole analytical process at multiple sites: sample preparation + ddPCR). A panel of 10 markers specific to cardiomyocytes is also being evaluated.
  - The Highly Efficient Culture (HEC) assay team completed the multi-site study (4 sites participating) and a manuscript has been submitted.

NEW *Advanced sequencing for detection of off-target mutations associated with genome editing*: This subteam completed the first phase of the project using an unbiased method (Induce-Seq) to determine the occurrence and frequency of DNA double strand breaks (DSBs) related to CRISPR Cas9 editing in human cells. Phase 2 of the study will use a targeted approach, DuplexSeq, to confirm mutations at sites with DSBs identified in the Induce-seq assay (launched May 2022).

NEW *Soft Agar Colony Forming and Growth in Low Attachment Assays:* This subteam is focusing on a multi-site study evaluating two functional assays for tumorigenicity assessment of genome-edited adherent cells (launched January 2022).

NEW *IL-2 Independent growth assay:* This subteam initiated a multi-site study for tumorigenicity assessment of modified T cells (launched January 2022).

Areas of Focus for 2023

- Develop the Cell Tracking database, with the addition of pre-clinical studies, and establish a process for maintenance and updates.
- Wrap-up the committee's first International Multi-site Study, *"in vitro methods to assess tumorigenicity in iPSC-derived cell therapy products"* and explore new areas of collaboration with project participants.
- Generate de novo data through several of the Working Groups' planned studies.
- Continue to align with and support ongoing international efforts on optimizing current tumorigenicity testing for cellular therapies and generate data to inform standards development.
- Convene an in-person Committee meeting to review the portfolio and reconnect after 3 years of virtual meetings.
- Accompany the development of the NC3Rs CRACK-IT Challenge "T-ALERT" and support it as part of the committee's role as partner.
- Continue engagement with other HESI committees, as part of the "HESI Advisory Core Group for Eng. T cells Safety" and its activities.
- Continue engagement with SCB. Currently participating in the development of a white paper (SCB initiative) on off-target effects following genome editing.
- Continue efforts towards broadening representation across all sectors, and raising awareness about HESI CT-TRACS activities in the cell therapy scientific community.
- Engage with the SOT community through participation at the 2023 annual meeting in Nashville, as part of the workshop session: "Safety Assessment Approaches for Stem Cell Therapy" (accepted).

Strategic Impact Areas

Catalysis of new science
Testing new NGS methods to enable the identification of off-target mutations derived from genome editing: CT-TRACS initiated a project to address emerging safety concerns in genome editing, provided initial seed funding from CT-TRACS budget to enable the realization of a pilot study, and secured additional funding to support a second phase of the study (Foresight award from HESI EIC and matching funds from companies).

Exploring new human models (ex-vivo organ perfusion) to evaluate the fate of cellular therapy products after administration, via PhD studentship support.

Increasing the audiences for collaborative safety science
New projects launched this year address safety needs specific to CAR-T cell therapy and other modified T cells, genome edited therapies, in addition to the initial projects related to iPSC derived cell therapies.

Development of scientists skilled in translational science
The committee is co-sponsoring a PhD student via a three-year studentship. Through this collaboration, the student will gain unique skills and have opportunities for substantial leadership development by working with a global network of leading experts in ATMPs.

2022 Awards, Grants and Recognition

- CT-TRACS' 2019 tumorigenicity position paper (Sato et al.) passed 60 citations.

Publications

Submitted

Watanabe et. al. International multisite study for validation of a highly efficient culture assay for detection of residual undifferentiated human pluripotent stem cells in cell therapy products.

In Progress

Morrow et. al. Regulatory Considerations when Evaluating Biodistribution of Cell Therapies: Benefits of Incorporating *In Vivo* Imaging.

Participating Organizations

Government/Regulatory Agencies

Medicines Evaluation Board (The Netherlands)
Medicines & Healthcare Products Regulatory Agency (MHRA)
National Institutes of Health (NIH), National Cancer Institute (NCI)
National Institutes of Health (NIH), National Heart, Lung, and Blood Institute (NHLBI)
National Institute of Health Sciences (Japan)
US Food and Drug Administration (FDA)
US National Institute of Standards and Technology (NIST)

Academic/Research Institutes

Brunel University London
Freiburg University
King's College London
Leiden University
Newcastle University
Memorial Sloan Kettering Cancer Center
Stanford Cardiovascular Institute
University College London
University of Sheffield
University of Sydney
Wageningen University & Research

Industry

Astellas Pharma, Inc.
AstraZeneca
Athersys, Inc.
Bayer
Bristol-Myers Squibb
Broken String Biosciences Ltd.
Charles River Laboratories
CRISPR Therapeutics
Cytiva
Fujifilm Cellular Dynamics, Inc.
Genetech/Roche
GentiBio
Janssen Pharmaceuticals
Novartis Pharmaceuticals
Sanofi
Sonoma Biotherapeutics, Inc.
Sumitomo Pharma Co., Ltd.
Takeda Pharmaceutical Company, Ltd.
TwinStrand Biosciences
VisiCell Medical

Other

Cell and Gene Therapy Catapult (UK)
European Infrastructure for Translational Medicine (EATRIS)