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# Production Assistance for Cellular Therapies

**Educational Web Seminar**

***Methods for Cellular Therapies: Tracking Cells In Vivo and Assessing Biodistribution In Patients–***

***What are your cells doing? Where do they go?***

**Thursday, 03 September 2020**

**12:00 PM – 1:00 PM ET**

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## Speakers

Bill Shingleton, BSc, PhD

Alliances Manager, Cytiva – UK

Brooke Helfer, PhD

Director of Research and Development
Celsense, Inc. – USA

David Morrow, PhD, MBA

ATMP and Vaccine Scientific Program Manager
EATRIS – The Netherlands

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## Disclosures

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***Unless otherwise noted, individuals did not indicate any relevant affiliations or financial interests.***

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## CE Credit

**Accreditation Statement**

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CE credit is **only** offered to participants who have attended this **live** web seminar. To claim CE credit or receive a Statement of Participation, each attendee must:

**1)** Complete the web seminar evaluation and credit tracker within 1 week of the web seminar, by Thursday, September 10:
http://z.umn.edu/PACTEvalCredits

- You will be directed to this link when you exit the web seminar.
- The link is also provided in the web seminar email reminder sent on 03 September 2020 to registered attendees.

**2)** Complete the attendee roster within 72 hours of the web seminar (group attendees).

- The attendee roster is provided in the web seminar email reminder sent on 03 September 2020 to registered attendees.

**Note:** After the online evaluation/credit tracker and live web seminar attendees list have been processed, the CE credit or Statement of Participation will be issued via email from the University of Minnesota, within 4-6 weeks, to those requesting CE/Statements of Participation.

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## Production Assistance for Cellular Therapies

PACT

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## Objectives

- Describe available and emerging non-invasive cell tracking modalities and their value in assessing cell fate and safety *in vivo*.
- Identify the benefits of these technology applications to the clinical translation of cell therapies.
- Describe strategies to help translate cell therapies into the clinical setting.
- Outline a process for therapy developers to communicate their challenges and needs that will allow for the development of technologies and tools to address their needs.

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Health and Environmental Sciences Institute (HESI)

## **HESI CT-TRACS***: a Collaborative Effort to Address Collective Challenges & Needs.

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

**William Shingleton, BSc, PhD**
Alliances Manager, Cytiva
CT-TRACS Committee Co-Chair



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HESI *Cell Therapy-TRAcking, Circulation, & Safety* (CT-TRACS) Technical Committee

## What is HESI CT-TRACS and how can we contribute?

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**Health and Environmental Sciences Institute (HESI)**

HESI 1989-2019

- Non-profit scientific organization based in Washington DC USA
- Address **risk assessment** and **safety** challenges.
- Operating Internationally.




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*After 30 years, we KNOW the model works.*

Bringing together **multidisciplinary teams** to solve the tough scientific challenges around **risk assessment and safety.**

- Facilitates collaboration across academia, government, industry, and NGO scientists.


Generating/making available/disseminating **sound, evidence-based science for better, more informed decisions.**

**Move Knowledge into Application:** creating and testing technology platforms and scientific frameworks that can be used to more effectively predict effects on humans or the environment



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# CT-TRACS' Vision

**SECURING THE SAFETY OF CELL THERAPIES TO REALIZE THEIR POTENTIAL**

**MISSION:**

To facilitate the translation of cell-based therapies to the clinic by driving the development of **tools, methods** and **knowledge** required to evaluate safety and fate of therapeutic cells.

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**Universities/ Research Centers:**

Imperial College London · King's College London · Memorial Sloan Kettering Cancer Center · Radboud University · Stanford · Cardiovascular Institute · UCL

**NGOs / Consortia:**

CATAPULT Cell Therapy · eatris · FIRM · PACT


**Government & Regulatory bodies:**

FDA · EMA · MHRA · NIH · NIHES · RIVM

**CTPs developers, CROs, tool providers:**

Astellas · AstraZeneca · Athersys · Boehringer Ingelheim · Bristol Myers Squibb · Caladrius Biosciences · Celsense · CSL Behring · cytiva · janssen · NOVARTIS · SANOFI · Takeda · VisiCELL

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# Rationale for creating CT-TRACS

**Novel Therapies, new safety assessment needs:**

- *"Living drugs"* - Need to evaluate "cell fate" after administration of cell therapies, i.e., the localization, persistence, migration, distribution and/or eventual phenotypic changes of cells, in the patient.
- Conventional PD/PK methodologies not always transferrable to CGT.
- Regulatory landscape not clearly defined, *yet*.
- Need for stakeholders' interaction.

➢ ***Issues that are best resolved through international multi-sector interaction, pooling resources and knowledge for a common goal.***



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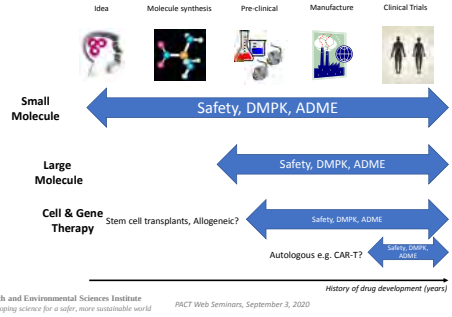
# Safety Testing: Time & experience for different drug types



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## Rationale for creating CT-TRACS


Dawn of a New Era

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## Strategies to help translate cell therapies into the clinical setting.

**Step 1:** Identifying knowledge gaps

CT-TRACS' stakeholder survey 2017 : **Assessing the needs for cell-based therapies translation**

Cross-sector discussions in CT-TRACS monthly teleconferences

**Step 2** – Establish focused groups to address issues identified

Tools, tests, and confidence to ensure cell therapy safety

**PoA:** Localization, persistence, survival, proliferation.

**Biodistribution:** Types of effects, ability to detect, ability to assess fate and distribution.

**Step 3** – Strategies to fill gaps

- ✓ **Knowledge sharing** across sectors and organizations
- ✓ **Review paper** (Helfer et al. *In submission*)
- ✓ **Public resources, making data accessible:** Cell Tracking Database
- ✓ **Communication & International Outreach:** HESI workshops, sessions, presentations at conferences.



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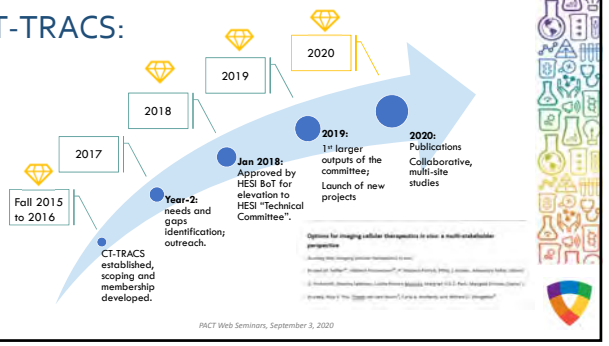
## CT-TRACS:



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## A channel to communicate challenges and needs
## Mechanisms for practical solutions

| Collaborators | Data Sharing | HESI Support | Resources | Work Products |
|---|---|---|---|---|
| **Multi-Sector** participation (academia, government, research institutions, industry, etc.)<br>**Expert knowledge**<br>**International** Forum<br>**Multidisciplinary**<br>**Collaborative** Work<br>**Public-Private Balance** | Pooling of resources.<br>Pooling of data (larger datasets; more robust studies) | Neutral platform<br>Scientific staff<br>Facilitator, Convenor<br>Program coordination<br>Organizational support<br>Global network | Members' **financial** contributions are pooled to support projects'* development.<br>**In-kind efforts** from all participants drive projects' design & execution | Public domain<br>Broad scientific interest across public and private sectors.<br>Support science-based, data-driven decisions<br>Engaging regulators across countries + academe/govt |

* Projects address a need or issue relevant to a broad cross-section of the scientific community (academia, industry, government) and have public health significance.



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2/14/2018, CGT Catapult, London

6/07/2018, IABS/CIRM, Los Angeles, CA

May 2017, ISCT 2017 London


March 7-8, 2017, FIRM and JSRM, Sendai, Japan

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HESI Convene Translate Protect

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

www.hesiglobal.org

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# Tracking cells after administration: Imaging modalities and probes

Brooke Helfer, PhD
Celsense, Inc. Pittsburgh PA, United States
HESI CT-TRACS Point of Administration Co-chair

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## Conflict of Interest

- I am an employee of Celsense, Inc. the manufacturer and provider of the fluorine based imaging agent mentioned herein.

Celsense

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## A Fundamental Question

*If there is no clinical response, did the cell product not work, or did the cell product not reach and/or persist at the site of action?*

Cell Therapy: Technology and Markets, Jain Pharmabiotech August 2008

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## Cell Trafficking Questions

- How many cells were delivered?
- How many cells migrate?
  - Site of action?
  - Off target?
- How many cells persist?
  - Site of administration?
  - Site of action?
- Strategies that affect cell trafficking?



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## Cell Trafficking Biomarkers

- Does cell trafficking data support hypothesized mechanism of action?
- Does cell trafficking data correlate with efficacy and safety endpoints?
- Is cell trafficking data a predictor of efficacy and safety?
- Can cell trafficking data guide dosage and/or repeat administration?

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## Requirements for an imaging agent

- Imaging reagents need to be:
  - Non toxic to cells
  - Not alter the phenotype and function of the cells
  - Non toxic to surrounding tissues
  - Indicates the location, migration and quantity of labeled cells
  - Allow for repeated, non-invasive detection
  - Accurately reflects the behavior of labeled cells

* adapted from Frangioni *et al* 2004 *Circulation*

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| Modality | EM Spectrum | Advantages | Disadvantages |
|---|---|---|---|
| Positron emission tomography (PET) | High energy gamma rays | High sensitivity; isotopes can substitute for naturally occurring atoms; quantitative; translational research, targeted, multiple probes | PET cyclotron or generator needed; relatively low spatial resolution; ionizing radiation |
| Single photon emission computed tomography (SPECT) | Lower energy gamma rays | Many molecular probes; can image multiple probes simultaneously; adaptable to clinical imaging systems | Relatively low spatial resolution; ionizing radiation |
| Optical bioluminescence imaging | Visible light | Highest sensitivity; quick, easy, low cost and relatively high throughput, multiple probes | Low spatial resolution; relatively surface weighted |
| Optical fluorescence imaging | Visible light or near-infrared | High sensitivity; detect fluorochrome in live and dead cells, low cost, high throughput, multiple probes | Low spatial resolution; 2D imaging only; relatively surface weighted; limited translational research |
| Magnetic resonance imaging (MRI) | Radio waves | Highest spatial resolution; combines morphologic and functional imaging | Relatively low sensitivity; long scan and post processing time, mass quantity of probe may be needed |
| Computed tomography (CT) | X-rays | Bone and tumor imaging; anatomic imaging | Limited molecular applications; limited soft tissue resolution, ionizing radiation |
| Ultrasound | High frequency sound | Real time; low cost | Limited spatial resolution; mostly morphologic. |
| Photoacoustics | near-infrared stimulation/sound wave detection | low cost; moderate spatial resolution; tomographic image | limited penetration depth |

* CT-TRACS adapted from *Gambhir S, 2007 mi gateway*

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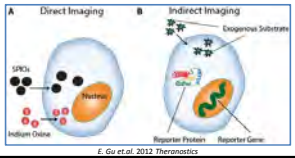
# Multiple Modalities Different Approaches

Direct Labeling

- Where the label is applied to cells prior to administration – directly linking the cells and the label

Indirect Labeling / Reporter Genes

- Where the cells either create the label, or the label binds to a receptor which the cell creates




*E. Gu et.al. 2012 Theronostics*

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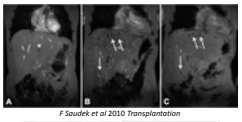
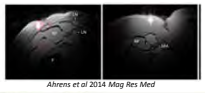
# Magnetic Resonance Imaging




*F Saudek et al 2010 Transplantation*



*Ahrens et al 2014 Mag Res Med*

**Pros**

- Highest spatial resolution
- Combines morphologic and functional imaging
- Quantitative

**Cons**

- Low sensitivity
- Potentially long scan and post processing time
- Mass quantity of probe may be needed

*Ahrens 2013 Nature Reviews Immunology*

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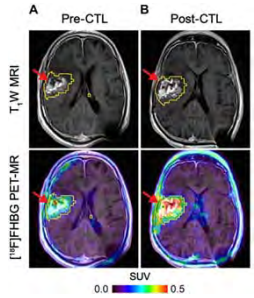
# Positron Emission Tomography




*Keu 2017 Science Translational Med*

**Pros**

- High sensitive
- Isotopes can substitute for naturally occurring atoms
- Targeted
- Multiple probes
- Quantitative
- Cell survival
- Proliferation

**Probes:**
Zirconium-89
Fludeoxyglucose (F18)
Reporter genes

**Cons**

- PET cyclotron or generator needed
- Low spatial resolution
- Ionizing radiation
- Half-life decay
- Cytotoxicity
- Translation barriers

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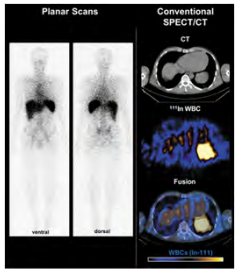
# Single Photon Emission Computed Tomography




*Caobelli et al. 2017 Eur Heart J*

**Pros**

- Many molecular probes
- Can image multiple probes simultaneously
- Adaptable to clinical imaging systems

**Cons**

- Low spatial resolution
- Ionizing radiation
- Half-life decay
- Cytotoxicity
- Translation barriers

**Probes:**
Indium 111
Technetium 99

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## Optical

**Pros**

- Sensitivity
- Low cost
- High throughput
- Multiple probes
- Quantitative
- Cell survival
- Proliferation
- Well established preclinically

**Cons**

- Low spatial resolution
- Surface weighted
- Limited to 2D imaging
- Toxicity
- Mostly preclinical
- Translation barriers

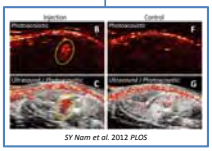
## Photoacoustic

**Pros**

- Low cost
- Moderate spatial resolution
- Tomographic image

**Cons**

- Limited Penetration Depth




*SY Nam et al. 2012 PLOS*

## Ultrasound

**Pros**

- Low cost
- Real time

**Cons**

- Low spatial resolution
- Surface weighted

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## Potential benefits of imaging

- Visualize delivery, homing, and persistence
- Ability to answer unsolved questions:
  - Do transferred cells migrate to sites of disease or off-target sites?
  - Is migration correlated with clinical effectiveness
  - Can outcomes be improved by modifying migration/delivery/homing?
- Preclinical rodent models may not be predictive to activity in humans

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## Administration vs. Misadministration

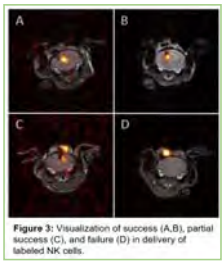


**Figure 3:** Visualization of success (A,B), partial success (C), and failure (D) in delivery of labeled NK cells.

*Dean Lee* Innate Killer Summit 2016 Presentation
*Kennes 2019 Journal Neuro-oncology*

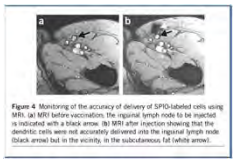


Figure 4 Monitoring of the accuracy of delivery of SPIO-labeled cells using MRI. (a) MRI before vaccination, the inguinal lymph node to be injected is indicated with a black arrow. (b) MRI after injection showing that the dendritic cells were not accurately delivered into the inguinal lymph node (black arrow) but in the vicinity, in the subcutaneous fat (white arrow).

*de Vries 2005 Nature Biotechnology*

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## Are there imaging trade offs?

- Toxicity versus information
- Sensitivity versus spatial resolution
- Complexity versus translatability
- Quantitation
- Cost

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## Acknowledgements:


The CT-TRACS subcommittee on Biodistribution and Point of Administration Monitoring

Coauthors on pending review manuscript "Options for imaging cellular therapeutics *in vivo*: a multi-stakeholder perspective"

Colleagues at Celsense


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## The need for collaboration across stakeholders to address the challenges facing the translation of cell therapies into the clinic


David Morrow PhD MBA
EATRIS Scientific Program Manager for Advanced Therapies


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## Are Cell Therapies Reaching Patients?

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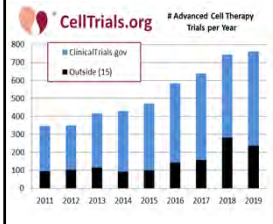


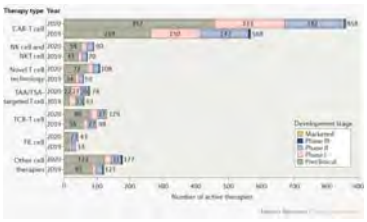


Despite the large numbers of clinical trials overall, the **clinical trial failure rate for cell therapies is over 80%**.
The main reason for clinical trial failure is poor efficacy.

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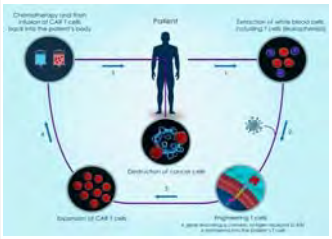
## Realizing the Opportunities of Cell Therapies- *A case Study of CAR-Ts*




KYMRIAH® (tisagenlecleucel) (a CAR-T therapy) is indicated for the treatment of paediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse.



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## Realizing the Promise of ATMPs


Emily Whitehead's life was saved using Kymriah. In 2012, she was the first child in the world to have her immune cells trained to fight cancer. Today, she is more than eight years cancer-free.

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*Combination therapy with CAR T cells and Checkpoint Blockade*

## CAR T-cell therapy for solid tumors?


IMAGE:
Prasad Adusumilli Laboratory,
Memorial Sloan Kettering
Cancer Center

**SECOND CHAPTER**

T-cell therapy has successfully targeted blood cancers. A bigger challenge is to make it work on solid tumors.

ASCO-SITC Clinical Immuno-Oncology Symposium | #immunosym

Presented by: Prasad S Adusumilli

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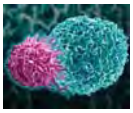
## The Challenges of novel Cell therapies in solid tumors



***Cell biodistribution?***

***Cell numbers at tumor?***

***Proliferation at tumor site?***

***Tumor infiltration?***

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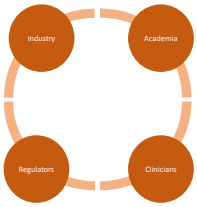
## The Challenges

- Many **systemic bottlenecks in Cell therapy development** are due to weak/non-existent cross-sector cooperation. Challenges include:
  - The need for the **right** Non-invasive imaging solution and approach
  - The need for the right preclinical models to validate cell therapies
  - Innovative Manufacturing Solutions
  - The regulatory challenges to combining cell therapy and imaging
  - Clinical uptake of novel cell therapies and the utility of cell tracking




**Cross-sectoral collaboration is a critical success factor**

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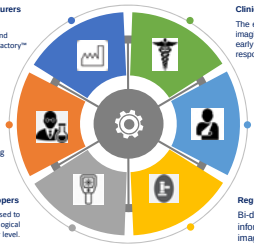
## Developing A Broadly Applicable Imaging Platform for Cell Therapies

*Bringing the needed expertise together*

**Manufacturers**
Need to simplify, integrate and automate the manufacturing workflow that can upscale cells and incorporate imaging agents for tracking e.g FlexFactory™

**Pre-clinical Scientists**
Essential to directly enumerate tumor accumulation and amplification in various preclinical models - correlate it with 'pre-conditioning' regimens including tumor debulking

**Imaging Agent Developers**
Novel imaging agents and approaches used to non-invasively visualize and measure biological processes at the cellular level.



**Clinicians**
The end-user at point of care. How can imaging potentially stratify patients early into responders versus non-responders

**Patients**
Exchange of knowledge with patient. Why use imaging to track the cell therapies they want to be treated with?

**Regulators**
Bi-directional exchange of expertise and information to define clear pathways for such imaging agents to the clinic

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Identify early on if a cell therapy is right for a patient
Bringing the right expertise together


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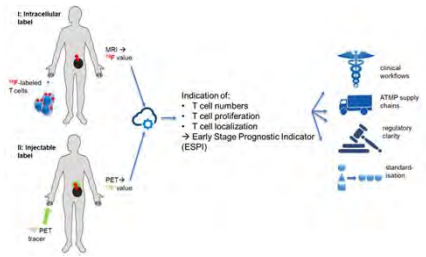
A possible Early Stage Prognostic Indicator?




Approach 1 Multimodal Approach

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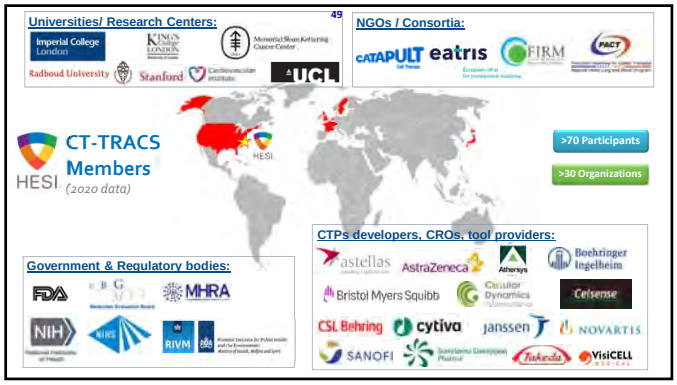
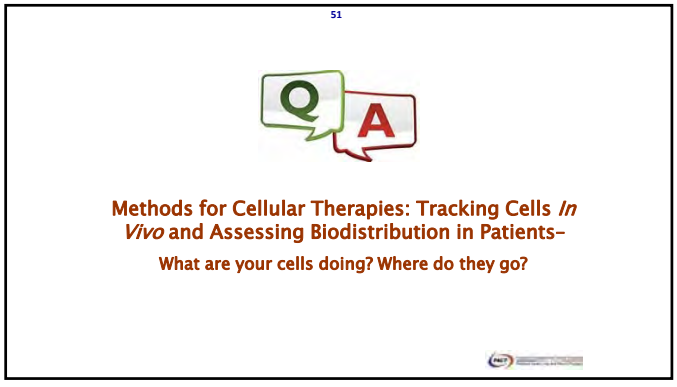
Creating the right community to develop the right imaging platform at the clinic

HESI

HESI CT-TRACS represents **a platform** where an international network of experts from multiple sectors (public and private sector research scientists, European research infrastructure for Translational Medicine (EATRIS), clinicians, health foundations, and technology developers) can collaborate sharing knowledge, experience and resources in the rapidly evolving field of cell therapy.


49
Universities/ Research Centers:
Imperial College London
King's College London
Memorial Sloan Kettering Cancer Center
Radboud University
Stanford
UCL
NGOs / Consortia:
CATAPULT
eatris
FIRM
PACT
CT-TRACS Members
HESI
(2020 data)
>70 Participants
>30 Organizations
Government & Regulatory bodies:
FDA
MHRA
NIH
RIVM
CTPs developers, CROs, tool providers:
astellas
AstraZeneca
Boehringer Ingelheim
Bristol Myers Squibb
Celsense
CSL Behring
cytiva
janssen
NOVARTIS
SANOFI
Takeda
VisiCELL


50
Thank you!


51
Q
A
Methods for Cellular Therapies: Tracking Cells In Vivo and Assessing Biodistribution in Patients–
What are your cells doing? Where do they go?

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## Speaker Contact Email

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Brooke Helfer
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David Morrow
Davidmorrow@eatris.eu

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## CE Credit

CE credit is **only** offered to participants who have attended this **live** web seminar. To claim CE credit or receive a Statement of Participation, each attendee must:

**1)** Complete the web seminar evaluation and credit tracker within 1 week of the web seminar, by Thursday, September 10:
http://z.umn.edu/PACTEvalCredits

- You will be directed to this link when you exit the web seminar.
- The link is also provided in the web seminar email reminder sent on 03 September 2020 to registered attendees.

**2)** Complete the attendee roster within 72 hours of the web seminar (group attendees).
- The attendee roster is provided in the web seminar email reminder sent on 03 September 2020 to registered attendees.

**Note:** After the online evaluation/credit tracker and live web seminar attendees list have been processed, the CE credit or Statement of Participation will be issued via email from the University of Minnesota, within 4-6 weeks, to those requesting CE/Statements of Participation.

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