ENCITE The European Network for Cell Imaging and Tracking Expertise

ENCITE's key promotional activities

Within the framework of ENCITE's Dissemination Plan, particular attention has been paid to the development and long-lasting establishment of the ENCITE Multi Centre Cluster for Training as well as the promotion of ENCITE's training (e-)courses and teaching files and its scientific advances. These promotional activities aimed to present promising developments for pre-clinical validation and particularly for the application into the clinics, to share experiences with scientists on cell imaging and tracking and to train scientific and medical staff on ENCITE's new technologies, addressing experts from various disciplines with a focus on imaging.

Starting with the first ENCITE workshop in 2009, open to all interested experts within the imaging community, **more than 30 hands-on workshops, scientific sessions, lectures, hot topic workshops, educational courses and other training activities** were organised and held by the ENCITE consortium partners presenting and showcasing the latest advancements. Most of them were open to the European community on molecular imaging and other disciplines interested in this field.

One of ENCITE's training highlights were the symposium "New Horizons in Preclinical MR" (Freiburg/DE, 09/2012), the symposium "Red Hot MRI: in vivo 19F imaging" (Nijmegen/NL, 10/2012), the ENCITE final workshop "Cell imaging and tracking: now and the future" (Leiden/NL, 11/12).

To raise awareness of ENCITE and its excellent training programme throughout Europe, a huge number of promotion and dissemination activities were carried out by the European Institute for Biomedical Imaging Research (EIBIR) and the ENCITE consortium and thanks to the excellent support from European training providers and other organisations. **Different communication channels relevant to the imaging community and those research groups linked to imaging were used and a huge number of promotion materials were distributed, such as:**

- Press articles, annual reports, posters, flyers, event calendars, print newsletter, articles and announcements in magazines, scientific journals, brochure on proceedings and outlook, etc.
- Presentations and distribution of materials at public events, congresses, relevant trainings and ENCITE training courses on a national/international level, booth presentations, etc.
- Project website, partners' and other organisations' websites, e-mailings, e-newsletters, online information portals and event calendars, social media platforms, etc.

Some of the promotional highlights include:

- The ENCITE video, showcasing how the ENCITE scientists have been working towards making cell therapy a reality. The video was launched at the ENCITE final Workshop in Leiden where it was very well received by the audience, and it has subsequently been widely disseminated to a broad audience via numerous communication channels.
- The ENCITE Blog - a dedicated blog site where the ENCITE partners can continue to post news on their training events and achievements, even after the project completion.

- The Auntminnie press article on the Round Table Discussion at the ENCITE final Workshop. This excellent article provided an overview of the discussion, and captured the key opinions and ideas being discussed.
- The regular e-newsletters and a targeted press campaign, where a press release was drafted following every key training event, and circulated via numerous communication channels, as part of a concentrated effort to reach a broad audience amongst the European Community.

Scientific and promotional highlights are described in further detail below.

This Large Integrated Project was submitted to the call HEALTH-2007-1.2-4 “In vivo image-guidance for cell therapy” and is co-funded by the European Commission within the 7th Framework Programme with a financial contribution of €12m. The 4.5-year project started in June 2008. The overall objectives with respect to the scientific work as well as to the dissemination and training activities have been achieved thanks to the strong collaboration of and interactions between 29 project partners from eleven countries with outstanding scientific expertise in cell imaging and tracking, co-ordinated by the European Institute for Biomedical Imaging Research (EIBIR).

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1. Illustration of scientific highlights

Novel Pulse Sequences

ENCITE has developed a number of novel cell therapies pointing to clinical applications, and some of them are key innovations for the visualisation of cell therapy.

New imaging biomarkers were developed and new MR imaging reporter probes for in vitro and in vivo applications tested. New pulse sequences featuring a higher sensitivity, which is a crucial requirement for MR imaging technologies, were used. This included the accurate in vivo detection and segmentation of cells, or clusters of cells and imaging methods for specific contrast agents, like 19F-MRI and ultra-short TE (UTE) imaging for bright contrast. In addition, MR imaging sequences for established biomarkers used to monitor cell fate were further improved to facilitate the evaluation and image post-processing of these markers. The most significant improvements were reached with the implementation of multispectral MR imaging biomarkers that could gain more Information from a single experiment. Within the field of image post-processing, efforts were focused mainly on the integration of molecular, functional and anatomical imaging data. New algorithms were investigated that can be used to facilitate registration, matching and correction of motion at the anatomical level, and detection and tracking of functional events at the cellular level. The developed methodology will enable quantified monitoring of disease progression and treatment response that is not possible with current visual interpretation (Fig. 1 and Fig. 2).

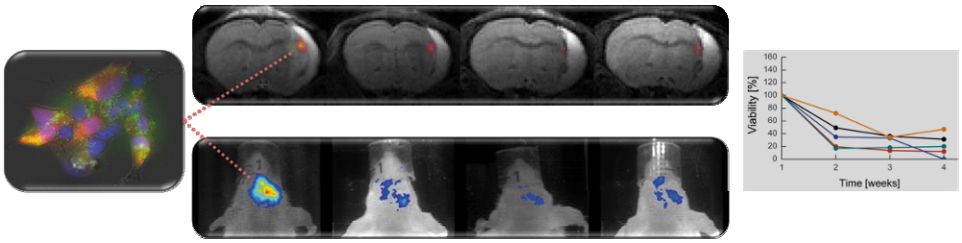


Fig. 1: Imaging implanted neural stem cells
by combined 19F MRI and bioluminescence imaging

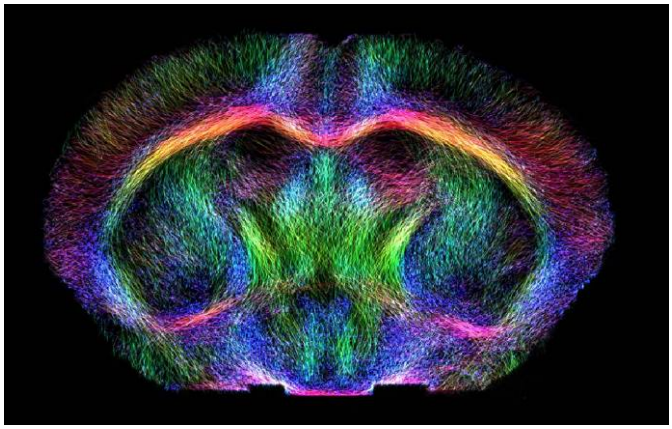


Fig. 2: High resolution fiber tracking of the living mouse brain

Probe Chemistry

ENCITE has contributed to the improvement of CEST agents (Chemical Exchange Saturation Transfer) and their use in cellular labelling and the introduction of third harmonic generation microscopy into tumour biology.

The frequency-encoding property of this class of agents has been exploited for pursuing the visualisation of different types of cells in the same anatomical region. Two approaches have been followed: by entrapping into cells paramagnetic CEST agents or by exploiting the intracellular water molecules as source of exchangeable protons once their absorption frequency is suitably shifted by the entrapment of a proper Lanthanide Shift Reagent (Cell-CEST). Proof of concept in vivo on animal models has been obtained for both approaches.

For optical imaging, third harmonic generation microscopy was successfully introduced into tumor biology, to delineate the tissue structures that guide cancer cell invasion into the peritumoral stroma.

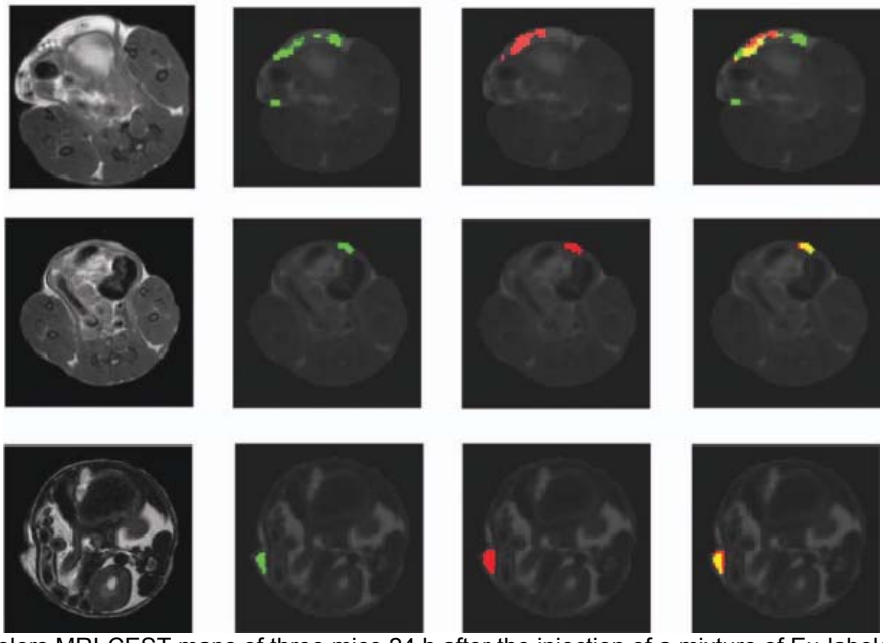
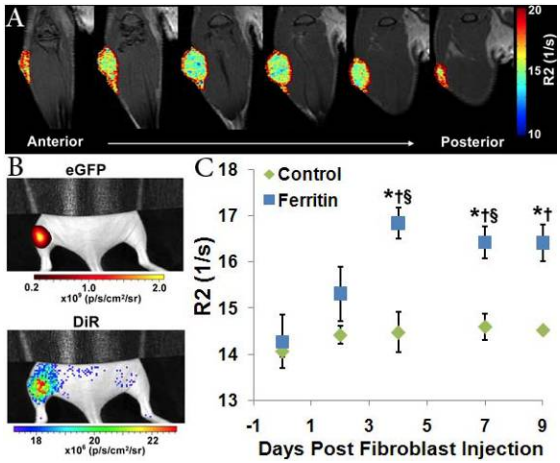


Fig.3 False colors MRI-CEST maps of three mice 24 h after the injection of a mixture of Eu-labeled melanoma cells and Yb-labeled macrophages:
(a) T_{2w} map, (b) green ¼ map at 66 ppm (YbHPDO3A), (c) red ¼ map at 15.6 ppm (EuHPDO3A), (d) yellow ¼ merge.

Novel tools for cell labelling

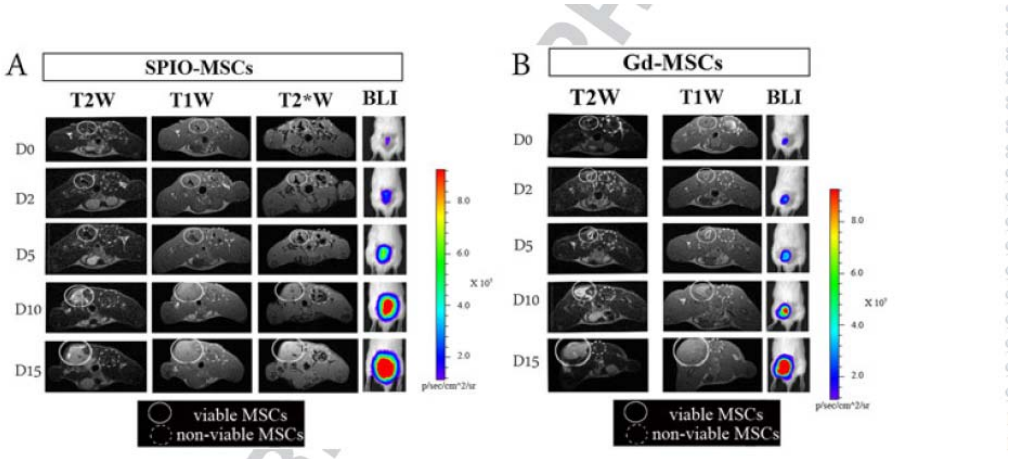
Tumour associated fibroblasts are a key component in cancer and affect tumor angiogenesis, progression and metastasis.

In ovarian carcinoma, these cells are critical for exit from dormancy and initiation of tumor growth. However these cells are part of the tumor mass and cannot be detected by conventional imaging. In this project, fibroblasts were genetically engineered to express h-ferritin. These h-ferritin expressing cells were visualized by MRI allowing to detect them as they homed to the tumor and infiltrated into the angiogenic rim of human ovarian carcinoma xenograft. This approach will potentially enable to use these cells for targeted imaging and potentially also for targeted delivery of therapy.



In vivo detection of systemic recruitment of ferritin tagged fibroblasts by a remote tumor. (A) Representative R2 maps (day 7 post injection) of a hind limb tumor illustrate preferential recruitment of FHC-over expressing fibroblasts to the tumor rim. (B) In vivo fluorescence imaging confirmed the recruitment of CV-1 fibroblasts (DiR) to the tumor (eGFP), and not to the opposing limb. (C) Tumor R2 measurements elucidate the time-course of fibroblast recruitment (*p<0.05 vs. Control, †p<0.05 vs. Day 0, §p<0.05 vs. Day 2). Vandsburger et al, Presented at the ISMRM 2012.

Using a Gd-based probe a method to allow for a nonambiguous distinction between cell death and viability in vivio was developed. A combined interpretation of the quantitative (ΔR2/ΔR1) and qualitative findings (contrast changes) may present an important noninvasive tool to track the actual cell fate of transplanted cells in real time, using mere MRI. In fact, visual evaluation of contrast changes from Gd-cells, allows us to assess overall cell viability of a transplanted cell graft.

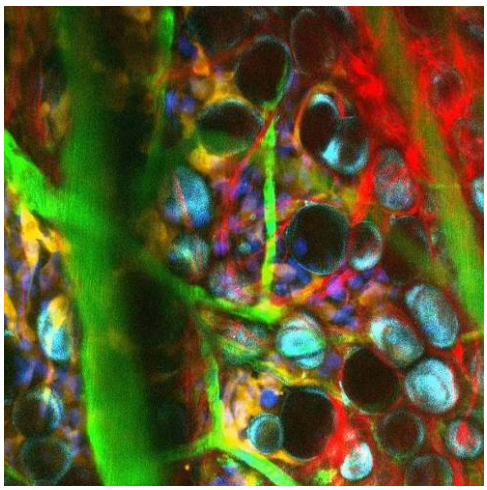


Dual modality longitudinal imaging of MSCs transplanted in the lower back muscle. Imaging of SPIO-MSCs (a) and Gd-MSCs (b) on T2-weighted FSE (TE 120ms, TR 3000, number of experiments is 4), T1-weighted spin echo (TE 10ms, TR 1200ms) and T2-weighted GRE (TE 8ms, TR 50ms, a 16º) images. Bioluminescence imaging (BLI) shows considerable viable cell proliferation, visible on MRI as a gradual decrease (Gd-MSCs) and increase (SPIO-MSCs) in signal intensity. Gd-labelled cells show clear differences in signature between living and death cells in acute setiings.*

Translation towards clinical application

ENCITE has successfully achieved developments for the translation towards clinical application for cancer, diabetes and cardiovascular diseases

In the field of cancer research, the infrastructure for the production of tracers was established and cancer patients were monitored with a tracer in order to detect an antigen-specific immune response in vivo shortly after vaccination. The used tracer offers a sensitive tool to study the kinetics, localisation and involvement of proliferating lymphocyte subsets. It was possible to measure activities even 3 weeks after vaccination, which will assistant clinicians in the future to be able to select responding patients at an early stage for follow up vaccinations. In the field of diabetes, patients were examined according to a new, refined protocol and the first data on the clinical application of the MR method was published. In the field of cardiovascular disease, initial studies have been performed towards the clinical application of imaging methods with tools developed in the two work packages cell labelling and preclinical validation.



Diffuse collective invasion of B16/F10 melanoma cells into fat tissue, detected by infrared multiphoton microscopy. Third harmonic generation was used to detect tissue structures that guide invasion, including adipocytes (cyan). Other colors: tumor cells (orange cytoplasm in 30% of the cells; blue nuclei in all cells), vessels (green), collagen fibers (red, second harmonic generation).

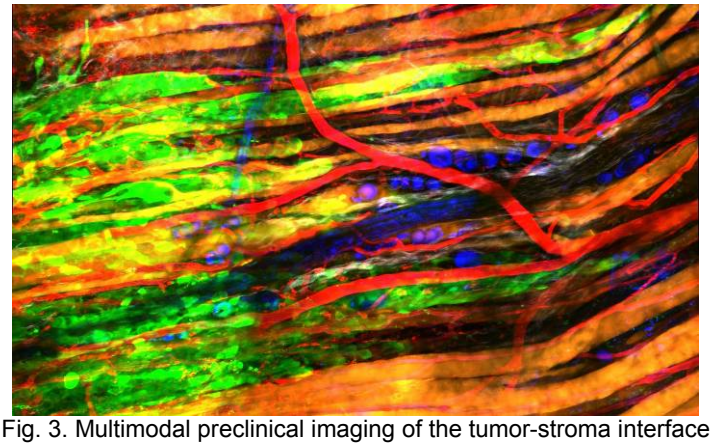
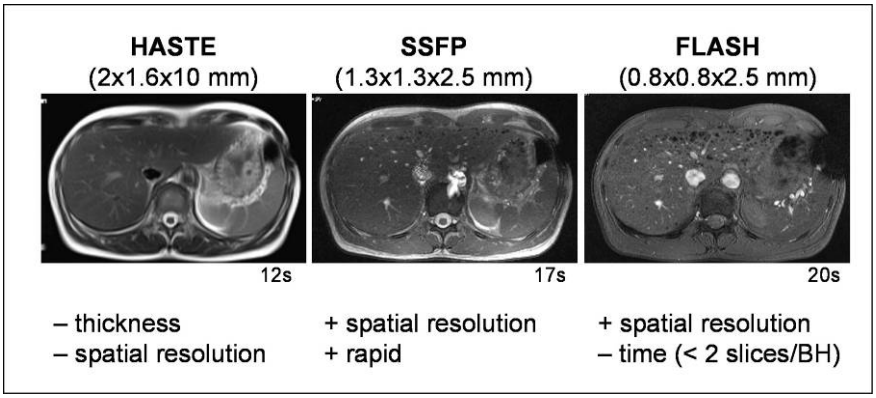


Fig. 3. Multimodal preclinical imaging of the tumor-stroma interface

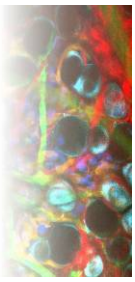
In addition, the successful transplantation of labelled pancreatic islets to the patients and long term observation of their fate and function was achieved. New techniques for the visualization and function of transplanted PI in human liver were developed. Pancreatic islets (PI) transplantation into the liver or another site in the body is a suitable model of cell transplantation and, additionally, the production of insulin is a marker of good function of beta cells (in PI). In humans, the success of the transplantation depends on many factors and observed changes in MR images of transplanted islets in the liver can precede clinical symptoms. The set of MR sequences and evaluation techniques were optimized to be suitable for routine examination of patients before and after PI transplantation to provide a sufficient amount of images useful for post-processing and calculating of the amount of transplanted PI.



Typical MR images of human liver with transplanted PI. Due to the thickness of the slice, PI are visible only in bSSFP and FLASH images (advantage or disadvantage of the method is described in last two rows)

2. Illustration of research and educational activities

ENCITE Final Programme and Proceedings
Final brochure on abstracts, statements as well as achievements and outlook/impact
November 2012, Leiden/NL



Small animal imaging workshop, ENCITE hands-on Session
November 7-11, 2011, Münster/DE


Imaging technologies for studying rodents


Attendees studied animals with several different imaging modalities

ENCITE workshop "Imaging cancer: from Models to Patients"
January 9 – 13, 2012, Nijmegen/NL


Discussions


Exchange of experiences

TOPIM 2012 - 6th Winter Conference
Processing Biomedical Images: Visualisation, Modelling, Segmentation, Quantification, Registration
April 15-20, 2012, Les Houches/FR


Auditorium


TOPIM participating group

ECR 2012, ENCITE Session
Vienna/AT, March 6, 2012

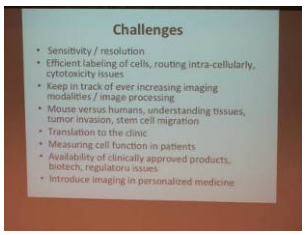
ENCITE – Workshop on Molecular Imaging in Skeletal Tissue
Tel Aviv University, October 25-26, 2011

Gil Navon (TAU),
Local host and speaker

Gadi Pellet (HUJI),
speaker

Auditorium

ENCITE Final Workshop
Cell Imaging and Tracking: now and the future
Leiden University Medical Centre, Leiden/NL, November 5, 2012



Badges

Boudewijn Lelieveldt (LUMC),
Local host and speaker

Bettina Weigelin (RUNMC),
speaker

Jeff Bulte,
Invited key note speaker

Eva Sykova,
Invited key note speaker

Marc Ellisman
Invited key note speaker

Round Table Discussion

Round Table Discussion

More than 120 enjoyed fruitful discussions

ESMRMB 2011 – Congress participation
Booth presence, three consecutive mini-categorical courses dedicated to ENCITE's advancements
October 6-8, 2011, Leipzig/DE


Audience

Key questions discussed


Dr. Monique Bernsen, speaker, Mini-Categorical Course

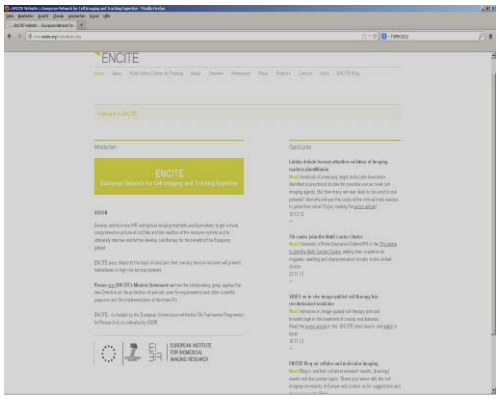
EMIM 2011, ENCITE Educational Session
Molecular MRI in experimental neuroscience
June 19, 2011, Leiden/NL

MR projekty IKEM: buněčné zobrazování transplantovaných pankreatických ostrůvků v projektu ENCITE (Visualization of transplanted pancreatic islets in the project ENCITE)
November 15-16, 2012, Bratislava/SK

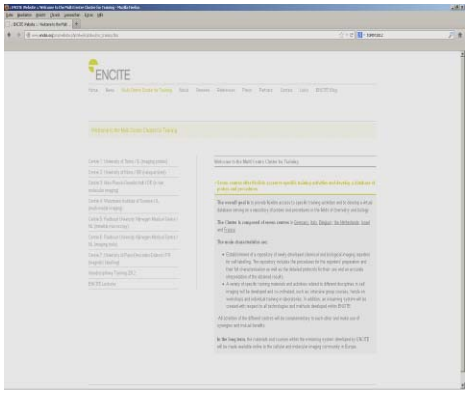

Teaching and understanding


Listening

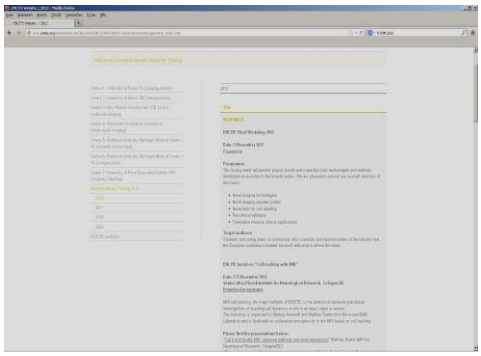
3. Visualisation of ENCITE's training and communication @ www.encite.org



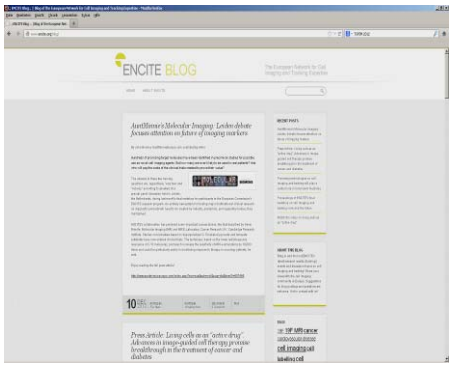
Quick links – News on spot



ENCITE Multi Centre Cluster 2012

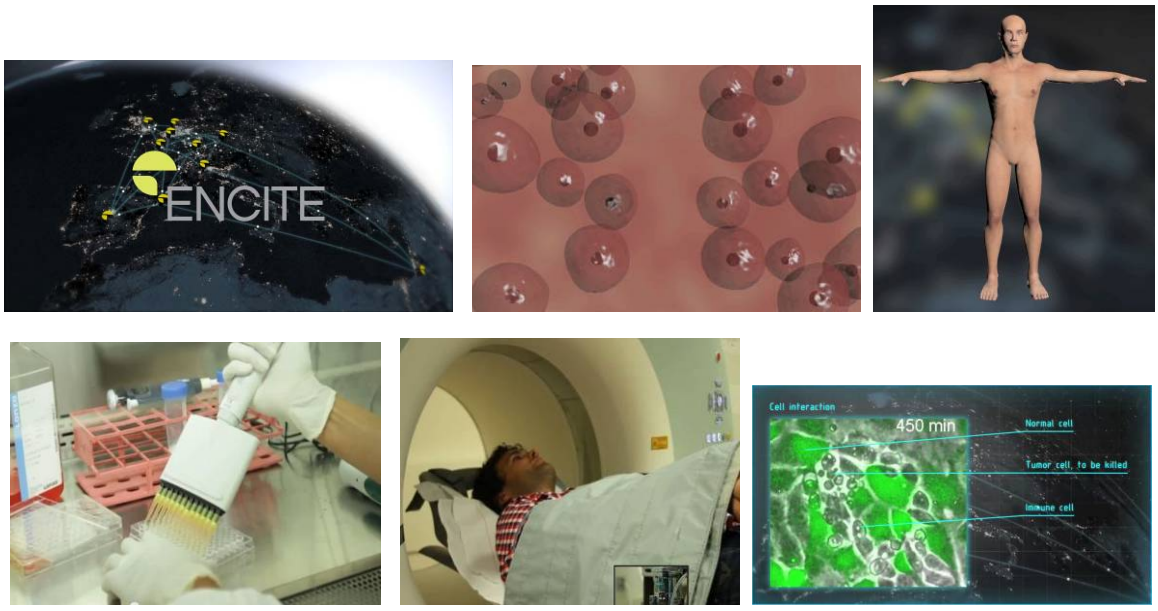


ENCITE Interdisciplinary Training platform 2012



ENCITE Blog

4. ENCITE Video "living cells as an active drug" @ www.encite.org > ENCITE Blog



5. List of all Beneficiaries

European Institute for Biomedical Imaging Resesarch, AT, Gabriel Krestin

Agencia Estatal Consejo Superior de Investigaciones Cientificas, ES, Marisela Velez

BioSpace, FR, Serge Maitrejean

Cage Chemicals, IT, Camilla Cavalotti

Consorci Institut Català de Ciències Cardiovasculars, ES, Lina Badimon

Erasmus MC, NL, Monique Bernsen

Foundation for Applied Medical Research, University of Navarra, ES, Ignacio Melero

Friedrich-Alexander University, Universitätsklinikum Erlangen, DE, Eckhart Kämpgen

Institut Curie, FR, Sébastian Amigorena

Institute for Clinical and Experimental Medicine, CZ, Milan Hajek

Katholieke Universiteit Leuven, BE, Uwe Himmelreich

King´s College London, UK, Mike Modo

Leiden University Medical Center, NL, Clemens Lowik

Max-Planck Institut für Neurologische Forschung, DE, Mathias Hoehn

Medres, DE, Stefan Wecker

Radboud University Nijmegen Medical Centre, NL, Carl Figdor

Tel Aviv University, IL, Gil Navon

The Chancellor, Masters and Scholars of the University of Cambridge, UK, Kevin Brindle

The Hebrew University of Jerusalem, IL, Dan Gazit

The University of Milano - Bicocca, IT, Francesca Granucci

Università di Torino, IT, Silvio Aime

Universitätsspital Basel, CH, Klaus Scheffler

University of Freiburg, DE, Jürgen Hennig

University of Mons, BE, Robert Muller

University Paris Descartes, FR, Oliviér Clément

Vrije Universiteit Medisch Centrum Amsterdam, NL, Bert Windhorst

Weizmann Institute of Science, IL, Michal Neeman

Westfälische Wilhelms-Universität Münster, DE, Cornelius Faber