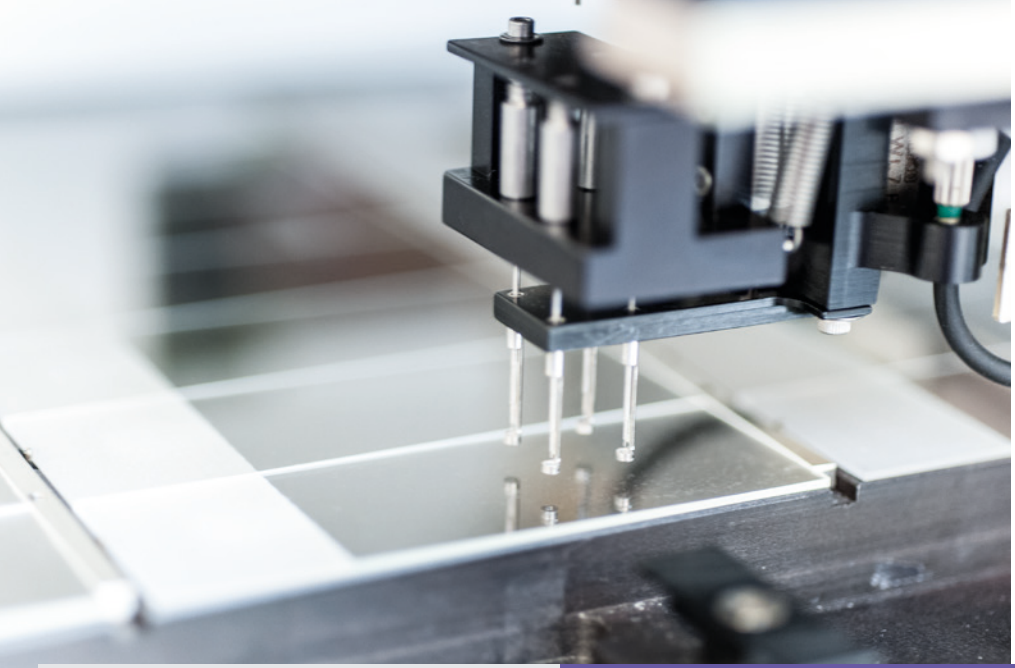

The EATRIS network of advanced screening centres

EATRIS is an expanding European network of qualified translational centres that offers high-end infrastructure for preclinical and clinical studies to support development. Contact EATRIS to find an institution with the relevant expertise to match with your research request.

- National Cancer Institute, IRCCS G. Pascale, Naples, Italy
- Institute of Molecular and Translational Medicine, Olomouc, Czech Republic
- Institute for Molecular Medicine Finland, FIMM, Helsinki, Finland
- Vall d'Hebron Institut de Recerca, Barcelona, Spain
- Mario Negri Institute for Pharmacological Research, Milan, Italy
- University of Oslo (UiO), Norway

Literature

- **Das V, Bruzzese F, Konečný P, Iannelli F, Budillon A, Hajdúch M.** Pathophysiologically relevant in vitro tumor models for drug screening. Drug Discovery Today 20, 848-55 (2015)
- **Edwards AM et al.** Preclinical target validation using patient-derived cells. Nature Reviews Drug Discovery 14, 149–150 (2015)
- **Roca MS et al.** Oncotarget, doi: 10.18632 (2016)
- **Noto A, Raffa S, De Vitis, C et al.** Stearoyl-CoA desaturase-1 is a key factor for lung cancer-initiating cells. Cell Death Dis. 4, e947, (2013)

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European infrastructure for translational medicine

www.eatris.eu, info@eatris.eu, +31 (0)20 4442254
De Boelelaan 1118, 1081 HZ Amsterdam, The Netherlands

How can **in vitro screening with 3D spheroids and primary cells** enhance the success rate of your drug development programme?

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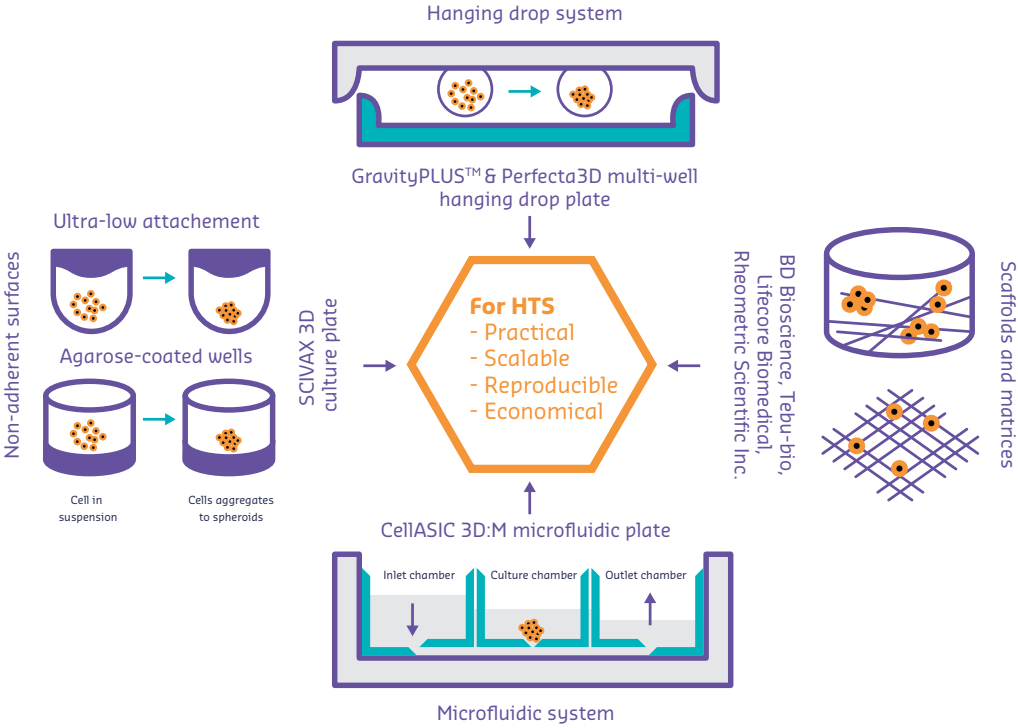
ADVANCED TRANSLATIONAL DRUG SCREENING:

USING 3D SPHEROIDS AND PRIMARY CELLS

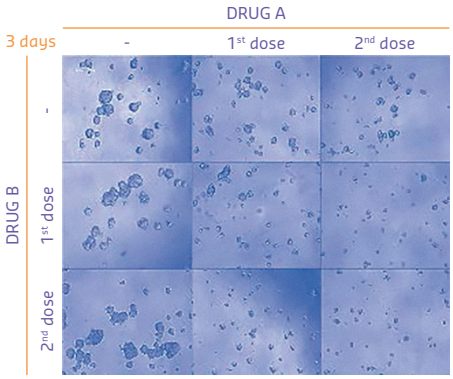
ENHANCE PREDICTIONS, IMPROVE INSIGHTS, INCREASE VALUE



When working to identify novel, high-quality drug leads, one significant hurdle remains the low predictive value of preclinical models, which are associated with high attrition rates owing to a lack of clinical efficacy. Drug screening models involving three-dimensional, multi-cellular cultured (3D) spheroids use culture methods that mimic their most natural in vivo environment. As such, these kinds of advanced screening are more predictive than artificial, conventional screenings that rely on monolayered cells. In oncology, such in vito 3D cellular models more closely resemble in vivo tumour conditions, such as hypoxia, which allow for a more detailed study of the effects of anticancer drugs on the tumour microenvironment. Alternatively, screening with patient-derived primary cells enables precision medicine approaches by taking into account the genomic heterogeneity of individuals or sub-populations deemed most likely to respond to drug treatment. Access to high-end infrastructures with advanced translational screening technologies, and integrated access to wellannotated patient samples, is essential for the cost-effective selection and repurposing of promising drug candidates.

How can in vitro screening with 3D spheroids and primary cells enhance the success rate of your drug development programme?

- Accurate delineation and identification of disease to be targeted by the drug;
- More predictive testing on drug sensitivity, resistance, and ADME tox profiling;
- Cost-efficient and maximum data collection from small sample amounts in miniaturised screening;
- Assessment of repositioning, de-risking, and rescuing strategies of existing and investigational drugs;
- Development and optimisation of drug combination therapies;
- Better resemblance of tumour tissue with more reliable prediction of compound tumour penetration;
- Study the enhanced permeability and retention (EPR) effect of drug candidates, or mimicry of specific conditions (e.g. hypoxia or pH);
- Detailed assessment of cell behaviour, such as differentiation, gene and protein expression, cell function, morphology, proliferation, stimulation, and viability;
- Exploration and validation of polypharmacology strategies;
- Improved (ex-vivo) monitoring of emerging resistance towards, for example, tyrosine kinase inhibitors; and
- Implementation and optimisation of therapies with overall decreased attrition rates in drug development



Key technology offering

- Access to patient-derived primary cells (e.g. tumour cells, cancer associated fibroblasts, and normal fibroblasts);
- High-throughput and high-content analysis compatible 3D cell cultures, combined with automated dispensing techniques (up to 1536-well format);
- Modified liquid-overlay culture for spheroid production (up to 384-well format);
- Flow cytometry read-outs to detect cell differentiation;
- Transcriptomic analysis of multi-drug resistance;
- Cellular screening for novel drug candidates (and drug combinations) including radiochemotherapy using X-rays;
- Automated confocal imaging;
- Study of the penetration of DNA de-methylating drugs in reporter cell spheroids; and
- Application of pH microsensors for screening under extracellular acidosis conditions.

Technical and regulatory (QA/QC) aspects of advanced screening

- State of the art HTS screening and compound storage facilities
- Automated liquid dispensing systems for consistent homogenous formation of spheroids; and
- Patient samples for primary cell culture follow strict ethical rules (i.e. signed informed consent and local independent ethical committee approval).

FIGURE 1: Drug screening on NSCLC primary cultures by using in vitro 3D-systems, as an ethically and technically sound alternative to in vivo experiments, to mimic the heterogeneity and complexity of in vivo lung human tumors. Roca MS, Ciardiello C. Leone A, Noto A. Mancini R, Ciliberto G and Budillon A (2016).