JOINT NEWS RELEASE

World's First Long-Term Colorectal Cancer Model by 3D-Bioprinting as a Mechanism for Screening Oncolytic Viruses.

- **Scientists developed an innovative technology platform harvesting of metastatic colorectal cancer from patients, to manufacture three-dimensional Bioprinted microtumours as cancer drug-candidate screening products.**
- **Three-dimensional microtumours were kept alive for the longest time ever recorded in vitro from primary tumours, allowing longitudinal studies, screening of oncolytic viruses and realistic modelization of colorectal cancer.**
- **The joint research study by CTIBIOTECH and MEDICAL UNIVERSITY OF PLOVDIV, with the support of TRANSGENE was published in a Special Issue on Recent Advances in Basic and Clinical Colorectal Cancer Research of the international scientific journal "Cancers".**

Lyon, France and Plovdiv, Bulgaria, October 26th, 2023, CTIBIOTECH and MEDICAL UNIVERSITY OF PLOVDIV worked together, with the support of TRANSGENE to create and validate a unique technology platform allowing bioprinting of the world's first long-term colorectal cancer model for cancer drugs screening.

Three-dimensional bioprinted colorectal cancer microtumours were successfully produced in this study and maintained for growth for between 1 day and more than 5 months. Short- and long-term growth was mimicked in vitro and provides an important cost-effective screening system not only for basic chemotherapies but also for advanced therapeutics, such as oncolytic viruses that can "detect, target and destroy" cancer cells.

Colon cancer or colorectal cancer is the third leading cause of cancer with more than 1.8 million new patients diagnosed each year worldwide. Liver metastases, also known as metastatic liver cancer, are associated in about one-quarter of patients. The World Health Organization (WHO) predicts up to 12 million deaths in 2030 worldwide, with high incidence, high mortality and high costs to health care systems. The need for new drugs to treat cancer with systemic therapy is very urgent. However, the development of anti-cancer drugs is long and costly.The global failure rate of bringing new drugs to market is immense but exacerbated when it comes to advanced therapies. What can look good in simple standard experimentation often does not translate well to animal testing and on towards phased human clinical trials.

Personalized and precision cancer medicine requires the production of reliable, robust, reproducible, predictive human biological models in sufficient quantity to accelerate the development of drug candidates for new chemotherapies and immunotherapies. For some cancer diseases, the nature of the tumour environment may be difficult to reproduce *in*

vitro in 3D in a manner that allows for rapid and efficient testing of personalized medicine against cancer.

In this collaborative study, the scientists first collected, post-surgical treatment, colorectal cancer tumours from liver metastasis of patients who consented to donate these samples for scientific research. They further established and validated **3D Bioprinting protocols, an additive manufacturing method to reproducibly and precisely, produce patient-specific microtumours, that could be grown, maintained and tested for their response to cancer drugs for at least 5 months. A major and significant achievement in the development of personalized medicine strategy as well as advanced drug development against cancer.**

> ***"CTIBIOTECH has been innovating for ten years in tissue engineering and 3D-bioprinting for the benefit of human health. The development of drugs with human-like tumour models is essential for the next generation of cancer treatment"*** **explained Professor Colin McGUCKIN, President and Chief Scientific Officer, CTIBIOTECH.**

Bioprinting allows this important advance in a way that other in vitro systems or animal testing do not. Many 3D models, mostly static or self-assembling, have been applied in cancer research with limited data endpoints. 3D Bioprinting consists of designing “biocartridge” of the different cells present in a patient’s tumours mixed in a “bioink” containing nutrients and materials enabling 3D architecture of the microtumours. The creation of these real 3D models is important to advance beyond these of simple manually assembled organoid models which are variable. **3D-Bioprinting on the other hand, uses additive manufacturing technologies to assemble human cells to biomaterials and nutrients in a precise and organized architecture with high level of reproducibility.**

> ***Dr Eric QUEMENEUR, Executive Vice President & Chief Scientific Officer at TRANSGENE added: " Patient-derived tumouroids have become an important component of our preclinical characterization process, overcoming some critical limitations of current in vitro and in vivo models for oncolytic viruses. This recent achievement with 3D-bioprinted metastatic colorectal carcinoma cells will allow the long-term follow-up of the evolution of tumour features, and of its microenvironment, under treatment. More generally, this step was essential in the path towards more representative models for the complexity, and diversity of tumour phenotypes, and will be useful in developing better therapeutic strategies for the future."***

These bioprinted models, termed microtumours, are representative of the patient's tumours and are therefore powerful tools for obtaining robust and transferable results to humans in the testing of drug candidates. In addition, these models can eventually be used to determine the most effective therapy for each patient in a personalized medicine approach.

> ***Professor Victoria SARAFIAN, Director of the Research Institute at at MEDICAL UNIVERSITY OF PLOVDIV underlined: " Being a part of this interdisciplinary team it was a challenge and a great satisfaction to be able to contribute to the development of this innovative strategy which gives great promise for presicion therapy, as well as for drug development and testing in oncology."***

This scientific study published in a special issue of the medical journal CANCERS, on Recent Advances in Basic and Clinical Colorectal Cancer Research demonstrate a

robust and validated platform to support better cancer treatments to be developed more quickly. By combining their expertise, CTIBIOTECH, TRANSGENE and MEDICAL UNIVERSITY OF PLOVDIV have produced better and more predictive models of immunotherapy activity in metastatic liver cancer.

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About CTIBIOTECH – Cell Therapy Research Institute

CTIBIOTECH™ develops and produces predictive models of human tissues and cells for biomedical, pharmaceutical and dermatocosmetic research and development. CTIBIOTECH hosts a team of world-class experts who have pioneered innovation in bioengineering and regenerative medicine over the past 30 years. CTIBIOTECH partners with public and private organizations to develop innovative solutions for the efficacy and safety testing of active ingredients, dermatocosmetics, drug candidates, cell therapies and medical devices. CTIBIOTECH is organized around three Business Units:
1. CTISkin™: advanced human skin models to test new product ideas with scientific innovation and credibility for dermatology and cosmetics;
2. CTIPharma™: robust and predictive biological bioassays on human cells to accelerate the development of drugs, medical devices and cellular therapies;
3. CTIBiosourcing™: manufacturing of biological models, tissues and human cells. More than 50,000 tissue samples in stock or on demand for biosourcing through a network of 200 healthcare partners worldwide.

As part of the future-oriented PIA3 investment programs, CTIBIOTECH is receiving support from the Auvergne-Rhône Alpes Region for its platform for the production of microtumours by 3D-bioprinting for cancer research. CTIBIOTECH is the winner of the "Transformation of SMEs through innovation" prize, which promotes ambitious innovation in Auvergne-Rhône-Alpes for international technological influence.
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About Medical University of Plovdiv

Plovdiv Medical University is a leading medical institution in Bulgaria, established in 1945. **MU-Plovdiv** is located in the city of Plovdiv, the second largest city in Bulgaria and a cultural and economic center. It is a research university ranked first in the country in the filed of medicine and public health and hosts the largest Medical Simulation Training Center. It is known for the high quality of its medical education and research at the international level too. Plovdiv Medical University offers a range of undergraduate and graduate programs in medicine, dental medicine, pharmacy, and health care management. The programs are taught both in Bulgarian and in English languages. The curriculum in these programs focuses on providing students with a solid theoretical foundation and practical experience in a clinical setting. Further information mu-plovdiv.bg/

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About TRANSGENE

Transgene (Euronext: TNG) is a biotechnology company focused on designing and developing targeted immunotherapies for the treatment of cancer. Transgene's programs utilize viral vector technology with the goal of indirectly or directly killing cancer cells. The Company's clinical-stage programs consist of a portfolio of therapeutic vaccines and oncolytic viruses: TG4050, the first individualized therapeutic vaccine based on the myvac® platform, TG4001 for the treatment of HPVpositive cancers, as well as BT-001 and TG6050, two oncolytic viruses based on the Invir.IO® viral backbone. With Transgene's myvac® platform, therapeutic vaccination enters the field of precision medicine with a novel immunotherapy that is fully tailored to each individual. The myvac® approach allows the generation of a virus-based immunotherapy that encodes patient-specific mutations identified and selected by Artificial Intelligence capabilities provided by its partner NEC. With its proprietary platform Invir.IO®, Transgene is building on its viral vector engineering expertise to design a new generation of multifunctional oncolytic viruses.
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