

SYNOPSIS

BIOENGINEERING AND MEDTECH AGAINST CANCER

Cancer is the second leading cause of death globally, and is responsible for an estimated 9.6 million deaths in 2018. Globally, about 1 in 6 deaths is due to cancer.

Cancer is a generic term for a large group of diseases that can affect any part of the body. One defining feature of cancer is the rapid creation of abnormal cells that grow beyond their usual boundaries, and which can then invade adjoining parts of the body and spread to other organs, the latter process is referred to as metastasizing. Metastases are a major cause of death from cancer.

It arises from the transformation of normal cells into tumour cells in a multistage process that generally progresses from a pre-cancerous lesion to a malignant tumour. These changes are the result of the interaction between a person's genetic factors and 3 categories of external agents, including physical, chemical and biological carcinogens.

In 2017, the World Health Assembly passed the resolution Cancer Prevention and Control through an Integrated Approach (WHA70.12)¹ urges governments and WHO to accelerate action to achieve the targets specified in the Global Action Plan and 2030 UN Agenda for Sustainable Development to reduce premature mortality from cancer.

MAKE IT HAPPEN

Bioengineering and medtech are powerful tools to fight cancer and provide better health outcomes and better quality of life, while at the same time, ensure the sustainability of cost-effective health systems.

Although therapies based on bioengineering are already benefitting many cancer patients, there is a long way ahead before the new paradigm of precision medicine and smart health is a reality.

Some of the barriers that affect all innovations related to cancer, not only those based in bioengineering and medtech, include: lack of a mature open innovation model of cooperation between all the stakeholders involved (researchers, clinicians, start-ups, big companies, patients, investors, public funders...); lack of funding at all stages of the valorisation process, slow pace of uptake of these technologies due to lack of awareness by healthcare providers and managers, regulatory issues and ethical concerns.

We need to work as a community in developing a strategy for overcoming these barriers, as has been highlighted by the selection of Cancer as one of the Mission of the European Commission for Horizon Europe.

It is usually not possible to know exactly why one person develops cancer and another does not. But research has shown that certain risk factors may increase a person's chances of developing cancer. Cancer prevention is action taken to lower the risk of getting cancer. This can include maintaining a healthy lifestyle, avoiding exposure to known cancer-causing substances, and taking medicines or vaccines that can prevent cancer from developing. Although some of these risk factors can be avoided (Alcohol, Tobacco, Sunlight...), others—such as growing older—cannot. Limiting your exposure to avoidable risk factors may lower your risk of developing certain cancers.

Partly inspired by the Apollo 11 mission to put a man on the moon, the European research and innovation missions aim to deliver solutions to some of the greatest challenges facing our world. They are an integral part of the Horizon Europe framework programme beginning in 2021.

Cancer affects everyone regardless of age, gender or social status and represents a tremendous burden for patients, families, and societies at large. If no further action is taken, the number of people newly diagnosed with cancer every year in Europe will increase from the current 3.5 million to more than 4.3 million by 2035.

By joining efforts across Europe, more people would live without cancer, more cancer patients would be diagnosed earlier, would suffer less and have a better quality of life after treatment. This is why continued discussion between bioengineers, physicists, imaging specialists and cancer biologists and investors is thus essential in driving the field of tumour mechanobiology forward, and more opportunities for establishing collaborations between these fields should exist. Investors and companies play an important role.

To this purpose, BIOENGINEERING AND MEDTECH AGAINST CANCER short course put together all the relevant actors and combined the more recent bioengineering and medical technologies, providing innovative solutions that specifically treat cancer, while protecting the overall health of the patient and by limiting side effects. Therefore, the consortium promoted an innovation model where scientists, engineers and doctors worked in close collaboration.

CONCLUSION

Cancer is one of the pathologies that can benefit most from the novel bioengineering approach, bringing together fields such as nanomedicine, biophysics, mechanobiology, biotechnology and ICT.

To accomplish this, we need to progress in an open innovation model, creating a shared space between scientists, physicians, engineers and entrepreneurs, and encourage a framework for relations with clinicians and biomedical and medical technologies companies, through a multidisciplinary approach.

One of the first actions needed is to raise awareness among the European healthcare professionals of the opportunities that bioengineering and medical technologies can bring to innovation in cancer diagnosis and treatment. This technological approach is often not included in the curricula of these professionals.

The following hot technological topics that are already revolutionizing healthcare and assistance to cancer patients are:

- **Liquid biopsies:** In view of epidemics of non-communicable disorders characteristic of the early 21st century, liquid biopsy has become a key instrument in the context of predictive, preventive, and personalized medicine (3PM)ⁱⁱ.

- **Tumour on chip** has recently emerged as powerful tools in cancer research. The suitability of tumour-on-chip devices is increasing in many areas of cancer research and in the years to come, additive manufacturing (3D bioprinting and 3D printing), computational fluid dynamics, and medium- to high-throughput omics will become powerful enablers of a new wave of more sophisticated and effective tumour-on-chip devices.

- **CAR-T therapies** have offered significant promise in the **treatment** of patients with hematologic malignancies, providing a foundation for the development of treatment strategies for other cancers. It is clear that CAR-T cell therapies are heavily entrenched in the future of cancer immunotherapy.

- **Mechanobiology approaches to cancer** holds promise for increasing the understanding of tumour invasion. A synthesis of the biology of cancer cell invasion and cellular mechanobiology may offer new targets for the treatment of malignant disease.

- **Targeted drug delivery systems** have an important role considering the absence of diagnostic and prognostic markers and also unresponsiveness to current therapies. The current therapies are not sufficient to provide effective treatment for PC patients due to rapid drug solubility and metabolism, insufficient drug concentration at the specific site and adverse side effects. To eliminate this disadvantage, nanoparticle based drug delivery systems are being investigated.

Cancer treatment has benefited in recent years from the implementation of personalized therapeutic drugs targeting specific mutations in signalling pathways. However, even with the use of such personalized drugs, still tumours develop resistance and progress. Therefore, we require a better fundamental understanding of how biochemical signalling interacts with additional factors, such as mechanical ones to drive tumour dormancy and progression. Advanced drug delivery strategies are being developed using modular multivariant nanomaterials and nanorobots allowing for functionalization with multiple targeting ligands and photoactivated antimetabolites for chemotherapy with high efficacy and low side effects. Model in chip of relevant tumours will allow to test these novel therapies in vitro, reducing animal experiments and time to the patient. At the same time,

liquid biopsies have the potential to dramatically improve the diagnosis and prognosis of cancer, while CAR-T therapies are already giving hope to many patients.

1. LIQUID BIOPSIES – TOWARDS AN EARLY DIAGNOSIS AND REAL-TIME MONITORING OF CANCER

Early detection of cancer through a screening program for healthy and high-risk individuals is a key application of liquid biopsy approach. Current therapeutic strategies allow the successful treatment of many patients if the disease is detected early enough, whereas metastatic disease still remains incurable with very few exceptions (for example, small liver metastases in colon cancer).

The analysis of tumour cells and tumour-derived products that are detectable in the blood and other body fluids was introduced by Pantel et al. as ‘liquid biopsy’, and has attracted substantial interest in recent years.

By determining the temporal and spatial complexity of tumours, it represents a promising solution to diagnose and monitor cancer. It is non-invasive or minimally invasive, sensitive, and convenient diagnostic tool that provides specific, accurate, and personal molecular information. The tumour biopsy depicts only a single timeframe from a single site, and might be inadequate to characterize a tumour because of its heterogeneity. Circulating tumour DNA offers a «real time» tool for serially monitoring tumour genomes in a non-invasive manner providing accessible genetic biomarkers for cancer diagnosis, prognosis, and response to therapy by providing an analysis of biomarkers in patients’ biofluids (non-solid tissue) such as blood, urine, cerebrospinal fluid (CSF), pericardial effusion.

The liquid biopsy can be used for a variety of clinical and investigational applications and the choice of biomarkers for early detection is crucial. Clinical applications of liquid biopsies in early-stage cancer patients include early detection of small tumours, improved risk assessment, and monitoring of minimal residual disease. This diagnostic information can now be implemented into new clinical trials designed to cure cancer patients before overt metastasis. Many liquid biopsy tests have been established and validated over the past 10 years, and some have already reached the clinic. However, the majority of the new tests suffer from insufficient clinical and technical validation and lack clinical utility.

Liquid biopsy approaches have the potential to become a cornerstone of personalized medicine.

2. TUMOR-ON-CHIP- A 3D TOOL FOR PRECISION ONCOLOGY

The escalating cost of drug development is a deterrent for conducting clinical trials, leading to a decrease in number of innovative treatments. For example, in oncology, the success rate of drugs entering clinical trials and obtaining Food and Drug Administration approval is only 5.1%. The cancer microenvironment is known for its complexity, both in its content as well as its dynamic nature, which is difficult to study using two-dimensional (2D) cell culture models. This situation offers an opportunity to stimulate the development of physiologically relevant tissue models with improved preclinical testing outcomes. Tumours are complex three-dimensional (3D) tissues that establish a dynamic cross-talk with the surrounding tissues. Several advances in tissue engineering and extensive body of experimental evidence have established that 3D culture systems more closely replicate the architecture and the physiology of human solid tumours when compared with traditional 2D systems and allow more physiologically relevant three-dimensional (3D) in vitro cancer models, such as spheroid cultures, biopolymer scaffolds, and cancer-on-a-chip devices.

The ideal in vitro recreation of the micro-tumour niche—although much needed for a better understanding of cancer aetiology and development of better anticancer therapies—is highly challenging. Moreover, conventional 3D culture systems fail to recreate the dynamics of the tumour niche. Tumour-on-chip systems, which are microfluidic devices that aim to recreate relevant features of the tumour physiology, have recently emerged as powerful tools in cancer research.

In tumour-on-chip systems, the use of microfluidics adds another dimension of physiological mimicry by allowing a continuous feed of nutrients (and pharmaceutical compounds). One of those new 3D models is tumour-on-a-chip technology that provides a powerful in vitro platform for cancer research, with the ability to mimic the complex physiological architecture and precise spatiotemporal control. Tumour-on-a-chip technology can provide integrated features including 3D scaffolding, multicellular culture, and a vasculature system to simulate dynamic flow in vivo.

Tumour-on-chip models based on these organ-on-chip systems can recreate human tumour microenvironments and now hold great promise as a new resource for cost-effective and higher-throughput screening of anticancer drugs and powerful enablers of precision medicine.

These approaches will allow in the future for the tumour-on-a-chip systems to test therapeutic approaches for individuals through using their cancerous cells gathered through techniques like biopsies, which then will contribute toward personalized medicine treatments for improving their outcomes.

3. CAR-T THERAPIES

Cancer therapy has evolved throughout the decades and is beginning to branch off into new and exciting fields including immunotherapy. The hope of this new field stems from the lack of success of chemotherapy in general. Chemotherapy and radiation have long been the mainstay of nonsurgical cancer treatment options. However, many cancers remain refractory to treatment and develop resistance to treatment modalities over time. Despite recent therapeutic advances, such as the introduction of monoclonal antibodies and small-molecular inhibitors, treatment responses vary considerably among patients and a high relapse rate with poor prognosis continues to be a major challenge. In case of persistent or relapsed disease, few or no treatment strategies are capable of definitely eradicating residual malignant cells, necessitating therapies with greater efficacy. Immunotherapy is relatively new compared to the three primary pillars of cancer treatment: surgery, chemotherapy, and radiation. Significant leaps in molecular biology techniques, in particular, have advanced the understanding on how the immune system works, in addition to how it can be modulated. This has led the scientific community to identify the chimeric antigen receptor (CAR) as a potential target for molecular genetics to insert new epitopes on the receptor region, allowing a degree of control of the immune system. The development of novel targeted therapies with acceptable safety profiles is critical to successful cancer outcomes with better survival rates. Immunotherapy offers promising opportunities with the potential to induce sustained remissions in patients with refractory disease. Recent dramatic clinical responses in trials with gene modified T cells expressing chimeric antigen receptors (CARs) in B-cell malignancies have generated great enthusiasm. CAR- T cell therapy is today one of the most recent innovative immunotherapies and is rapidly evolving.

Years of successive and significant innovations have finally culminated in clinical studies demonstrating the tremendous potential of second-generation CAR expressing T cells. The adoptive transfer of gene modified T cells is a rapidly evolving innovative treatment for cancer. CAR redirected T cells are renewable drugs with the capacity to proliferate in the patient after infusion and further to persist and provide sustained functional immunity. The efficacy has been demonstrated in a range of haematological cancers and multiple myeloma and further by some encouraging clinical data reported in early phase I trials in solid tumours. Improvements in gene modification, T cell selection, and expansion techniques, as well as the development of safe and more effective viral and nonviral vectors, will further enhance the integration of T cell gene therapies.

Patients own T cells are used to make the CAR T cells, and this is the reason why this therapies are so promising as the immune system of the patient should not detect them as foreign so will not attack them.

4. MECHANOBIOLOGY APPROACHES TO CANCER

In the last decade, research from diverse fields has converged to establish a fundamental concept: that physical forces play key roles in both the initiation and progression of cancer.

The primary cause of cancer treatment failure is invasion and metastasis, and invading tumour cells utilize many of the motility patterns that have been documented for normal morphogenesis. Recently, the role of mechanical forces in guiding various tissue and cell movements in embryonic development has been systematically analysed with new experimental and computational methods. The tissue and cellular mechanobiology approach holds promise for increasing the understanding of tumour invasion. Understanding the role of genetic mutations and their associated biochemical signalling pathways in the onset and progression of cancer has been the focus of cancer research since the advent of sequencing technology. However, there is a reciprocal interplay between biochemical and biophysical signalling which influences cancer hallmarks including migration, metastasis, and angiogenesis.

This special issue will highlight the many roles of mechanobiology in cancer, from primary tumour initiation to metastatic progression and drug resistance. The role of the cancer mechanobiologist is to develop controlled model systems that incorporate components of the tumour microenvironment and can be used to monitor live cells and quantitatively assess mechanical cell behaviours involved in cell invasion. Results from such models have already contributed to a more robust understanding of tumour cell invasion and continuing work in the field seeks to expand upon the mechanobiological characterization of *in vitro* tumour invasion by elucidating how microenvironmental factors, such as those identified through clinical observations, affect tumour cells' mechanical state and behaviours such as cytoskeletal dynamics, cell force generation, cell adhesion, and cell migration.

Clinically, the identification of tumour invasion occurs as an endpoint observation and depends primarily upon qualitative characterization of malignant epithelial cells and components of the tumour microenvironment such as the basement membrane, myofibroblasts, and stromal extracellular matrix. While this perspective is important for diagnosis and management of patients' tumours in the clinic, understanding the process of tumour invasion will ultimately enable more effective diagnostic and therapeutic strategies for improved patient care. The mechanobiological study of tumour cell invasion has enabled physical cell biologists to identify the mechanical cellular functions that are involved in each step of tumour cell invasion and demonstrate how histopathological phenomena, including desmoplasia and ECM remodelling, affect each step of the process through a complex mechanical-biochemical feedback system broadly termed mechanotransduction. Continued work with mechanobiology models of cancer invasion and

metastasis should seek to more fully integrate the biochemical and biophysical properties of the tumour microenvironment to better characterize the effects of therapeutic strategies, identify mechanobiological biomarkers of cancer progression, and further define the “invasive phenotype”.

5. TARGETED DRUG DELIVERY

Although conventional chemotherapy has been successful to some extent, the main drawbacks of chemotherapy are its poor bioavailability, high-dose requirements, adverse side effects, low therapeutic indices, development of multiple drug resistance, and non-specific targeting. The main aim in the development of drug delivery vehicles is to successfully address these delivery-related problems and carry drugs to the desired sites of therapeutic action while reducing adverse side effects.

The emergence of nanotechnology has had a profound impact on clinical therapeutics in general in last two decades. Compared to conventional chemotherapeutic agents, nanoscale drug carriers have demonstrated the potential to address some of these challenges by improving treatment efficacy while avoiding toxicity in normal cells due to features such as high selective accumulation in tumours via the enhanced permeability and retention (EPR) effect and active cellular uptake.

Although nanocarriers offer many advantages as drug carrier systems, their lack of biodegradation, poor bioavailability, instability in the circulation, inadequate tissue distribution and potential toxicity raise concerns over their safety, especially for long-term administration. Cancer chemoresistance, which is accountable for most failure cases in cancer therapy, is a phenomenon in which cancer cells that are initially suppressed by an anticancer drug develop resistance towards the particular drug. For this reason, novel drug delivery systems with better targeting ability are needed for cancer prevention, the suppression of adverse side effects and pain management associated with cancer chemotherapy. Compared with the direct administration of bare chemo-drugs, drug encapsulation in a carrier offers a number of advantages, such as protection from degradation in the bloodstream, better drug solubility, enhanced drug stability, targeted drug delivery, decreased toxic side effects and improved pharmacokinetic and pharmacodynamics drug properties.

To date, an impressive library of various drug delivery vehicles has been developed with varying sizes, architectures, and surface physicochemical properties with targeting strategies. Novel drug delivery systems promise a bright future for cancer treatment in the next decade or so; they might become major arsenal for safer and more efficient treatments by ensuring proper drug localization at the site of action in a controlled manner.

The enhanced therapeutic efficacy of targeted nanocarriers has been established in cancer treatment using multiple animal models that target tumours and deliver drugs for targeted radiotherapy, imaging-guided radiotherapy and precision medicine. Although major

advances have been made by current drug delivery systems in the treatment of most cancers, much work lies ahead to monitor the mortality rate due to cancer. Most of these carriers have been designed and tested in small animal models, achieving great therapeutic results; however, the translation of animal results into clinical success has been limited. More clinical data are needed to fully understand the advantages and disadvantages of these vehicles.