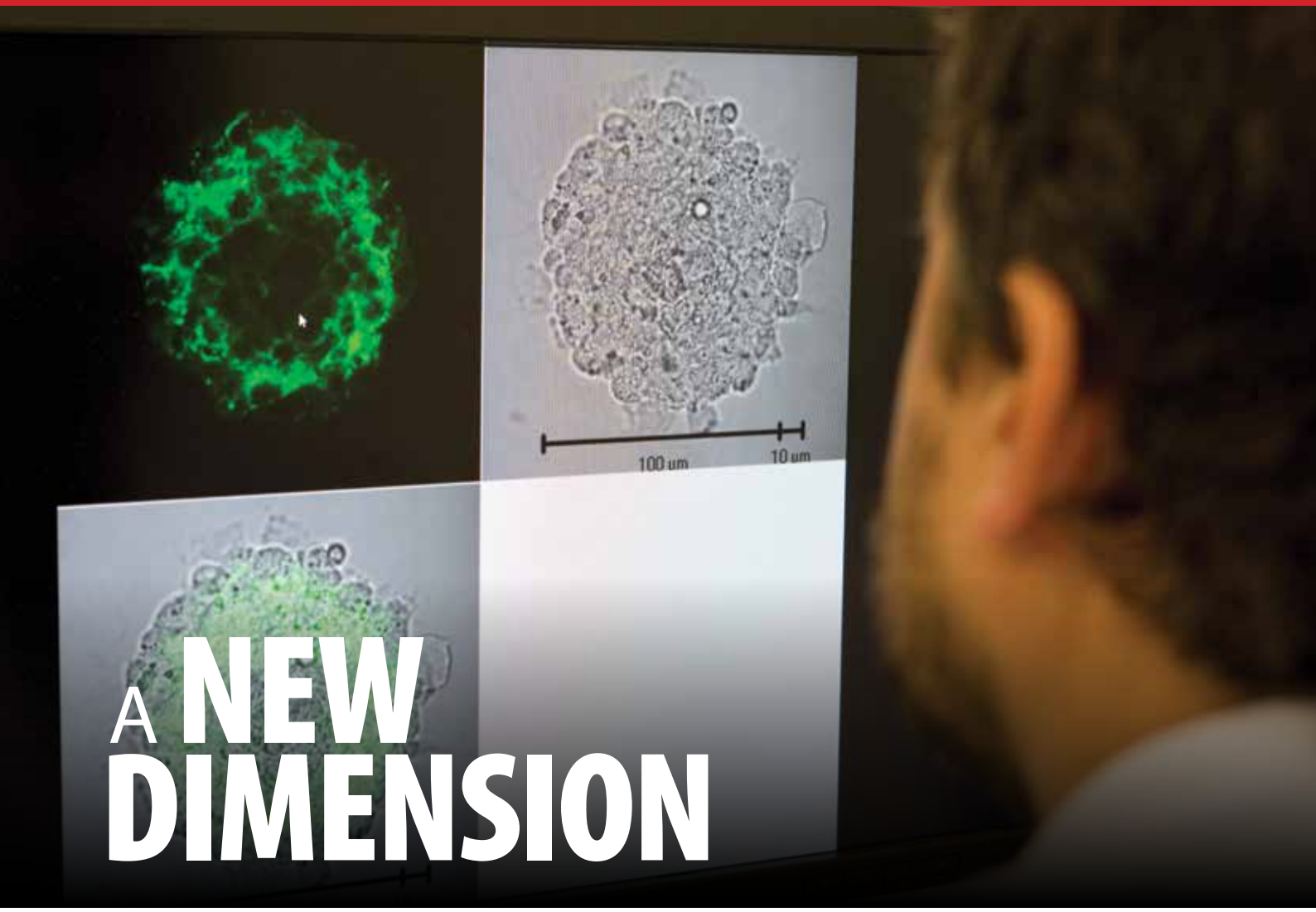



# A NEW DIMENSION

***Biology is not flat, so one expert in the sector is aiming to make 3D cell culture a commodity, explains Angel Garcia Martin***

Pharma companies realise that most of the pre-clinical testing they have been doing just isn't good enough. As many as 9 in 10 drug candidates fail in clinical testing, and the majority of this attrition is due to toxicity and efficacy issues. This suggests that the translational tools currently used for predicting efficacy and clinical response are not optimal. Pharma is reviving the 'fail fast, fail cheap' philosophy it used to try to improve pre-clinical and clinical testing outcomes in the setting of early-stage R&D and screening.

Cells grown in the bottom of plastic plates as monolayer, 2D cell cultures have very different expression patterns of genes, proteins and potential drug targets compared to what those cells would be expressing in the body. In 2D culture, the cells are not exposed to the same mechanical influences, external signals or rates of diffusion, which can all affect gene expression. These factors can be simulated in 3D microtumours, such as switching from 2D to 3D cell models, and adopting more advanced testing methods earlier in the research workflow.

Almost all the drug screening efforts carried out currently for discovering novel anti-cancer compounds rely on *in vitro* immortalised cancer cell line models grown in 2D, which have demonstrated a poor success in predicting clinical efficacy, resulting in an alarming 95% failure after clinical testing, representing a waste of precious resources and time.

Over the past year-and-a-half, we have seen a trend toward pharma wanting to model physiologically relevant tumour phenotypes to screen compounds. Biology is not flat: cells, tissues, organs, even tumours, live in a 3D environment, thus it is desirable to test for novel compounds in systems that recreate the architecture and behaviour of cells in their natural 3D environment to understand how those compounds would behave in the natural setting. Pharma needs 3D tissue models that will better allow it to predict more accurately how a compound will function in humans.

The convenience, availability and homogeneity of conventional continuous cell line models used for

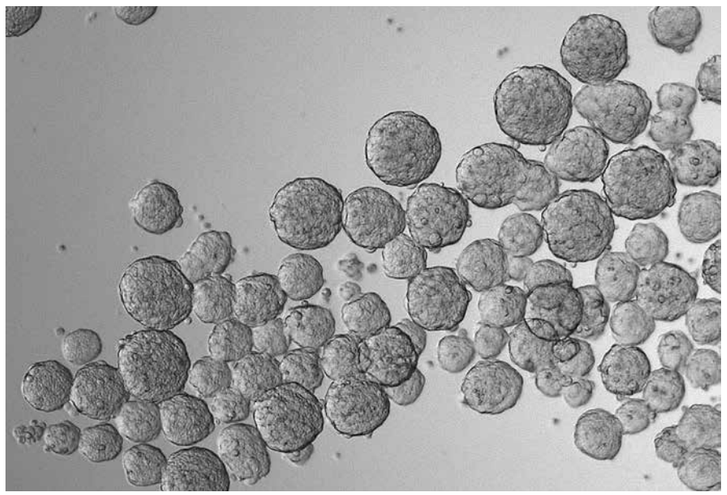
**Models that better recapitulate the physiological features of human tumours are a step towards rational drug development**

cancer research, which have been cultured for decades and have helped us understand the molecular biology behind cancerous transformation, are still valid models for routine drug profiling in the early stages of drug development, allowing for rapid identification of potential hit molecules. Cell lines provide a rapid and low cost assay for screening, with the development of 3D cell cultures derived from cell lines we can give pharma companies a ready to use platform to reduce their attrition rate early in drug development. The throughput and reproducibility provided by cell lines models is unparalleled. StemTek's Cell2Sphere technology provides just that – a convenient, ready to use platform for routine drug discovery and drug validation that is delivered frozen for flexible planning of experiments. Available for the most common cell lines, it can also be set up to suit the researcher's specific needs, and is set to become a standard in anti-cancer drug profiling.

## Step towards rational drug development

A step forward is represented by models that better recapitulate the physiological features of human tumours. Highly predictive patient-derived xenografts (PDX) represent a diversity of the human patient population in a close to real physiological model. These models grow human tumour fragments in mouse models in an attempt to identify responders for a 'go or no go' decision for drug positioning before a new agent enters the clinic. PDXs preserve both the genomic integrity and heterogeneity of the disease. The use of these well-characterised models in human surrogate trials can provide data on responder populations, which can be further interrogated based on the genetic features of the models. Understanding these mechanisms of response and resistance can provide predictive biomarkers and genetic signatures of response to a given agent, which delivers an important stratifying tool for the clinic. Leveraging these biomarkers and signatures to select patients for efficacy based, late-phase clinical trials provides the greatest likelihood of success of an agent in the clinic, and a reduction in the attrition rate for novel oncology therapies.

PDX model data closely resembles patient clinical response, and retrospective analyses have shown that PDX models have a predictive power for tumour response to treatment. Each PDX model reflects the pathology of its original patient (behaving as a patient avatar), and the cohort of patient avatars represent a diversity of the human patient population. Analysis of avatar response can identify responder and non-responder populations, identifying which patients will benefit most from a given treatment, based on their genetic profile and that of their tumour. Establishing a responder population before entering clinical trials will allow better stratification of potential clinical



**Left: 3D spheroid images**

## First frozen 3D cell-based assay now available

StemTek Therapeutics has started serving Cell2Sphere ready to use 3D cell culture kits to researchers throughout the world.

Designed for drug discovery research in industrial, biotech, pharma and academic fields, Cell2Sphere represents a geometric evolution in cell based assay development. Using a scaffold-free technology, 3D spheroid cells arrive frozen and grow in a standard 96 well ultra low-adhesion plate for use in molecular compound testing.

Cell2Sphere is the first simple 3D tissue culture kit for labs interested in more accurate, scalable and dynamic experimental research, the frozen spheroid tissue culture samples considerably increase the shelf life of today's 3D cultures.

trial participants, a greater likelihood of response in the clinic and a reduced oncology drug discovery attrition rate.

However, running a battery of tests for drug screening and validation *in vivo* on PDX models is a costly and time-consuming proposition. Perhaps the greatest drawback to this technique is the fact that tumours grow at the same rate in mice as they do in humans, and implantation, propagation and drug screening in mouse avatars is a time-consuming process. With the technology developed for Cell2Sphere, StemTek can provide ready-to-use PDX derived 3D spheroids *in vitro* to reduce these times and costs, allowing for testing a panel of tumour indications in just one experiment. Growing patient tumours in mouse avatars allows the amplification of precious and necessarily limited patient sample material, creating a convenient replicable model to generate patient samples on demand. Think of this as a clinical trial *in vitro*. With this information, pharma companies can then validate the effect of their compounds specifically in the *in vivo* PDX model that is more likely to respond to this particular compound, allowing a significant time and cost reduction in drug development before entering in clinical trials and increasing the probability of compound efficacy, thus reducing the attrition rate.

## Personalised drug evaluation

Personalised medicine is a concept based on treating an individual according to their tumour characterisation. It is defined by the US National Cancer Institute as "a form of medicine that uses information about a person's genes, proteins, and environment to prevent, diagnose and treat disease." Targeted therapies are an excellent example of this type of medicine – developed based on specific factors within a person's tumour, such as a mutated protein or an overexpressed gene. Personalided medicine can only go on to fully become a reality with improvements in efficiency and decreases in costs in oncology R&D development. With Cell2Sphere technology, StemTek aims to provide 3D spheroid avatars directly from each patient, allowing treatment of the patient's tumour outside of their body, with response rates to different agents supplied back to clinicians to guide patient treatment. The future is here today: treating oncology patients on an individual patient-by-patient basis.

**Above: StemTek can provide ready-to-use PDX derived 3D spheroids in vitro**

**Below: This technology is leading the way for personalised medicine**

*Angel Garcia Martin is CEO of StemTek Therapeutics.*
*www.stemtektherapeutics.com*