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Developing Innovative Cancer Medicines of the Future via Patient-Relevant Models

There is currently a high attrition rate for new cancer drugs which enter into clinical trials, due to pre-clinical models not accurately predicting efficacy and/or toxicity. In a recent study provided by Cancer Research UK, it was shown that between 1995 and 2007, 77% of 800 cancer drugs entering Phase I clinical trials failed to reach the market (1). As a result, there is a growing need within the pharmaceutical and biotech industry for more patient-relevant and predictive cancer modelling for anti-cancer drug development. This requirement is particularly important as a new generation of molecular-targeted cancer drugs, with fewer potential side-effects, are coming through the drug discovery pipeline. In response to this requirement, new technology is now being developed in an effort to create patient-relevant models which ensure pre-clinical efficacy assessment. It is important to evaluate the innovative cancer medicines of the future via these patient-relevant models to ensure they are predictive of how the drug is likely to behave in clinical trials with cancer patients.

This article will provide examples of two innovations that have been specifically developed in order to fast-track new agents into the clinic. Advantages of these innovations will be explored, detailing how they are superior when compared to traditional cancer models in that they provide maximum data over a short timeframe together with associated cost benefits, and aid in successfully attaining regulatory approval. The need for specialist service providers is driven by increasing regulatory and scientific rigour and the pressure to reduce ever-increasing cancer drug attrition rates and R&D costs through outsourcing, thereby identifying potential ‘lead candidates’ as early as possible.

The Challenge
The high attrition rate for new drugs entering clinical trials can be related to a variety of factors. A key problem is that the large majority of major pharmaceutical and biotech companies developing products in oncology use only a limited and basic portfolio of cancer models, most of which are based on the use of animal cells or tissue. These basic models typically use cells that are not relevant to the human situation, and models that either do not allow continuous measurement of response and/or optimally model the biology of the cancer. Failure to do this has resulted in new cancer drugs not being challenged to the same degree as in the patient, with a number of false positive drugs entering into clinical trials as a result. For effective cancer drug development it is crucial to maximise pre-clinical information and ensure the drug is challenged in models reflective of the patient, many of whom have advanced cancer and may have lost responsiveness to existing standards of care.

The global cancer market was forecast to grow to $53.1 billion by 2009 (2). Based on an estimated 18% of domestic sales spent on R&D (3) the potential R&D spend on anti-cancer therapies is currently $7 billion, with approximately one-quarter of this spend devoted to pre-clinical R&D ($1.75 billion). An estimated 25% of this is outsourced, with outsourcing predicted to expand significantly further by 2015.

Although currently human tissue research is not something which the pharma and biotech community is required to do by law, there is increasing demand from regulators for non-clinical human safety data. It is interesting to note that oncology, one of the areas of drug development with the highest rate of attrition, is also the area in which animal models are not very predictive of the true human pathophysiology. For example a large majority of pharmaceutical companies continue to use basic xenograft models for oncology testing. When using this model, a tumour cell line that might have little relevance to the patient’s tumour is injected into a non-human model. This method is vulnerable to flaws due to the immunology of the non-human model not resembling the immunology of the human target, and the artificial location of the tumour offering no real resemblance to what happens in vivo during tumorigenesis. The scientific community must work with industry to advise on study design to ensure that results are patient-relevant and meaningful.

Innovative New Technology
The demand for pharmaceutical companies to meet their business objectives, alongside the demand from consumers for the contained cost of prescription medicines, is forcing the industry to develop new methods to increase efficiency and reduce attrition rates.

Innovative new approaches have targeted the urgent requirement to improve the efficacy of cancer modelling by expanding the utility of reporter systems and applying them to complex multi-cellular in vitro- and in vivo-based systems. Through the development of bio-imaging techniques applied to patient-relevant multi-cellular three-dimensional models, disadvantages of previous models, including aspects such as maintaining individual cell growth and hypoxia, can be overcome.

An established approach is the derivation of cancer models from cells derived from the patient’s tumour tissue, to evaluate drugs in patient-relevant models. This approach is being further developed by PRECOS under full ethical permission by modelling the tumour micro-environment in three-dimensional multi-cellular systems which challenge the new therapeutic entity to the greatest degree by incorporating relevant cell types, including those associated with the tumour stroma. This is opposed to evaluation in monolayer single cell cultures, which are standards within the pharma and biotech industries, and whilst predictive of the biology and mechanism-of-action, are not predictive of clinical efficacy. These 3D models with established human stromal epithelial interactions can then be transplanted in vivo.

Real-time imaging allows continuous temporal information from a single...
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experimental model resulting in improved efficiency and increased scientific information. In addition, lower costs are incurred due to more robust statistical analysis from fewer experimental repetitions. For example, it allows optimal timing of drug administration to be determined based on the micro-environmental signals measured. The technology also limits the need for additional monitoring and post-test procedures such as histology, and therefore reduced timeframes, thereby reducing cost and maximising the margin.

Use of medium throughput three-dimensional in vitro model screens may reduce the need for larger scale in vivo models, due to their capacity for modelling the tumour micro-environment more effectively, particularly in the discovery phase, resulting in a more streamlined drug development process. Further added value of the system is provided through the temporal analysis of cancer development in these models, which allows optimal timing of drug administration based on the micro-environmental signals measured by the innovations, delivering valuable insight in determining the efficacy of the new anti-cancer agent.

A second new approach allows the monitoring of the tumour micro-environment and biological changes within cells in real-time in the presence of a cancer drug. This new approach is facilitated by the development of innovative new technology which involves bioluminescent/fluorescent biological reporters. These biological reporters are expressed in human cancer cells so that they emit light or fluorescence in response to different environmental stimuli. The reporters also emit light in response to changes and progression of the disease in response to drugs. For example it is possible to monitor the presence of hypoxia (low oxygen levels), blood vessel formation and cell proliferation and cell death. In addition, the technology can also evaluate genes up-regulated in response to radiotherapy or similar insult, intra-cellar signalling activated by ligand binding to cell surface receptors and cells with cancer stem cell-like properties, and that are undergoing epithelial: mesenchymal transition; a phenotype linked to cell invasion and metastasis. These reporter systems therefore cover a number of key tumour properties including predictivity of secondary spread and resistance to standard of care treatments.

These approaches have been developed within an academic setting, and this academic link and pipeline ensures the technology remains ‘cutting edge’.

Overall, both of the discussed innovative approaches offer the advantage of reducing the need for additional monitoring and post-test procedures and the use of expensive supporting technology. In addition, these new approaches have the potential to ensure maximum data over a short timeframe with associated cost benefits and, most importantly, enable new cancer drugs to reach patients sooner.

Products that have been developed with the use of these discussed innovations include CCK-2 receptor antagonists (reached Phase II/III in pancreatic cancer), G17DT immunogen (reached Phase III in pancreatic cancer) and Her-2 ligand trap (pre-clinical Phase), c-met inhibitor (Phase I/II) and the HDAC inhibitor (Phase II/III).

Conclusion

There is currently a high attrition rate for new oncology drugs entering into clinical trials, due to flawed methods of toxicity and efficacy evaluation providing inconsistent and inaccurate results. Innovative new approaches are being developed to overcome these challenges through the creation of bio-imaging techniques which can be applied to patient-relevant three-dimensional models both in vitro and in vivo. These approaches have involved investment into designing reporter systems, performing molecular biological techniques to preserve the characteristics of the cancer cells, and testing to ensure that the systems still respond to standard of care cancer agents in a manner predictive of the patient, thus providing robust validation and documentation for each of the models.

As a result of these innovative developments, new anti-cancer agents feed into more robust, complex and clinically predictive models. The need for specialist service providers is driven by increasing regulatory and scientific rigour and the pressure to reduce ever-increasing cancer drug attrition rates and R&D costs, in order to identify potential ‘lead candidates’ as early as possible. As a result it is now becoming common practice to outsource this activity to specialised service providers. Advantages of such outsourcing to specialist providers include time- and cost-efficiency, in addition to independent validation of ‘in-house’ data which, as a result, generates a stronger pre-clinical package for regulatory submission by pharma and biotech organisations. Innovative technologies developed by specialist providers can quickly and cost-effectively be applied across all cancer types, benefiting the wider scientific community and, vitally, enabling new cancer drugs to reach patients sooner.

References


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