How Translational Science is Changing the Treatment Paradigm in Oncology

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For the past ten years or more, translational science has been pushing back the frontiers of medical research and oncologists have been its pioneers. Of all the medical disciplines, it is oncology that has taken the tools of translational science and used them most effectively to bring about fundamental changes in the way we treat disease.

Translational tools such as rational drug design, 'in silico' computer modelling, biomarkers and companion diagnostics, have allowed oncologists to begin treating cancer at a genetic and molecular level to go beyond simply focusing on the disease's relatively imprise clinical manifestations.

Some of the newest treatments are able to target genetic pathways and molecular alterations in specific cancers of identified subsets of patients. This raises the prospect of highly personalised medicine in which the right drugs are used in the right patients in the right doses and at the right time.

Such personalised medicine is a timely and logical response to the increasing demands from healthcare systems to become more patient-centred to gain the most effective treatment outcomes and avoid treating patients who will not benefit. The one-size fits all approach to treatment is increasingly viewed as outdated and inappropriate due to the recent appreciation that cancer is not a single disease but many sub-diseases.

The personalised approach may also help stimulate new interest in neglected areas of research. Previous interest in drug development was to only advance compounds that had potential in the 'big four' (lung, colon, breast and prostate cancer). With the new understanding that cancer is a subset of many different patient segments, drug developers can focus drugs on smaller patient populations with the goal of providing more effective treatments and determining utility in early clinical trials.

Indeed there has already been a strategic shift among major pharmaceutical companies away from large clinical trials in unselected patient populations to targeted disease subsets. These companies are also using translational science technology to streamline their early stage research and to make their go/no go decisions on drug development much earlier in the pre-clinical and clinical process.

What is translational science?

Translational science represents a significant shift in focus from the traditional approach to developing new drugs and therapeutic approaches. Originally conceived as a way of facilitating the passage of new molecules from scientific discovery to clinical application, it has now developed into something much more than that.

Translational scientists quickly realised that the 'bench to bedside' model needed to be expanded to incorporate feedback loops through which information would also flow from frontline clinicians back to the laboratory. With information flowing from bench to bedside and back again, research could be better targeted towards the areas in which it would eventually offer the most benefit to patients. Real-time data could be used to adapt trial designs and effective biomarker strategies could increase the success of phase III clinical trials by selecting those investigational molecules with the greatest promise earlier in the development process.

A number of different techniques have been incorporated into this approach.
These include:

- Rational drug design – in which knowledge of the intended biological target is used to direct drug discovery.
- In silico research – in which virtual screening is used to identify potential candidates for therapeutic molecules without the need for expensive and time-consuming laboratory trials.
- Biomarkers – a characteristic that can be measured in response to a biological process, disease or drug treatment such as a protein, DNA, RNA or cell.
  - Pharmacodynamic (PD) marker – a change that can be measured when the drug binds its target (first level of evidence that a drug is doing what it was designed to do).
  - Proof of mechanism (PoM) biomarker – a change that can be measured when the drug binds and inhibits/stimulates the target (second level of evidence the drug is doing what it was designed to do).
  - Proof of principal (PoP) biomarker – a change that can be measured and indicates the drug is affecting the disease (first level of evidence that the drug may be effective).
- Companion diagnostics – in which the identification of biomarkers allows a patient subset to be identified for being included or excluded from treatment due to predicting who will benefit from the drug therapy. Many new oncology agents are now launched together with a specific diagnostic test to identify the target patient population.
- Predictive modelling – in which PD markers are used to monitor the pharmacological response to treatment, allowing clinical outcomes to be predicted and doses optimised at a much earlier stage in drug development.

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Translational science in oncology

Within oncology these translational techniques have been used to produce highly specific treatments that have already benefited thousands of patients in terms of longevity, improved prognosis and raised quality of life.

For instance, when researchers discovered that chronic myelogenous leukaemia (CML) was linked to a chromosomal abnormality known as the Philadelphia translocation, they were able to use rationale drug design to identify a molecule that would inhibit the bcr-abl protein responsible for the leukaemia.

The result was imitanib (Glivec/Gleevec) a drug which has been targeted towards at least two different cancer-causing genetic mutations – bcr-abl and c-Kit mutations benefiting patients with CML – and also patients who test positive for the c-kit genetic mutation in a subset of gastrointestinal stromal tumour (GIST) patients [1].

In the treatment of metastatic colorectal cancer, identifying patient subsets has been greatly advanced by the identification and use of biomarkers. For instance, patients carrying the KRAS mutation have been shown not to respond to the monoclonal antibody cetuximab (Erbitux) and thus, this patient subset should be considered for treatment with other therapies [2].

Companion diagnostics have also resulted in some significant advances in cancer care. For instance, the monoclonal antibody trastuzumab (Herceptin) would not have been viable as a breast cancer treatment if it were not for the diagnostic tests that were developed alongside it to allow identification of the patient subset to treat.

These tests – immunohistochemistry (IHC) or fluorescent in situ hybridisation (FISH) – allow clinicians to identify the subset (around 20%) of patients with invasive breast tumours who exhibit an over-expression of the human epidermal growth factor receptor type 2 (HER2) [3].

In this group of patients trastuzumab improves survival and response to chemotherapy, while the remaining 80% are not suitable for the treatment.

The MedImmune approach: Case study MEDI-575

We, at MedImmune, have developed a unique way of effectively using the promise of translational medicine by incorporating biomarkers early in the development program. Among a number of our exciting drug candidates, we are currently conducting oncology phase II clinical trials of a monoclonal antibody, known as MEDI-575, that targets the platelet-derived growth-factor receptor alpha (PDGFRα) pathway.

PDGFRα is an important cancer target due to its role in regulating transformation, tumour microenvironment, progression and metastasis of solid cancer tumours.

Development of MEDI-575 began in preclinical studies in which we used a targeted approach to develop a human monoclonal antibody to PDGFRα. MEDI-575 was designed to selectively inhibit PDGFRα signalling. An additional characteristic of MEDI-575 is that it does not produce the inhibition of PDGFRβ that has been associated with clinical toxicities, including extra-vascular fluid accumulation.

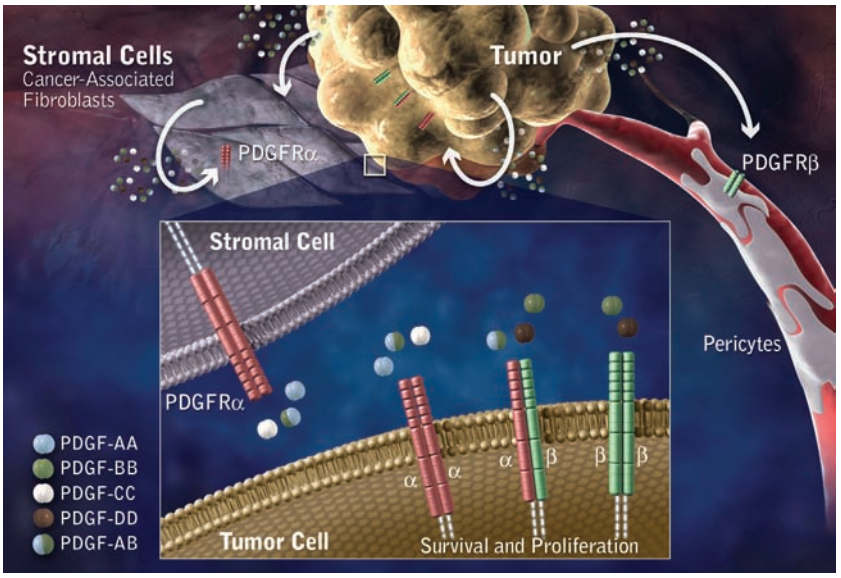


Figure 1: MEDI-575 Mechanism of Action.

In the preclinical development of MEDI-575, a panel of human epitheal tumour cell lines expressing PDGFRα was evaluated for antitumour response to treatment. The H1703 cell line, which has a high protein expression of PDGFRα, was the only epitheal cell line to demonstrate a robust antitumour response to treatment with MEDI-575 in preclinical models. However, when tumour models expressing human PDGFRα in the cancer associated fibroblasts were evaluated; MEDI-575 treatment resulted in antitumour activity in a broad range of models, irrespective of whether or not the tumour cell line itself expressed PDGFRα. Evaluation of human tumours using immunohistochemistry indicated that a number of epitheal tumours have prominent expression of PDGFRα in cancer associated fibroblasts and also have some tumour cell expression (non-small cell lung cancer being one of the best).

Evaluation of MEDI-575 using a panel of human meschymal tumour cell lines (glioblastoma) expressing PDGFRα resulted in significant antitumour activity in several models. Evaluation of human glioblastoma tumours using immunohistochemistry indicated that both primary and recurrent glioblastoma patient samples have a high prevalence of PDGFRα expression.

These preclinical studies led to the development of two working hypotheses that will be tested in Phase II clinical trials following safety, biomarker and dose selection in Phase I:

- That MEDI-575 inhibits tumour growth by its impact on the tumour stroma (cancer associated fibroblasts) that is supporting the tumour growth.
- That MEDI-575 inhibits tumour growth by direct anti-proliferative activity within the tumour cell;

In turn, these hypotheses directly contributed to the design of the current Phase II trials in patients with non small cell lung cancer (NSCLC) and glioblastoma multiforme (GBM).

These human clinical trials use the predictive modeling from the pharmacology and toxicology models developed at the preclinical stage to help us determine the right dosing and schedule in cancer patients.

They are also evaluating the expression of PDGFRα in tumour and stroma (cancer associated fibroblasts) in archival tissue (tumour from the patient when originally diagnosed) and the circulating tumour cells (CTCs – tumour cells in the patient at the time of treatment) for enumeration and PDGFRα expression, to determine if this biomarker can define a particular patient subset that may be more sensitive to MEDI-575. Protein biomarkers in the blood that may be able to identify patients with cancer associated fibroblasts will also be evaluated, as well as biomarkers for tumour cell apoptosis.

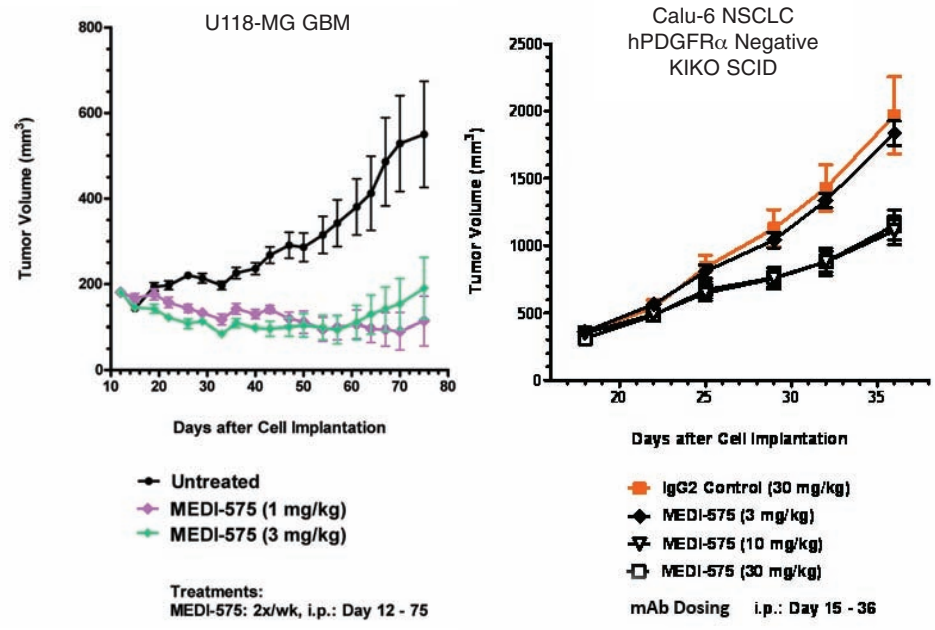
In this way the trials are designed not only to meet regulatory rigour for evaluating safety and efficacy, but also to identify specific molecular features of disease that regulate responsiveness to treatment and improve our understanding of the patient subset(s) that may be best suited for this treatment approach.

Future directions, possible obstacles

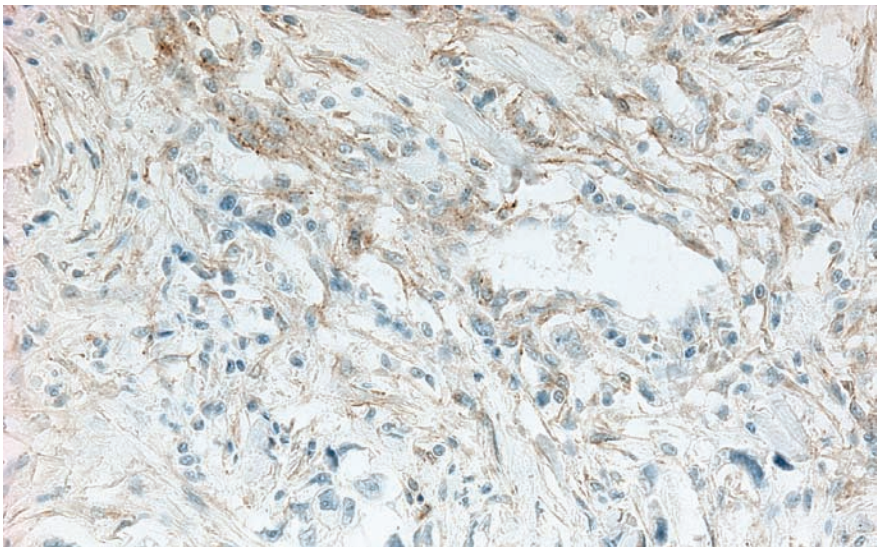
With translational strategies such as that used with MEDI-575 in the development pipeline, the future of oncological therapies appears promising for defining the right patient subsets to treat and enabling us to make go/no go decisions in early clinical development.

Indeed, our growing understanding of the

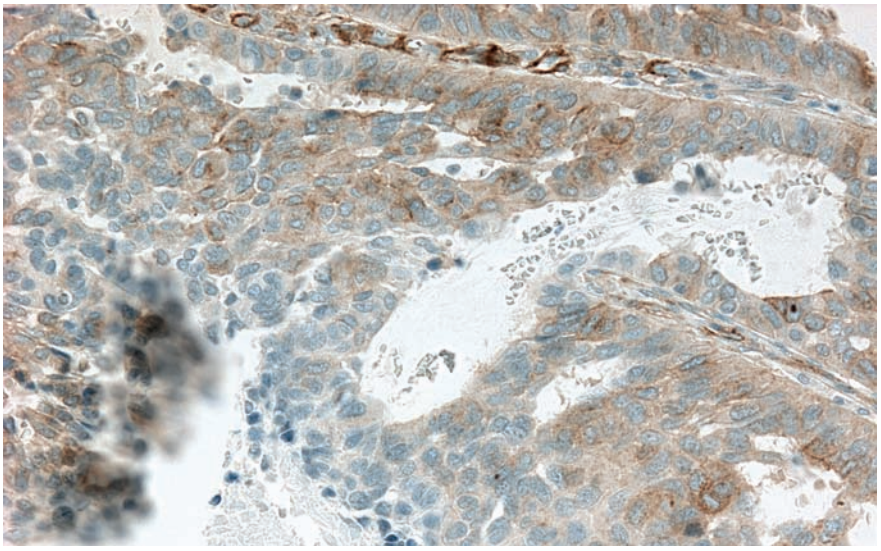
Figure 2: PDGFRα Expression in Human NSCLC Tumours.



PDGFRα expression: Tumour +ve; Stroma +ve



PDGFRα expression: Tumour -ve; Stroma +ve



molecular changes that take place in cancer are leading to new, rationally designed early detection, chemoprevention, and therapeutic strategies. The use of translational science based approaches to use tumour cell lines for pharmacology and predictive modeling, as well as human patient samples for disease linkage studies, allows the design of robust clinical trials to answer specific hypothesis to determine right drug, right target or right drug, wrong target. Moreover, the identification of global gene expression signatures from individual tumours raises the possibility of selecting therapies by molecular typing of individual tumours.

Investigations are also ongoing into a variety of minimally invasive approaches to assess cancer biomarkers such as the methylated or mutated tumour DNA sequences, miRNA, protein signatures and circulating tumour cells in blood or other accessible body fluids with the potential for diagnosis and possibly early detection of cancer.

Clearly, translational science has already achieved many successes both within oncology and beyond. There are however a few dark clouds on the horizon that could impinge on its future success. In an age of increasingly stringent budgetary restrictions there is no doubt that the higher initial costs of translational research programmes could be a major disincentive to investment. There is also a shortage of suitably skilled investigators and a number of administrative and regulatory barriers.

Conclusion

There has been a symbiotic relationship between oncology and translational science in which both have accrued significant benefits. It is a relationship that has resulted in the development of innovative approaches to drug development whose benefits extend well beyond the discipline of oncology itself. At the same time it continues to produce targeted treatments and diagnostic procedures that have extended patient survival, reduced the burden of disease and improved patients' quality of life. Despite some potential barriers to further expansion, the well-stocked research pipeline suggests that translational science and oncology drug development will together continue to develop effective therapies for patients. ■

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