Therapeutics Discovery at MD Anderson

making patients a priority during the drug development process

Our mission at The University of Texas MD Anderson Cancer is to eradicate cancer, which remains a major cause of mortality worldwide. It is the second leading cause of death in the United States and globally, claiming more lives than malaria, HIV/AIDs and tuberculosis combined (or ~1 of every 7 deaths)[1-3]. Still, the news about cancer is not all grim, given the incredible advances we have witnessed in cancer treatments over the past several years, highlighted by targeted therapies and novel immunotherapies, including immune checkpoint inhibitors, chimeric antigen receptor (CAR) T-cell therapy and cancer vaccines.

By Dr Phil Jones

Despite the recent success, improvements in drug design are of little value for patients if novel therapeutics cannot be advanced from the bench to the bedside both efficiently (minimising the failure rates to keeps costs down) and rapidly (to provide transformative, life-saving medications to as many patients as possible, as soon as possible). At present, the development of a new drug, from discovery to its clinical approval is about 10 years, with an average cost of $2.6 billon (including the costs of failures)[4]. Further slowing drug development is a 'herd mentality', where companies focus their research and development effort on the latest and hottest therapeutic target, while other equally-worthy targets are deprioritised or progressed with limited resources.

To address the issues in oncology drug development, we have instituted a unique approach that leverages the many attributes of MD Anderson and maintains a singular focus on our patients. We built the Therapeutics Discovery Division as a biotech-like organisation within the walls of the largest cancer centre in the United States, leveraging our size and the quality of our people to transform drug development in a way that places the patient front and centre. We envisioned an operation that would complement the research model of biotechnology and pharmaceutical companies by providing an alternative source of impactful therapies.

Already in the past several years we have made notable advances. We have multiple novel treatments, including small-molecule drugs, biologics and adoptive cell therapies, in early clinical trials and several others set to enter the clinic in the next six months. As we have built our programme and implemented our model for drug development, we have learned valuable lessons for more rapidly and efficiently advancing potentially life-saving medications out of the laboratory and into clinical settings around the world.

Patients are our shareholders

Ultimately, the aim of all drug development is to improve patient health and well-being, but we have taken this a step further. Patient-focused drug development is the central pillar in our model, guiding all work done within Therapeutics Discovery. Our teams are driven not by future profits, but by a desire to end the devastating effects of cancer on patients and their families. Being a part of the nation's leading cancer hospital allows us to work with unparalleled proximity and access to patients and clinicians daily.

Through those interactions, we are able to understand patients' clinical needs first-hand and can work to address those needs. At MD Anderson no cancer is rare, so the Therapeutics Discovery team focuses on advancing projects that specifically target unmet medical needs, including tumour types that occur infrequently and those for which therapies are either lacking or are suboptimal. We are acutely aware of the suffering cancer can cause, and each of our team members is passionate about improving the lives of our patients. We consider our patients to be our shareholders, and their survival our bottom line.

Our approach

As a drug development engine within the walls of a leading cancer hospital, our Therapeutics Discovery Division is not working to bring the bench to the bedside. Rather, we start with the bench at the bedside, with each patient and their cancer.

The Therapeutics Discovery Division consists of more than 100 clinicians, researchers and drug development experts from four research platforms at MD Anderson (see box). Our teams are built around scientists who operate at the highest level in their fields, have a multifaceted understanding of drug development and are able to work effectively in cross-functional teams. They traverse both the research and clinical sides of the process and understand what is required to move a medicine – whether it be a small-molecule drug, a biologic or cellular therapy – into and through the clinic. We have taken advantage of having multidisciplinary researchers and clinicians under one roof, enabling a focused effort dedicated to the mission of bringing impactful therapies to the patients here at MD Anderson.

Our strength does not rest solely in our teams though, but also within the broader institution we call home. Through daily interaction with world-renowned clinicians and researchers at MD Anderson, we can collaborate in ever more powerful and rapid ways to break down the traditional silos that have hampered others, yielding no shortage of novel ideas for our drug developers to pursue for therapeutic interventions.

A key advantage for members of Therapeutics Discovery is real-time access to clinical data and insights from physician-scientists, who treat more than 130,000 cancer patients each year, helping us to tailor our drug discovery and development projects to meet the needs of patients they see in the clinic. For example, ideas for Therapeutics Discovery projects may emerge from physicians seeking therapies for a subset of patients with a specific tumour type that fails to respond to treatment or who relapse on treatment due to molecular differences in their tumours. Ideas may also develop from an innovative discovery in a research lab or from the implementation of disruptive technologies, such as advanced high-throughput functional genomics. Often, based upon our collaborations, we are able to pursue ideas for therapeutic strategies long before the data appear in a peer-reviewed publication.

Once Therapeutics Discovery scientists are approached with a new idea, a cross-functional team is assembled to assess the programme around three key pillars: potential clinical impact/medical need, strength of the biological rationale and feasibility of developing a therapeutic (small-molecule, biologic or cellular therapeutic). In some instances, additional data needs to be generated to clarify gaps in the data package before a programme is adopted into the pipeline, while in other cases a limited set of 'killer' experiments are conducted within Therapeutics Discovery that allow us to make rapid go/no-go decisions in eight weeks or less.

Programmes that pass this hurdle are then brought into the Therapeutics Discovery portfolio, where a team of 10-25 researchers is empowered to

Four collaborative platforms within Therapeutics Discovery

- Institute for Applied Cancer Science (IACS): discovers and develops impactful small-molecule cancer therapies
- Center for Co-Clinical Trials (CCCT): identifies novel therapeutic targets and defines the specific Phase I clinical trials to conduct with therapeutics from IACS
- Oncology Research for Biologics and Immunotherapy Translation (ORBIT): discovers and develops novel monoclonal antibodies
- Neurodegeneration Consortium (NDC): develops therapeutics that can effectively alleviate symptoms in patients with a variety of neurodegenerative conditions

rapidly advance the project toward the clinic, using key objectives and milestones. The goal is to identify therapeutics that meet our criteria for effective use in humans. Simultaneously, the teams also work to define a focused clinical plan that includes patient-stratification biomarkers to identify those individuals most likely to benefit, as well as early 'proof-of-biology' biomarkers to show the drugs are working in humans. Progress on the portfolio is monitored through regular review meetings with internal and external advisory boards and resources are redirected according to needs and progress.

Culling investigational agents early in the development process can be a difficult step, particularly when substantial resources have already been expended. However, we know that more than half of drugs fail in Phase III clinical trials due to a lack of efficacy, thus we are ruthless in our assessments of target candidates and project advancement. We can be ruthless because we own the compounds under investigation and our decision-making is not bound by contractual agreements with other institutions. Through this approach, we maintain control of the programme and can commit a greater amount of time and resources to rapidly move the compound through clinical development.

Because we are treating patients with drugs developed within MD Anderson, we are now about as close as we can get to developing a drug at the bedside, conducting real-time assessments of the drug's effects on a tumour in patient-derived material, such as patient-derived xenografts and *ex vivo* organo-typic cultures. Leveraging patient-centric translational research catalyses knowledge transfer to the clinic to further refine our patient-stratification strategies for our new therapeutics.

A major milestone

One of our first successes using this approach is the compound IACS-10759, a small-molecule inhibitor of oxidative phosphorylation (OXPHOS). With the wealth of clinical data available to us at MD Anderson, we were able to identify OXPHOS as a critical, but often overlooked, tumour vulnerability in many cancer patients. Although the study of metabolic reprogramming in cancer is not new, much of the recent focus has been on upregulation of glycolysis. It is now becoming clear that OXPHOS is also upregulated in certain tumour types, such as lymphoma and leukaemia, which rely on use of the electron transport chain to sustain bioenergetic and biosynthetic processes[5]. Additionally, multiple solid tumours either are hardwired to depend on OXPHOS for their energetic needs, or they upregulate OXPHOS as a resistance mechanism to other therapeutic treatments. When we saw a need in our patients for therapies that combat tumours driven by OXPHOS, we were able to move quickly and decisively.

IACS-10759 is the first small-molecule drug to

Table 1: Lessons from MD Anderson Therapeutics Discovery

Focus on your patients; they are your shareholders and their survival is your bottom line
Prioritise intimacy and immediacy, breaking down silos between clinicians, researchers and patients
Start with the bench at the bedside, with each patient and their cancer
Foster an environment that encourages collaboration across teams and disciplines
Bring in professionals who have a multifaceted understanding of drug development
You never know where the next breakthrough idea is coming from; be prepared to invest time in exploring ideas from potential collaborators
Clarify the drug discovery process to potential collaborators; explain why rigorous target validation is required and why certain experiments are defined as go/no-go experiments
Assemble the best team to make projects successful and bring in additional external collaborators/partners if resources are required
Develop a 'ruthless' mindset when it comes to culling less-promising agents in development
Be open to a change of course along a project's development path; a programme might have more clinical impact elsewhere
Every programme needs a champion(s)
Aim for therapeutic targets that improve patient care rather than the bottom line
Although conducting research and clinical trials in-house has marked benefits for drug development, leverage external capabilities with CROs and CMOs when needed to improve efficiency

be developed from concept to clinical trial by the Therapeutics Discovery division, advancing to the clinical setting within 18 months of its identification. It is the product of an extensive medicinal chemistry campaign of lead optimisation to engineer in the molecule all the properties required to make it effective for use in humans. We have recently published the results from initial preclinical studies of IACS-10759 showing that, in models of AML and brain cancer dependent on OXPHOS, this agent reduces tumour growth through inhibition of cellular proliferation and induction of apoptosis at well-tolerated doses[6]. In another preclinical study by Lissanu Deribe and colleagues, IACS-10759 was demonstrated to have benefit in types of lung cancer characterised by mutations in the SMARCA4 gene[7]. Cancer cells with this mutation show an increase in respiratory capacity and oxygen consumption, increasing their vulnerability attack by agents such as IACS-10759 that inhibit OXPHOS. IACS-10759 has now advanced to Phase I clinical trials in relapsed/refractory AML, supported by the Leukemia and Lymphoma Society, and in solid tumours.

Summary of lessons we have learned

Many of the lessons we have learned about drug development are summarised in **Table 1**. It should be noted that some of these lessons are not translatable to pharmaceutical companies guided by a shareholder model of corporate governance, nor can they be easily implemented at smaller academic centres lacking the advantages of scale of major cancer centres such as MD Anderson. Above all else, we have learned that a patient-guided approach must underlie all that we do, starting with identifying the most compelling patient needs at our centre and working in close proximity to our patients to continually improve drug development. Aligned with this approach of breaking down walls between healthcare professionals and patients is the urgency of removing silos between clinicians and researchers that have historically hindered drug development.

Because the Therapeutics Discovery division at MD Anderson is not driven by profits, we are able to focus less on drugs that improve the bottom line and more on those that improve patient outcomes, including in patients with rare tumour types that

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would fly under the radar of other institutions. An important message for smaller cancer centres and community physicians is that if one of their patients seems to be out of treatment options, it is worthwhile consulting with the nearest comprehensive cancer center, such as MD Anderson, for additional assistance before considering hospice care. We often have multiple clinical trials underway for patients with refractory or relapsed disease, and we hope to make more physicians aware of the potentially-beneficial therapeutic agents available to their patients through enrolment in these studies. Enrolment in clinical trials is not only beneficial for patients but clinical research as a whole. We believe that if other centres prioritised clinical trial enrolment to the same extent as MD Anderson, we could drive clinical research forward much more rapidly and efficiently than we do today.

Breaking down walls with new collaborations

Our approach to drug development already has captured the attention of pharmaceutical companies, leading to beneficial collaborations that continue to bring the bench and bedside closer. Many of the programmes developed by Therapeutics Discovery are already partnered with biopharma companies, including GlaxoSmithKline, Astellas Pharma and Ipsen, while others have attracted the attention of venture capital investors to provide additional funding to accelerate the programmes. For instance, at MD Anderson we are collaborating with BridgeBio Pharma and have created a new company called Navire Pharma, with the primary aim of developing drugs that inhibit a tyrosine-protein phosphatase called SHP2. This phosphatase provides an important link to the RAS/ERK MAPK pathway involved in cellular proliferation and survival; excessive activation of this pathway has been found to contribute to many forms of cancer as well as resistance to targeted therapies.

It is important to remember as well that many cancer patients need more than just treatments to reduce or eradicate their tumours; they also need therapeutic approaches that can help alleviate the side effects of therapy and improve their quality of life. To this end, MD Anderson has partnered with Accelerator Life Science Partners to launch Magnolia Neurosciences Corporation. Using research from Therapeutics Discovery, this company will develop medicine to treat neurological problems that patients may experience after undergoing chemotherapy, such as 'chemobrain' (a condition associated with memory loss and general cognitive problems) and peripheral neuropathy.

Conclusion

Clinical development of cancer drugs remains a costly and time-consuming process. We believe that many of the improvements in this process made by the Therapeutics Discovery division at MD Anderson over the past several years – above all else, answering only to our patients – represent key building blocks in the long-term goal of eradicating cancer and improving the lives of patients worldwide. DDW

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