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EDITORIAL

Emerging therapeutic aspects in oncology

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Cancer remains a peculiarly stubborn disease to treat. Some forms of cancer have seen tremendous advances in the effectiveness of their treatments, whereas other forms have remained resistant to pharmacological control. This lack of hope for success is in part due to the types of drugs that are used in the clinic, and the targeted biological system being based purely on cellular growth rates. However, recent drugs designed to affect specific signalling pathways or proteins have been showing much success. Thanks to the ingenuity of pharmacologists in understanding and targeting these processes, there have been real improvements in treatment. Here we are presented with some of the research into such critical systems that have to be understood, so that they can be conquered. We will also look at the challenges facing cancer pharmacologists and what the field may present to us all in the future.

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Basis of chemotherapy

'Dad, how do antibiotics work?' My wife groans, as she knows my 9-year-old daughter has just asked a question that will clear the dinner table fast. 'Well, sweetheart', I begin, 'a bacterial cell wall has different chemicals in its body, that allow antibiotics to inhibit the bug from making more of its cell membranes, which it needs to grow'. 'And importantly', I continue, getting into my stride, 'humans don't have those same chemicals in their cell membranes, so antibiotics are much less poisonous to us, but will kill bugs dead! When the doctor gives us antibiotics, our cells still grow with them, but bugs' cells can't'. All five of them are disappearing fast now, so I bring out the big guns, the utterly memorable take-home message they'll all remember for the rest of their lives: 'antibiotics are poisonous to humans and bugs, but just a bit more poisonous to bugs'. At this point I'm talking to the dog who is the only other animal in the room, and all she cares about are scraps of food. However boring these answers are to children (and dogs), I have effectively described the basis of cancer chemotherapy over the last century.

There are only three treatments that can be used for cancer patients: surgery, radiotherapy and drugs. As can be seen from Table 1, before the 1940s and before radiotherapy was possible, if your tumour surgery failed, then as a cancer patient, your fate was in the hands of whatever drugs your physician had even heard about, never mind what agents they had at their disposal. Much of the cancer research and chemotherapy testing in the early 20th century was based on administering a range of toxic compounds to the cancer patient, then waiting to see what (if anything) happened. Many of these early trials were not successful, with effects of toxic compounds on seriously ill patients having variable effects, as we can imagine. However, there was some good pioneering science (Nicholls, 1936) that paved the way for scientists to systematically identify and develop cytotoxic agents that could be just tolerated by cancer patients, but with significantly greater toxicity towards their tumours.

Dawn of cancer therapeutics

As with the antibiotics, these 'new age' chemotherapeutic agents were slightly more toxic to cancer cells than they were to our normal cells. And just like antibiotics, some of them were actually antibiotics. From the mustard gas-based agents that emerged from the experiences in the two World Wars, to the antimetabolites, there was a range of compounds that were remarkably able to treat cancers in most patients with some success. Most of the notable successes were in the treatment of blood cancers, such as leukaemia, lymphomas and myeloma, with solid tumours being less susceptible to these

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Table 1

The development of cancer therapies

	Cancer is a major cause of death. Over 22 million people suffer worldwide and there are over 6 million deaths per year. In many cases there are no effective treatments.
Pre-18th century	Cancer is a death sentence, medically untreatable. Often not classified as cancer.
Eighteenth century	Certain cancers treatable by surgery. Cancer as a definition of a type of disease is improving.
Nineteenth century	Development of anaesthesia means radical, surgical solutions become more mainstream. Mastectomy developed. Excision of specific localized tumours more possible, improving survival rates.
Twentieth century	Surgeons become more skilled in excision of tumours. Bone and soft tissue operations developed, often avoiding amputation. Definition of cancer types and subtypes improves. William Blair-Bell treats breast cancer patients with colloidal lead.
1940s	The field of chemotherapy born following an accident where mustard gas, a chemical weapon used throughout World Wars I and II, is discovered to lower white blood cell counts. Louis Goodman and Alfred Gilman Sr (father of the Nobel Prize-winning Alfred Gilman) begin to test nitrogen mustard gas-like compounds on lymphoma patients, with apparent success. Sidney Farber tests antifolates, such as methotrexate, on childhood leukaemia patients with success.
1950s onwards	Jane Cooke Wright uses the antifolate methotrexate in the treatment of a solid tumour type in breast cancer patients. Expansion of the arsenal of cancer chemotherapeutics when drug screening identifies the *Vinca* alkaloids (from the Madagascar periwinkle) as useful agents. As found with microbes, cytotoxic antibiotics (e.g. doxorubicin) are more toxic to cancer cells than to normal non-cancerous cells. Serendipity favours the discovery of platinum-containing chemicals (cisplatin, carboplatin), as bacteria growing around platinum electrodes grow but have no cell division. Combination therapy (combining several chemotherapeutic agents to improve cancer treatments) is refined – this refining of a combination of drugs to reduce patient morbidity rates, is continuously being trialled, and has led to vast improvements in cancer survival rates over the years.
1980s onwards	Significant advances in conventional treatments – surgery, radiotherapy, hormone therapy and chemotherapy. The use of computers improves not only the machines used in the clinic, but the machines and software used to research cancer treatment discoveries, leading to faster assessments of potential breakthroughs. Taxane microtubule poisons (e.g. taxol) isolated from the bark of the Pacific Yew tree, are found to be significantly effective in ovarian cancer. Steroid hormone antagonists (e.g. tamoxifen) are developed and used to treat oestrogen receptor-positive breast cancer patients.
2000s	Some cancers – testicular, prostate, ovarian, endometrial and breast – become more treatable with more selective anti-hormone medicines such as aromatase inhibitors, gonadotrophin analogues, anti-androgens and improving anti-oestrogen drugs. Hormone-sensitive cancers are better treated with these newer agents. *Rational Drug Design*: Nicholas Lydon and Brian Druker took a more rational approach to designing an inhibitor of the Bcr-Abl Philadelphia chromosome found in CML. Their drug, Gleevec, was effective in those patients and its use has improved survival rates in CML cancer patients from 50 to 95% of all cases. This design of a more specifically targeted drug has encouraged the development of many similar agents aimed at more specific subtypes of cancers. *Stem Cell Transplants*: Autologous- (from self) or allogenic- (from a healthy donor) transplants of haematopoietic stem cells from bone marrow, greatly improves survival chances of many patients with blood cancers that do not respond well to conventional chemotherapies.
2010s	Success in the removal of primary tumours. Hormone therapies increasingly promising. Treatments such as chemotherapy and radiotherapy still have chronic side effects, but improvements are sought in the co-administration of drugs to improve the management of unwanted side-effects. *TKIs*: The success of Gleevec, an inhibitor of the Abelson tyrosine kinase, leads to a rapid expansion of knowledge of the effectiveness of TKIs in certain types of cancers. Because of the widespread nature of tyrosine phosphorylation, many of the side-effects of these drugs can be extreme. Inhibitors designed against growth factor receptors (EGF, FGF, PDGF, VEGF) prove useful in the clinic. Much of the success comes through refinement of the use of these agents in combination therapies. *Biological agents*: The use of 'humanized' monoclonal antibodies against TNF was hugely successful in treating of inflammatory diseases such as rheumatoid arthritis. The synthesis of 'humanized' monoclonal antibodies such as Herceptin (against the HER2 protein found in many breast cancer cases) or Rituximab (against the CD20 found in non-Hodgkin's lymphoma cases) revolutionize the treatment of those types of cancer, with morbidity rates falling dramatically after their introduction.
Today	The race to understand cancer, improve diagnosis and genotyping, as well as developing more selective and effective pharmacological treatments continues. A combination of clinical, genomic, and proteomic data may herald a new era of smart pharmacogenomics, where treatments are more targeted towards the individual subtype or phenotype of cancer that you have. Virtually all cancers have improved their overall survival rates as a result of these treatments. Some cancers (such as testicular cancer and CML) are nearly 100% 'curable'; whereas other cancers such as Hodgkin's lymphoma and childhood leukaemia, which were previously universally fatal, now have markedly better odds of survival, because of these improvements in treatment.
Tomorrow	The refining of cryosurgery – using liquid nitrogen to freeze, lasers to cut and vaporize cancers – and radiofrequency to heat cancer cells into submission. Better genotyping and proteomic methods for smarter screening of cancer subtypes. Personalized medicine with tumour cell genomic sequencing to define the exact drugs needed for each individual patient's disease. Development of more targeted therapies (nanotechnology) with fewer side effects. Increased use of monoclonal antibodies as immunoconjugates or radio-labelled immunoconjugates, or glycoconjugates to target specific cancer cells to improve the selective delivery of the cytotoxic payloads, only to the cancer cells. Keyhole surgery has saved the lives of many who could not survive the trauma of major surgery and, similarly, robotic surgery will allow effective excision of tumours with less surgical trauma.

Table 2

Some examples of recent, specifically targeted drugs used for cancer. Note that currently there are over 300 mAb-based potential therapeutic agents

Name	Target	Comment
Monoclonal antibodies		
Alemtuzumab	CD52	Mature B-cells (CLL), B-cell CLL
Belimumab	BAFF/BLyS	B-cell hyperactivity disorders/systemic lupus erythematosus
Bevacizumab	VEGF-A	Angiogenesis inhibitor
Catumaxomab	EpCAM	Tumour marker
Cetuximab, panitumumab	EGFR/ErbB/HER1	Colorectal cancer
Daratumumab	CD38	Multiple myeloma
Dupilumab	IL-4 receptor α-subunit	Asthma
Elotuzumab	CS-1	Myeloma
Gemtuzumab	CD33	Multi-lineage B-cells (AML).
Infliximab, adalimumab	TNF	Autoimmune diseases, e.g. rheumatoid arthritis, Crohn's disease, anklyosing spondylitis.
Ipilimumab	CTLA-4	Melanoma
MPDL320A	PD-1 ligand (CD274)	Kidney, lung, colorectal, gastric cancers
Nivolumab lambrolizumab	PD-1 receptor (CD279)	NSCLC, renal cell carcinoma, melanoma
Ramucirumab	VEGFR-2	Anti-angiogenesis, colon cancer
Rituximab, ibritumomab obinutuzumab	CD20. Yttrium-90/indium-111-labelled, glycosylation-engineered variants	Lymphoid B-cells (non-Hodgkin's lymphoma), CLL, diffuse large B-cell lymphoma
Trastuzumab tositumomab	HER2/neu receptor	Breast cancer
Tyrosine kinase small molecule inhibitors		
Axitinib	PDGFR/VEGFR/c-kit	Renal cell carcinoma
Bosutinib	Src	Leukaemia
Brivanib	VEGF and FGF	Colon cancer
Crizotinib, LDK378	ALK, ROS1	Anaplastic large cell lymphoma, non-small cell lung carcinoma, neuroblastoma,
Erlotinib, gefitinib	EGFR/ErbB/HER1	NSCLC
Ibrutinib	BTK	CLL, multiple myeloma, lymphomas
Imatinib, nilotinib	BCR-Abl	CML
Lapatinib	HER2/neu	Breast cancer
Lestaurtinib	FLT3, JAK2, TrkA/B/C	AML, myeloproliferative disorders
Ruxolitinib	JAK 1 and 2	JAK2 V617F MDS, AML, for polycythemia vera, myelofibrosis
Sorafenib	Raf kinases/PDGFR/VEGFR	Renal cell carcinoma, hepatocellular carcinoma
Vandetanib	VEGFR	
Vemurafenib, regorafenib	BRAF	Melanoma, colon cancer
Other		
Abiraterone	CYP17	Castration-resistant prostate cancer
Aflibercept	VEGF-A/B, placental growth factor	Fusion protein for colorectal cancer and macular degeneration
BIND-014	Prostate-specific membrane antigen	Docetaxel loaded nanoparticle for treatment of prostate, lung and bladder cancers
Bortezomib	Proteasome inhibitor	Multiple myeloma
Enzalutamide	Androgen receptor antagonist	Prostate cancer
Etanercept	TNF	TNFR2–TNFR2 fusion protein
Idelalisib	PI-3-Kδ	CLL, non-Hodgkin's lymphoma
Omacetaxine	Proteasome inhibitor	Imatinib-resistant T315I mutant BCR-Abl CML
Palbociclib	Cyclin-dependent kinases –4 and –6	Breast cancer
Perifosine	Akt and JNK pathways	
Talimogene laherparepvec	Oncolytic virus	Melanoma
Vismodegib	Sonic Hedgehog pathway	Basal cell carcinomas

ALK, anaplastic lymphoma kinase; AML, acute myeloid leukaemia; BAFF, B cell activating factor; BLyS, B lymphocyte stimulator; BTK, Bruton's tyrosine kinase; CLL, chronic lymphocytic leukaemia; CML, chronic myeloid leukaemia; CS-1, CD2 subset-1; CTLA, cytotoxic T lymphocyte antigen; DLBCL, diffuse large B-cell lymphoma; EpCAM, epithelial cell adhesion molecule; ErbB, epidermal growth factor receptor; FGF, fibroblast growth factor; FLT, Fms-like tyrosine kinase; HER, human epidermal growth factor receptor; JAK, Janus-activated kinase; JNK, c-Jun N-terminal- kinase; MDS, myelodysplastic syndrome; NSCLC, non-small cell lung cancer; PD, programmed cell death protein; PDGFR, platelet-derived growth factor receptor; PI-3-K, phosphatidylinositol-3-kinase; ROS1, c-ros oncogene 1; VEGFR, vascular endothelial growth factor receptor.

agents. Breast cancer was once again at the forefront of early chemotherapy towards solid tumours. It is interesting that these cancer types are again showing the greatest success in cancer research.

One outcome was clear from these range of compounds that constituted the entire arsenal for cancer therapy – although they may have had different molecular mechanisms of action, their cellular basis of action was to kill the rapidly dividing cancer cells rather than their slower-growing, non-cancerous counterparts. And for many decades, the pharmaceutical industry tried in vain to generate more targeted 'magic bullets'.

Targeted design

Brian Druker is credited with the dawn of rational drug design in pharmacology. His drug imatinib was certainly at the forefront of drug design in this new shiny era in pharmacology. Anything was possible. It is fortunate that this tyrosine kinase inhibitor (TKI) has good selectivity towards the Abelson TK, and also towards the BCR-Abl (breakpoint cluster region-Abelson chimaera or the Philadelphia chromosome or translocation t (9;22)(q34.1;q11.2)) chimeric TK of the Philadelphia chromosome found in many chronic myeloid leukaemia (CML) patients. This 'wonder drug' has sustained the majority of CML patients, turning the diagnosis from a death sentence 20 years ago into something to live with. Now, many of the challenges in this form of cancer are about the best way to treat those who are resistant to imatinib (Heasman *et al*. 2011).

This drug did infuse a new vigour into the pharmaceutical industry. If their TKI can work, maybe we can tailor our TKI into something effective too. Indeed, a significant part of the recent advances in oncology therapeutics has been just such refinement of TKI use (Table 2). The invention of humanized anti-TNG-α monoclonal antibodies (mAb) revolutionized the treatment of autoimmune diseases, especially rheumatoid arthritis. This success also encouraged industry to pursue the mAb approach and come up with rituximab for the treatment of non-Hodgkin's lymphoma (to which my mother-in-law owes her longevity). It is now pleasing to see the development of a wide range of mAbs that are increasingly used in the treatment of an equally wide range of cancer types (Table 2). As well as the more traditional small-molecule inhibitors, many of these cancer agents are mAbs, radiolabelled-mAbs, or chimeric proteins. Other exciting cancer agents include oncolytic viruses, or even nanoparticles loaded with chemotherapeutic agents. Both these types of therapy are able to direct the drug to more selectively to cancer cells and thus to deliver more effectively their payload of cytotoxic chemicals. As well as improvements in drug delivery systems, it should also be noted that much of the recent improvements in the treatment of cancers and in survival rates has come about by clinical trials to refine such therapies used either as monotherapies at various doses, or used in combination therapy. Although we are heading in the right direction, as summarized in Table 3, the overall success of these cancer drugs is dwarfed by many more treatments for much less life-threatening conditions.

Challenges

As shown by some of the reviews in this issue, there are still many challenges within oncology. For example, targeting the

Table 3

The top selling drugs of 2012

Rank	Name	Trade name	Target	Treating
1	Adalimumab	Humira	TNFα	Rheumatoid arthritis
2	Etanercept	Enbrel	TNFα	Rheumatoid arthritis
3	Fluticasone/salmeterol	Advair/Seretide	Glucocorticoid and β_2-adrenoceptor	Asthma
4	Infliximab	Remicade	TNFα	Rheumatoid arthritis
5	***Rituximab***	***Rituxan***	***CD20 mAb***	***Non-Hodgkin's lymphoma***
6	Rosuvastatin	Crestor	HMG-CoA reductase (inhibitor)	Atherosclerosis
7	Insulin glargine	Lantus	Insulin analogue	Type 1 diabetes
8	***Trastuzumab***	***Herceptin***	***Her2/Neu mAb***	***Breast cancer***
9	***Bevacizumab***	***Avastin***	***VEGF-A mAb***	***Tumour angiogenesis***
10	Atorvastatin	Lipitor	HMG-CoA reductase (inhibitor)	Atherosclerosis
11	Aripiprazole	Abilify	D_2/5-HT_{1A} receptor partial agonist	Antipsychotic/ antidepressant
12	Clopidogrel	Plavix	$P2Y_{12}$ receptor antagonist	Antiplatelet/ anticoagulant
13	Duloxetine	Cymbalta	Serotonin/noradrenaline re-uptake inhibitorl	Antidepressant/ anti-anxiety
14	***Imatinib***	***Gleevec***	***BCR-Abl tyrosine kinase***	***Philadelphia Chromosome positive CML***
15	Tiotropium	Spiriva	M_3 receptor antagonist	Asthma/COPD

Cancer drugs are in bold and italics.

stem cells is necessary to eradicate the cancer (Piccoli *et al.*, 2013). Cell maintenance and conditioning may require other cytokine co-factors that could be pharmacological targets of synthetic or naturally occurring compounds (Aggarwal *et al.*, 2013). Also a cancer stem cell may not behave the same in its native microenvironment (Sinclair *et al.*, 2013) as it would *in vitro*. Much of the way in which we attempt to treat cancers may require simultaneous targeting of several pathways to defeat the overlapping resistance mechanisms that can be created in tumours (Sale and Cook, 2013). We may also have to utilize nature's own attack systems, such as the death receptors (Micheau *et al.*, 2013) that belong to the TNF receptor superfamily (MacEwan, 2002). Cancer researchers may also need to look towards the death mechanisms within cells, given that no matter how a cell creates a cancerous phenotype, there are only a handful of ways that the cell can be killed (Kvinlaug *et al.*, 2011). Furthermore, there may be an absolute need to block the cancer cell's own repair mechanisms (Curtin, 2013) for therapy to be fully effective.

As can be seen from this issue, there is still a lot of work that needs to be done to understand the biology of each individual type of cancer. In this regard, patient-specific genomic sequencing of tumour biopsies is likely and this information will be translated into a personalized drug regime for each patient. The question is, do we have the right drugs to cope with such an ideal approach to treatment? Many questions remain to be solved. For example, one of the most successful cancer drugs in trial is ibrutinib, an inhibitor of Bruton's TK (BTK), in the treatment of B cell blood cancers (MacEwan *et al.*, 2013). The clinical success of this drug is clear. What is less clear is what makes this compound such a successful candidate with limited side effects, relative to other similar chemotherapeutic agents. It may be related to its physicochemical properties, affecting its pharmacodistribution and thus limiting adverse reactions to the drug in the body. It may be related to the selectivity of the BTK-signalling machinery in cellular processes such as apoptosis, adhesion, doubling time, differentiation or even platelet aggregation. Whatever the reason, this drug, along with the other successes outlined here, are a source of optimism for the eventual control and eradication of cancer. And with good science, we will prevail. To finish with my earlier analogy – unlike antibiotics, with cancer drugs, there have been enormous advances made over the last century. Long may it continue.

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