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REVIEW

The road to precision cancer therapy – history and strategies

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Summary: Human cancer has been recognized for thousands of years as a leading cause of death with complex pathophysiology and remains as the most challenging disease to achieve curative therapy. Selecting the right treatment for cancer patients based on molecular diagnostics continues to evolve. Recent explosion in the knowledge of molecular genetics, epigenomics, cellular biology and immunology of cancer has influenced the development of targeted therapies for specific tumour types as well as for the individual patients. Chemotherapy has remained as the backbone of cancer therapy, but limited response rates, side effects and resistance have increasingly shifted the focus on approaches to harness targeted therapy directed to specific molecular alterations at the intracellular genomic and epigenomic levels and the microenvironment which includes extracellular regulatory molecules and surrounding cells. Immunotherapies are designed to interfere with the immune escape mechanisms of cancer cells such as negative immunologic regulators (checkpoints) and/or by stimulating the patient's adaptive immune system against specific tumour antigens. Inherent complexity and heterogeneity of tumours as depicted by the multi-modular molecular network (MMMN) cancer progression model suggest that most cancers may not be treatable with just monotherapy and would require a combination of therapies, both traditional and targeted therapies as well as immunotherapies to lengthen the patients' life. The availability of novel technologies and generation of large-scale oncology data from multiple sources of analysis including genomics has created a promising environment for revolutionizing cancer diagnosis, drug discovery, treatment and prevention. Advanced computational algorithms are currently being developed for automatically interpreting input data to assist inter-professional teams to provide calibrated recommendations with minimal toxicities to help the physicians to make effective therapeutic decisions.

Keywords: Artificial intelligence (AI), computational algorithms, genome, multi-modular molecular network (MMMN), oncogenes, precision cancer therapy, targeted cancer therapy, tumour suppressor genes.

History of cancer therapy

Human cancer has been described as early as 2500 to 1500 BC in ancient Egyptian papyri and hieroglyphic inscriptions referring to the soft tissue and fatty tumours involving the skin, breast, stomach, rectum and uterus. Egyptians made attempts to treat the cancer patients using surgery, religion and magic/charm. They also differentiated benign as well as malignant tumours and found limited success with surgical resection of surface tumours while acknowledging lack of curative therapy (American Cancer Society; National Cancer Institute). The great Greek physician Hippocrates (460-360BC) who is considered as the father of medicine, first referred to cancers as karkinoma (Carcinoma) as it looked like karkinos (Greek for crab) because of the swollen blood vessels around the central body/lump resembling the claws and legs of a crab. Hippocrates promoted the belief that an imbalance of the main four body fluids or humors (blood, phlegm, yellow bile and black bile) caused diseases. He suggested the overrepresentation of black bile in the flesh as the cause and suggested diet, rest, and exercise to address this imbalance. He advocated surgery if the carcinoma was on the surface and not too deep. The most prominent successor of Hippocrates was Claudius Galen (AD 130 to 200). He used the word oncos (Greek for mass or swelling) to describe tumours, which resulted in the term for studying and treating cancer, oncology (Papavramidou *et al*., 2010). Galen considered that the patients are incurable after a diagnosis of cancer; however, he did write about surgical cures for breast cancer if it could be completely removed at an early stage. For many centuries, while there was progress in medicine, there was little progress in the treatment of cancer and surgery

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remained as the mainstay despite being primitive with many complications, including blood loss, infection, and death. It was not until the 19th and early 20th centuries that significant advances were made in general surgery and cancer surgery as well as from the development of better microscopes enabling the study of cancer tissues to reveal that cancer cells to be markedly different in morphology from the normal surrounding cells from which they originated. In 1838, German pathologist Johannes Müller demonstrated that cancer is made up of cells and not lymph but did not believe it came from normal cells. In 1855, Rudolf Virchow, a student of Johannes Müller, coined his now famous aphorism, omnis cellula e cellula (every cell stems from another cell) and launched the field of cellular pathology and known as the father of cellular pathology. He correlated the clinical course of illness with microscopic pathology findings following surgery and provided the scientific basis for cancer diagnosis and metastatic spread (Tulbah *et al*., 2014).

The American surgeon William Halsted at Johns Hopkins pioneered radical cancer operations in 1894, attempting to outpace tumour growth by more and more extreme removal of tissue, but recurrence indicated that some of the tumour cells have spread. Halsted developed the radical mastectomy, a surgery that removed not only the breast, but also the underlying muscles and nearby lymph nodes, and was the most effective treatment for breast cancer for decades. While radical surgery left many patients disfigured, it also left a legacy. One of Halsted's students at Johns Hopkins Hospital in Baltimore, Hugh Young, under his guidance focused on urological cancers and developed radical prostatectomy, the removal of the prostate gland which cured many men with prostate cancer. Surgery remained as the mainstay of the treatment of solid cancers, until it was joined by radiation and drugs (Tulbah *et al*., 2014).

Radiation kills both healthy as well as cancer cells, but because cancer cells divide faster, it was easy to kill them at higher rate by X-rays. Radiation therapy was pioneered in 1896 by a medical student, Emil Grubbe, without knowing how the treatment worked but now we know it breaks the DNA present in every cell and blocks cell division which subsequently results in cell death. While radiation therapy was believed to be an absolute cure for all forms of cancer, it was soon realized it is only a localized therapy and couldn't be used to treat cancers that have already spread. Additionally, it caused collateral damage to healthy cells and often leading to fresh cancers. Apparently, Grubbe also died of cancers caused by his experiments.

The search for a therapy that in principle can seek out cancer cells wherever in the body even after they have spread was chemotherapy. The era of chemotherapy began with the approval of nitrogen mustard, a poison gas from the First World War that caused destruction of lymphocytes – white blood cells of the soldiers exposed to it was rechristened as mustine, the first licensed chemotherapy agent approved in 1949 by the US Food and Drug Administration to treat lymphoma, a tumour of the lymph system. After this initial success, more chemotherapeutic drugs appeared in rapid succession based on biological insight as well as derived from pure guesswork. In 1947, Sidney Farber at Boston Children's Hospital inspired by the work of British hematologist Lucy Wills's use of Marmite, which is rich in folic acid, a key precursor for DNA synthesis used for treating some forms of anemia, as a potential drug to treat childhood leukemia. When it turned out to be ineffective in treating childhood leukaemia, Sidney Farber decided to try an antifolate drug, aminopterin, the precursor to methotrexate, and found that it caused remissions of leukemia in some patients. This remains as one of the greatest triumphs ever achieved by chemotherapy. Major improvements to cancer therapy were achieved by combining surgery with chemotherapeutic drugs – adjuvant therapy. Because most standard chemotherapies act on all rapidly dividing normal and cancerous cells, improvements were achieved by switching from non-specific brute force to specific targeted interventions that disable or block processes that promote the rapid growth, division and spreading of cancer cells. Prominent successful early targeted therapies include, therapeutic monoclonal antibodies such as trastuzumab (Herceptin) for breast cancer, imatinib (Glivec), a competitive inhibitor of the ATP-binding site of the tyrosine kinase, which prevents substrate phosphorylation, used for treating chronic myeloid leukaemia, and certuximab (Erbitux), a recombinant human/mouse chimeric monoclonal antibody, an inhibitor that binds to the extracellular domain of epidermal-growth-factor receptor (EGFR), used in the treatment of head and neck, lung and colorectal cancers (Arteaga & Baselga, 2012). While classical immunotherapy is considered as the fourth kind of cancer therapy, together with surgery, chemotherapy, and radiotherapy, despite its existence for a long time, it only became very popular due to the recent advances that target the immune checkpoint pathways.

Cancer genome, epigenome and cancer genes

Cancer cells manifest their functional properties due to genetic and epigenetic make ups which continue to evolve. The cancer genome is defined by the 3 billion

base pairs of haploid DNA sequence and the sequence variations at a frequency of less than 1% in a population are arbitrarily designated as mutations and those at a higher frequency are referred to as polymorphisms. DNA polymorphisms are primarily assessed by single nucleotide polymorphisms (SNPs) and are the most abundant form of human genetic variation (~10^7) which can be effectively assayed using comprehensive high throughput technologies such as the microarray profiling or simply by using next generation sequencing (NGS) strategies. On the other hand, reversible epigenetic changes consisting of various epigenetic marks are represented by collection of gene specific DNA methylation patterns, unique combinations of post-translational modifications of histones, polycomb group (PcG) proteins, transcription factors and non-coding RNAs/regulatory RNAs [e.g., miRNA (microRNA), lincRNA (large intergenic non-coding RNA) etc.] affecting the mRNA content, define the overall epigenome, which ultimately determines differential gene expression patterns under normal conditions as well as in cancer.

Cancer is a consequence of hyperactivity of growth promoting genes (i.e., oncogenes) which elicit their effect by gain of function and the inactivity of growth constraining genes (i.e., tumour suppressor genes) that manifest their effect due to loss of function. Inherited gene alterations are classified based on their contribution to cancer progression. Alterations in the high penetrance genes (e.g., *APC, p53, BRCA1, BRCA2*) exhibit dominant inheritance of susceptibility and corresponds to two-fold increase in cancer in first-degree relatives and are also known as genes that cause familial cancer syndromes. On the other hand, low penetrance genes (e.g., *CYP, IGF1, UGT1A7, GST*) are represented by subtle sequence variations or polymorphisms and contribute to small to moderate increase in relative risk of cancer and are relatively common in the general population and hence confer higher attributable risk than high penetrance genes.

Cancer phenotypes are driven by gain-of-function alterations as seen with oncogenes such as the *AKT1*, *ALK*, *BRAF,CTNNB1*, *DDR2*, *EGFR*, *ERBB2*, *FGFR1*, *IDH1*, *IDH2*, *KRAS, MDM2*, *MITF*, *MYC*, *MYCN*, *MYCL1, NKX2.1*, *PIK3CA, REL* and *SOX2* and/or loss-of-function alterations as frequently observed with specific tumour suppressor genes such as the *APC*, *BMPR1A*, *CDH1*, *CDKN2A*, *NF1*, *NF2*, *MAP2K4*, *MLH1*, *MSH2*, *PIK3R1*, *PTEN*, *RB1*, *SMAD4*, *SMARCB1* and *TP53*, mediated by either genetic or epigenetic changes (Thiagalingam, 2006; Leary *et al*., 2010). The gene alterations that provide a selective advantage during the evolution of a tumour are regarded as the 'drivers' while the alterations that are coincidental in their appearance and do not play a role in the cancer progression are termed the 'passengers' (Haber & Settleman, 2007). While, traditionally, genetic changes were regarded as the drivers and epigenetic alterations as passengers, recent evidence suggest that either type of alteration to be passengers or drivers (Sawan *et al*., 2008). It is also noteworthy that not all mutations in the same gene are drivers as exemplified by *APC* mutations in colorectal cancer (Kinzler & Vogelstein, 1996; Vogelstein *et al*., 2013). Furthermore, some driver genes are more frequently mutated and referred to as the 'mountains', while others, despite their importance, are less frequently mutated and are known as the 'hills', thus shaping the landscape of genetic alterations during cancer progression (Wood *et al*., 2007).

Multi-modular molecular networks (MMMN) of cancer progression

Heterogeneity in the genetic and epigenetic alterations of cancers that correspond to the advancing stages of cancer progression including the terminal metastatic stage, has posed major challenge to accurate diagnosis, prognosis and therapeutic efforts. While there has been significant progress in cataloguing the various genomic and epigenomic alterations with the advent of high throughput technologies, streamlining the available and emerging data into a coherent scheme of events depicting the drivers and the modifiers that culminates in localized and metastatic tumours, requires novel strategies (Thiagalingam, 2006). To address this challenge faced by the cancer research community, I proposed a strategy for the formulation of a detailed framework known as a multi-modular molecular network (MMMN) cancer progression model as a road map to dissect the complexity inherent to cancer (Thiagalingam, 2006; 2015; Figure 1). This model predicts that cancer initiation and progression are mediated by dysregulation/inactivation of a series of interconnected functional sub-network modules. By formulating cancer specific models, one can define functional stages of cancer progression to help design biomarker screening tests for effective diagnosis/prognosis as well as development of target specific cancer therapies.

The MMMN cancer progression model defines a cascade of events encompassing multiple targets within each module, in which one or more alternate target gene(s) could alter the functionality of each of the specific module. This provides a molecular basis for the genomic and epigenomic heterogeneity that is observed during the progression of tumors which exhibit similar pathological

characteristics (Figure 1). Furthermore, the absence of consistent alterations in specific gene(s) in sporadic cancers, and in cancers that are primarily induced by environmental effects resulting in neoplastic precursor cells, could be predicted to emerge from inactivation/overactivation of multiple alternate gene targets that act in one or more interconnected axes of events, within a defined sub-network in a module of the global network (Figure 1). The first network module that becomes inactivated leading to the initiation of cancer could be considered as the gatekeeper functional unit (Kinzler & Vogelstein, 1997). The cancer precursor cells harbouring an inactivated gatekeeper module become receptive to additional genomic and epigenomic alterations that occur in interconnected but defined modules of sub-networks through multiple stages, leading to the development of advanced and terminal stages. Therefore, an imaginary frame-work of a succession of modules, the functional inactivation or aberrant hyper-activation of individual network modules occurs in a series of events that advance the tumour from the early to late stages of cancer. Despite the possibility that the overall phenotypic effects elicited by the target tumour or tumour precursor cells could be influenced by the surrounding cells and/or extra-cellular matrix (ECM) components, the genomic and epigenomic and alterations in the resident target cells

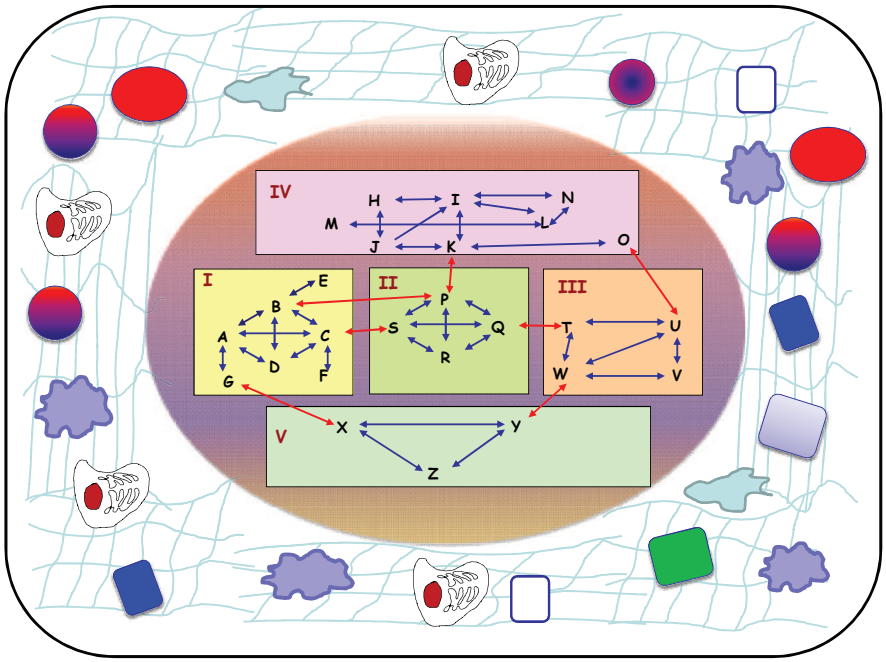

Figure 1: A cascade of aberrant network modules define multi-modular molecular network (MMMN) model for cancer progression

A MMMN cancer progression model predicts that aberrant activations/inactivations of functional modules of networks in a series of steps would be necessary to elicit properties of metastatic cancer. In this model, cancer initiation is mediated by inactivation of the gatekeeper network module (e.g., Module I). We predict that the gatekeeper function is mediated by an interconnecting network of pathways (axes). Dysregulation/inactivation of the gatekeeper module predisposes the cells to become more receptive and susceptible to acquiring additional neolplastic alterations, which occur in a series modular (Modules II, III, IV etc.) inactivations or hyper-activations leading to intermediate and late carcinoma and finally to the metastatic stage. Modules II and III in this model represent the intermediate stages of tumor progression. The terminal module may represent the metastatic stage (module IV). The fact that there could be alternate target genes in any one of the modules of the network could explain why there is often genetic/epigenetic heterogeneity in multi-step cancer progression resulting in similar histologic sub-types of cancer. In this model, the double headed blue and red arrows represent intra- and extra-modular connections, respectively. The alphabetical letters represent specific genes or functional protein-protein and protein-DNA interactions that are nodal points/driver alterations in each network. While the modular organization depicted inside the inner oval represents the alterations within the target tumour cells, the web structures that represent the extracellular matrix and the surrounding stromal cells constitute the tumour microenvironment. Reprinted from the book chapter by Thiagalingam (2015), copyright (2015), with permission from Cambridge University Press.

remains as a pre-requisite for the effects caused by the microenvironment and surrounding stromal and immune cells (Joyce & Pollard, 2009; Taddei *et al*., 2013). It is also noteworthy that overlaps in the functional contributions of the specific gene alterations may be responsible for simultaneous dysregulation of different modules of cancer progression. While any alteration is capable of inactivating/dysregulating a specific sub-network module at any time, its effect will be fully realized to manifest the corresponding cancer stage only when the preceding module(s) have also become inactivated/dysregulated. Thus, the rates at which tumour evolution occurs and the time required for the transition from an early to a later stage of cancer will be dependent upon the preexisting genetic and epigenetic alterations (familial or sporadically acquired) and the tumour microenvironment. This notion is also consistent with an accelerated cancer progression when there is a preexisting inherited alteration that corresponds to a specific module as it has been observed with familial cancers.

The development of cancer cells and their expansion are regulated by immune systems (adaptive and innate) in the tumour microenvironment which recognize the abnormal cells as foreign entities even before they become clinically significant due to external stimuli including cytokines like interferon gamma (IFNγ) and remove them to maintain the normal state. Immune surveillance is mediated by T-cells and other immune cells such as NK-cells that are able to recognize new tumour-associated antigens (TAs) such as the mutated proteins when they are bound to self MHC molecules. There is continuous interaction between cancer cells and the immune system, and the cancer cells may develop escape mechanisms due to low level of immunogenicity or suppression of the immune system by immune checkpoint*s* or due to weakening of the immune system due to spreading of cancer to the bone marrow.

Targeted cancer therapy

After decades of conventional anti-cancer treatment strategies using surgery, radiotherapy and chemotherapy, targeted cancer therapies directed to specific components of cancer cells, such as proteins or genes, that help cancers grow and spread have been developed to minimize the collateral damage to normal cells and to enable the therapies reach the maximum number of abnormal affected cells. Targeted therapies may also be directed at the tumour microenvironment consisting of factors such as cytokines as well as other types of cells that help cancer cells to grow and spread. When samples of tissue (e.g., biopsy) and/or bodily fluids (e.g., blood/serum) derived from a specific patient is subjected to genetic (e.g., mutations/gene amplification) or epigenetic (e.g., DNA methylation/histone modifications) testing and cell surface proteins of the tumour cells/immune cells (e.g., PD-1, PDL-1) and/or molecules in the surrounding microenvironment (e.g., cytokines) are identified, the diagnosis is more accurately made to select the safest and most effective treatment. The two main types of targeted therapies employ either small molecules or monoclonal antibodies. Small molecules are small enough to slip inside cancer cells, block the growth signals or enzymes that make the hormones promoting growth in some cancers such as breast and prostate and destroy them. The small molecule drugs often have their generic name ending in "-ib." (Table 1). On the other hand, monoclonal antibodies which are often referred to as biologics are too big to get into cells and they target the outside of cells or right around them. The generic names of monoclonal antibodies end in "-mab." (Table 2). The third type of targeted therapeutic agents are directed to epigenome coders (Table 3, Thiagalingam, 2020). The FDA in the US and other similar bodies in other countries have approved targeted therapies for more than 15 types of cancers, including those of the breast, prostate, colon, and lung. Targeted therapies may work better than other treatments. Companion diagnostic (CDx) tests and companion biomarkers are often used as the companion to a specific drug and are co-developed for selecting or excluding patient groups for treatment based on biological characteristics that prospectively determine responders and non-responders and predict likely toxicity to the therapy (Duffy & Crown, 2013).

Due to inherent complexity and heterogeneity of tumors (Figure 1), some cancers may not be treatable with just monotherapy and may require a combination of therapies, both traditional and targeted therapies to achieve better patient outcomes (Plana *et al*., 2022). Synergistic interaction is also a common explanation for new combinations. For example, the five-drug R-CHOP regimen cures most patients with diffuse large B-cell lymphoma (DLBCL) (Palmer *et al*., 2018). Erlotinib (EGFR inhibitor) and gemcitabine (antimetabolite chemotherapeutic) are used to treat pancreatic cancer. To target pathways, two strategies can be employed: vertical pathway inhibition, targeting several effectors in the same signalling pathway; or horizontal inhibition, to prevent the overactivation of another pathway in response to targeting one. An example of vertical pathway inhibition is the combination of the BRAF and MEK inhibitors, vemurafenib and cobimetinib for the treatment of advanced BRAF-mutated melanoma. Another example

Table 1: Approved small molecule inhibitors and indications

Drug	Drug target	Biomarker	Indications
Alectinib, Brigatinib, Crizotinib	ALK	ALK fusion	Non-small-lung cell carcinoma
Venetoclax	BCL2	c.CHR17p deletion	Chronic myeloid leukaemia, acute myeloid leukaemia
Bosutinib, Dasatinib, Nilotinib, Ponatinib	BCR–ABL	BCR–ABL	Chronic myeloid leukemia
Imatinib	BCR–ABL, ABL1, KIT, PDGFRA, PDGFRB	BCR–ABL, ABL1, KIT, PDGFR fusion	Chronic myeloid leukemia, acute lymphoblastic leukaemia, myelodysplastic and myeloproliferative disease (with *PDGFR* gene re-arrangements)
Vemurafenib	BRAF V600E	BRAF V600E	Melanoma, Erdheim-Chester disease
Dabrafenib	BRAF, RAF1	BRAF V600E	Melanoma, non-small-lung cell carcinoma, anaplastic thyroid cancer
Ibrutinib	BTK, EGFR, FGR, HER2, RET	c.CHR17p deletion	Chronic lymphocytic leukaemia and small lymphocytic lymphoma
Abemaciclib, Palbociclib, Ribociclib	CDK4 and CDK6	ER positive, PR positive, HER2 negative	Breast cancer
Pexidartinib	CSF1R, KIT, FLT3	Tyrosine kinase	Tenosynovial giant cell tumour (TGCT)
Afatinib, Gefitinib, Osimertinib	EGFR	EGFR T90M, EGFR exon 19 deletion,	Non-small-lung cell carcinoma
Erlotinib	EGFR	EGFR L858R, EGFR exon 19 deletion,	Non-small-lung cell carcinoma, pancreatic cancer
Neratinib	EGFR and HER2	HER2 amplification/ overexpression	Breast cancer
Lapatinib	EGFR, HER2, HER4	HER2 positive, ER Positive, PR Positive	Breast cancer
Enasidenib,	IDH2	IDH2 mutation	Acute myeloid leukaemia
Binimetinib, Cobimetinib, Trametinib	MEK1 and MEK2	BRAF V600E, BRAF V600K	Melanoma, non-small-lung cell carcinoma, anaplastic thyroid cancer
Everolimus	mTOR	ER Positive, PR Positive, HER2 negative	Breast cancer, neuroendocrine tumour, renal cell cancer
Tamoxifen	ER	ER positive	Breast cancer
Olaparib	PARP1 and PARP2	Poly (ADP-Ribose) polymerase, BRCA1/ BRCA2 defects	Breast, ovarian, fallopian tube, and primary peritoneal cancers
Talazoparib	PARP1 and PARP2	Poly (ADP-Ribose) polymerase	Breast cancer
Alpelisib	PI3K	Phosphatidylinositol 3-kinase	Breast cancer
Duvelisib, Idelalisib	PI3K	Phosphatidylinositol 3-kinase	Chronic lymphocytic leukemia and small lymphocytic lymphoma, follicular lymphoma
Letrozole	Aromatase	ER positive, PR positive	Breast cancer
Cabozantinib	c-MET, VEGFR, RET	Tyrosine; CMGC; TKL	Medullary thyroid, hepatocellular carcinoma, and renal cell cancer
Regorafenib	VEGFR	VEGFR	Colorectal cancer, Gastrointestinal stromal tumours, hepatocellular carcinoma
Sorafenib	VEGFR	VEGFR	Hepatocellular carcinoma, renal cell cancer, thyroid cancer (iodine refractory, differentiated)
Sunitinib	VEGFR, PDGFR	VEGFR	Gastrointestinal stromal tumours, pancreatic cancer, neuroendocrine tumour, and renal cell cancer

Table 2: Approved and experimental biologics and indications

Biologic	Target	Mechanism of action	Indications
Bevacizumab (Avastin)	VEGF	Neutralizing antibody	Metastatic colorectal cancer, Non-small-lung cell carcinoma, Glioblastoma, metastatic renal carcinoma
Trastuzumab (Herceptin)	HER2	Receptor blocking antibody	Metastatic breast cancer
Cetuximab (Erbitux)	EGFR	Neutralizing antibody	Colorectal, lung, and head and neck cancers.
Alemetuzumab (Lemtrada)	CD52	Triggers CDC and ADCC on CD52+ immune cells to induce cell death	Chronic lymphocytic leukemia
Ofatumumab (Azerra)	CD20	Triggers CDC and ADCC in CD20 overexpressing B cells causing B cell lysis	Chronic lymphocytic leukemia
Nivolumab	PD-1	Blocks PDL-1 from binding to PD-1 receptor on T-cells	Melanoma, Hodgkin lymphoma, Colorectal cancer, Hepatocellular cancer, Non- small-cell lung cancer, Kidney cancer, Squamous cell carcinoma of the head and neck and Urothelial cancer, Bladder cancer
Pembrolizumab	PD-1	Blocks PDL-1 from binding to PD-1 receptor on T-cells	Gastric cancer, Head and neck cancer, Urothelial bladder cancer
Durvalumab, Atezolizumab	PDL-1	Blocks PDL-1 from binding to PD-1 receptor on T-cells	Urothelial cancer, Non- small-cell lung cancer, Metastatic breast cancer
Avelumab	PDL-1	Blocks PDL-1 from binding to PD-1 receptor on T-cells	Advanced Merkel cell carcinoma, urothelial cancer
Ipilimumab	CTL-A4	Blocks CTL A4 and B7 interaction	Melanoma
Relatlimab	LAG-3	Blocks LAG-3	Recurrent glioblastoma

PD-1 (Programmed death receptor-1) /PD-L1 (Programmed death receptor ligand-1) inhibitors or CTLA-4 (Cytotoxic T-lymphocyte associated antigen 4); LAG-3 (Lymphocyte-activation gene 3)

is anti-angiogenesis agents such as the VEGF inhibitor bevacizumab, in combination with FOLFOX [leucovorin calcium (folinic acid), 5-fluorouracil, and oxaliplatin] or IFL regimen (Irinotecan, 5-fluorouracil, leucovorin) based chemotherapy for treating colorectal cancer. For better benefit, the triplet combination of trastuzumab, pertuzumab, and docetaxel (two HER2 antibodies binding to different epitopes and a microtubule inhibitor) may confer greater antitumor activity for treating advanced stages of NSCLC and breast cancer (Baselga *et al*., 2012).

Cancer immunotherapy as targeted therapy has recently become the preferred treatment over others using chemicals as it is based on improving anti-tumor immune responses with little or no off-target effects. Cancer immunotherapies are designed to prime the immune response to make it more efficient. Different classes of immunotherapies include checkpoint inhibitors, lymphocyte activating cytokines, agonists for co-stimulatory receptors, cancer vaccines, oncolytic viruses, bispecific antibodies and T cell-based adoptive immunotherapy, adoptive cellular therapy (ACT) (Farkona *et al*., 2016; Schmidt, 2017). Cancer immunotherapy has recently received a significant boost from the approval of immune checkpoint inhibitors (ICIs), the anti-cytotoxic T lymphocyte associated protein 4 (CTLA-4) antibody and of anti-programmed cell death protein 1 (PD1) antibodies that cause the inhibition of CTLA-4 and PD-1/PD-L1 axis blockade, respectively, to prolong T cell activity and anti-tumoral effects by blocking co-inhibitory molecules binding to their cognate ligands on the surface of cancer cells (Table 2). For example, ICIs such as nivolumab and pembrolizumab have been demonstrated to mount highly durable response rates with minimal toxicity in patients with advanced melanoma, non–small-cell lung cancer, renal cell carcinoma, and other solid tumours. After failure of a platinum-based chemotherapy, high-PD1 expression in recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) tumour cells or associated immune cells showed better overall survival (OS) and progression-free survival (PFS) outcomes for pembrolizumab. Recent data also suggest that the use

of ICIs in combination with the standard chemotherapy regimen improves efficacy of cancer treatment and overall survival (Yan *et al*., 2018; Larroquette *et al*., 2021). For example, PD1/PD-L1 enriched tumours of non-small cell lung cancer (NSCLC) exhibited a potential synergistic effect with treatment combination of pembrolizumab and platinum-based chemotherapy, especially in first-line treatment. Statistically significant improvement in PFS for the pembrolizumab-chemotherapy [nanoparticle albumin-bound paclitaxel (nab-paclitaxel), paclitaxel or carboplatin-gemcitabine] combination compared with placebo-chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (TNBC) was observed. However, a limitation of immune checkpoint inhibitors is that they can cause immune-related adverse events (irAEs), usually related to autoimmunity in a dose-independent manner.

Table 3: Epigenome specific drugs and indications

Drug	Target	Mechanism of action	Indications
5-azacytidine (Vidaza)	DNMT	Nucleoside inhibitors	MDS, CML
Decitabine (Dacogen)			MDS, CTCL, PTCL
Vorinostat (SAHA), Belinostat (Beleodaq)	HDAC	HDAC inhibitors (Hydroxamates)	CTCL, PTCL
Depsipeptide (Romidepsin)		HDAC inhibitor (Cyclic peptide)	CTCL, PTCL
Valporate, Phenyl butyrate		HDAC inhibitor (Fatty acids)	MDS, AML, CLL
Pinometostat (EPZ-5676)	DOT1L	Small molecule inhibitor	MLL-rearranged leukemia
Tazemetostat, GSK126, EPZ6428	EZH2	Small molecule inhibitor	Malignant Rhabdoid Tumors, Lymphoma, Prostate cancer
JQ1, I-BET762, AZD5153, OTX-015, TEN-010, CPI-0610	BET family of BRD proteins	Small molecule competitive inhibitors	MLL-rearranged leukemia, NUT midline carcinoma

AML-acute myeloblastic leukemia; BET- bromodomain (BRD) and extra-terminal family of proteins; CML-chronic myelomonocytic lymphoma; CTCL-cutaneous T-cell lymphoma; DOT1L-disruptor of telomeric silencing-1-like, an exclusive H3K79 methyltransferase; DNMT-DNA methyltransferase, enhancer of zeste homolog 2 (EZH2); HDAC-histone deacetylase; MDS- myelodysplastic syndromes; MLL- mixed lineage leukemia; MM-multiple myeloma; NUT-nuclear protein in testis, p300; PTCL- peripheral T-cell lymphoma

In general, targeted therapies will only work if your tumour continues to harbour the right target and it can also stop working if the target changes as the cancer cells finds a way around the treatment by adapting to parallel or bypass pathways.

Precision cancer therapy

The same cancer type could behave differently from one patient to another, and that there is no one-size-fits-all treatment. Identification of molecular targets at the level of cancer genome, epigenome and the surrounding microenvironment that target the molecular characteristics of an individual's tumour is known as precision cancer therapy (Lee *et al*., 2018; Chen *et al*., 2019). Thus, precision oncology is an approach to diagnosis, treatment and prevention that considers the genes that you're born with (your genetic makeup) and the genes or other markers present within the cancer cells and their microenvironment to personalize therapy. Molecular pathology is playing an instrumental role in driving precision cancer therapy and is increasingly used to guide therapeutic decisions. Some genetic tests are specific to inherited risk, which means they look at your genetic makeup to determine your personal risk of developing cancer in your lifetime. Fundamentally, precision oncology is based upon the idea that tumour biomarkers are predictive of disease phenotype, clinical outcomes, and therapy responses. The emergence of this kind of targeted treatment that uses molecular information to match patients is an exciting moment in the battle against cancer.

The current trend is to identify the fingerprints of the tumours from multiple sources of analysis such as the tumour and cell-free DNA profiling using next-

generation sequencing (NGS) technologies, by taking advantage of other methodologies such as in situ hybridization (ISH), reverse transcriptase-polymerase chain reaction (RT-PCR) and immunohistochemistry (IHC) to reveal immunological, proteomic and RNA markers. While these analyses provide previously unavailable details about a patient's cancer that can point the oncologists towards a specific therapy, it also poses a challenge for the analysis of large amount of data from sequencing imaging, screens, and more that are ingested, transformed, and modelled by top open-source machine learning which require the use of advances in computational algorithms and artificial intelligence (AI) (Chakravarty *et al*., 2017; Xu *et al*., 2020; Shao *et al*., 2022). Thus, finding the next big drug candidate might seem merely a step away by "Entering" a key to provide a match with increased medication efficacy and decreased side effects. Of course, the reality is more convoluted, but still promising. All these novel therapeutics are designed to specifically target cancer cells and should cause fewer side effects. In summary, cancer care is among the first medical specialties to apply precision medicine, but for the precision-oncology dream to be fully realized, the therapies must help more people with cancer than the 5–10% who currently benefit.

Conclusions and perspectives

Cancer is one of the leading causes of death, with an estimated 19.3 million new cancer cases (18.1 million excluding nonmelanoma skin cancer) and almost 10.0 million cancer deaths (9.9 million excluding nonmelanoma skin cancer) occurred in 2020 (Sung *et al*., 2021). Cancer incidence is projected to increase to 27.5 million cases by 2040. In recent decades, cancer medicine has evolved from the traditional approaches that targeted any rapidly proliferating cell to an era of precision cancer therapy, in which therapies are targeted to the specific patient's cancer that minimizes side effects. To improve the implementation of precision cancer therapy, this approach should be used early in the course of the disease, and patients should have complete tumour profiling and access to effectively matched targeted therapy. However, due to difficulty in early diagnosis and because of the complexity of tumour biology, clinical trials with combinations of gene-targeted therapy with immune-targeted approaches (e.g., checkpoint blockade, personalized vaccines and/or chimeric antigen receptor T-cells), hormonal therapy, chemotherapy and/or novel agents are continuously being considered and undertaken in several parts of the world. These approaches will greatly benefit from the ability to formulate MMMN cancer progression models for each cancer and the ability to map the affected network(s) and cancer cell surface proteins, corresponding to each person's tumour biology and the dynamic alterations in abnormalities to eliminate minimal residual disease, as well as eradicate majority of the subclones that confer resistance to treatment.

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