Recent advances that are redefining oncology

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Since President Richard Nixon declared war on cancer more than 40 years ago, there have been significant increases in the number of people who survive cancer. Alongside advances in screening, detection, and diagnosis, the development of targeted anticancer agents has been a major contributory factor to this success. We highlight some of the key developments that have shaped oncological practice in recent decades and those that will likely have a significant impact in the near future (Figure 1).

Top 5 therapeutic developments

Monoclonal antibodies

Monoclonal antibodies (mAbs) are designed to specifically kill cancer cells by targeting tumor-associated antigens on their surface (Table 1). The first drug of this kind to be approved by the Food and Drug Administration (FDA) was rituximab. This anti-CD20 mAb has revolutionized the treatment of B-cell lymphomas (on which the CD20 antigen is expressed), producing response rates over 90% in combination with the CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy regimen.[1]

There have also been notable advances in the use of mAbs in the treatment of solid tumors. Trastuzumab reduces recurrence rates by half when used in combination with chemotherapy in the 20%-30% of women with metastatic breast cancers that overexpress the HER2 (human epidermal growth factor receptor) protein. HER2-targeted therapy continues to provide breakthroughs; in 2012, pertuzumab, which has a synergistic effect when combined with trastuzumab, was approved.

mAbs work via several different cellular mechanisms, of which researchers are now gaining a better understanding, and increasingly effective agents with fewer side effects are being developed.[2,3]

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Small-molecule inhibitors

The most easily "druggable" targets for small-molecule inhibitors (SMIs) are kinases, particularly cell surface tyrosine kinase receptors, which initiate signaling cascades that drive important cellular processes. SMIs differ from mAbs in that they are administered orally rather than intravenously, are less specific, and require more frequent dosing.

Imatinib was the first agent of this kind and was also the first to target a specific molecular defect in cancer cells; a chromosomal translocation (Philadelphia chromosome) that resulted in the formation of the BCR-ABL fusion protein, a tyrosine kinase that is always active and therefore oncogenic. This defect is present in almost all patients with chronic myelogenous leukemia, so imatinib therapy results in a complete hematologic response in 98% of patients. Imatinib has also revolutionized the treatment of gastrointestinal stromal tumors, a rare abdominal cancer that was virtually untreatable before its approval.[2]

There are at least 90 tyrosine kinases in the human genome[4] and many of these have now been targeted with inhibitors that are either approved (Table 2) or in various stages of development.

Conjugated drugs

Chemotherapy and radiotherapy remain important components of treatment for many types of cancer, but their efficacy is limited by systemic toxicity and lack of tumor specificity. Conjugated agents combine the potent cytotoxic abilities of traditional therapies with the specificity of a mAb (Figure 2).

Currently, there are 4 antibody–drug conjugates (ADCs) that have been approved by the FDA; 2 conjugated to chemotherapeutic agents, and 2 to radiotherapeutic agents. The most recent approval came in 2013 for ado-trastuzumab emtansine (T-DM1), which conjugates the HER2 mAb trastuzumab to the cytotoxic agent emtansine. T-DM1 was approved for patients with HER2-positive metastatic breast cancer previously treated with trastuzumab and a taxane, following the demonstration that median overall survival in pa-

tients receiving the conjugate was increased by more than 5 months, compared with patients receiving a combination of capecitabine and lapatinib.[5]

Genentech alone has over 25 ADCs in the pipeline, and these are rapidly becoming an important component of cancer treatment, particularly as researchers begin to improve their design to maximize efficacy and limit toxic side effects.[6,7]

Identification of defects that drive different cancers

Cancer-causing genetic changes are referred to as "driver" events because they confer a growth advantage to cancer cells and can be directly linked to the development of a cancer. Genome sequencing technology has allowed researchers to uncover many of these events. The most frequently altered gene in human cancer is *p53*. Other common mutations occur in the kinase enzymes that are essential to intracellular signaling pathways. Driver events also occur in the form of chromosomal rearrangements and gene overexpression, with 2 significant examples being the *EML4-ALK* fusion gene in non–small-cell lung cancer, and overexpression of the *HER2* gene in breast cancer.

The identification of driver events has been instrumental in developing targeted therapies and assessing which patients benefit the most, and a number of tests have been approved by the FDA for this purpose (Table 3). Continual assessment of the cancer genome is also important as subsequent mutations can develop in response to targeted therapy that may drive resistance.[8]

Inhibiting angiogenesis

Tumors require oxygen and nutrients from their surrounding environment to be able to grow and they initially obtain them through diffusion. However, they are unable to grow beyond 2 mm without stimulating the growth of new blood vessels (a process called angiogenesis) to provide for their growing needs. When

FIGURE 1 Timeline of developments in targeted therapies, beginning with the FDA's approval of rituximab in 1997 through 2013 to date, with the approval of T-DM1 for breast cancer.
Abbreviations and definitions: *ABL*, gene that encodes abelson murine leukemia viral oncogene homolog 1; *BRAF*, gene that encodes B-Raf kinase; CDC, Centers for Disease Control and Prevention; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; CRC, colorectal carcinoma; CTLA4, cytotoxic T-lymphocyte antigen-4; EGFR, epidermal growth factor receptor; *EML4-ALK*, fusion between echinoderm microtubule-associated protein-like 4 and anaplastic lymphoma kinase genes; FDA, Food and Drug Administration; *KRAS*, gene encoding a member of the Ras family of kinases; mAb, monoclonal antibody; NCI, National Cancer Institute; NHL, non-Hodgkin lymphoma; NSCLC, non–small-cell lung cancer; *PIK3CA*, gene that encodes phosphatidylinositol-3-kinase; RCC, renal cell carcinoma.

TABLE 1 Monoclonal antibodies approved by the Food and Drug Administration

Antibody	Target	Indications	Advances to treatment
Naked antibodies			
Alemtuzumab (Campath)	CD52	CLL	Significant improvements in PFS[a]
Bevacizumab (Avastin)	VEGF	Metastatic CRC, advanced NSCLC, metastatic kidney cancer, glioblastoma	The first anti-angiogenic agent to be approved, initially for CRC, in which it improved OS by about 5 mos; has since been approved for other cancer types[b]
Cetuximab (Erbitux)	EGFR	EGFR+ CRC, head and neck cancer	Most recently approved for patients with colorectal cancers with mutant *EGFR* but wildtype *KRAS* after it showed significant improvement in PFS in combination with the FOLFIRI chemotherapy regimen[c]
Ipilimumab (Yervoy)	CTLA-4	Metastatic melanoma	First treatment for metastatic melanoma in over 40 years with any proven benefit; showed an increase in 3-year survival of over 20%[d]
Ofatumumab (Arzerra)	CD20	CLL	As a single agent, it achieves over 40% ORR in patients who are refractory to a combination of fludarabine and alemtuzumab[e]
Panitumumab (Vectibix)	EGFR	EGFR+ CRC	Significant improvement in PFS[f]
Pertuzumab (Perjeta)	HER2	HER2+ breast cancer (with trastuzumab)	Synergistic effect in combination with trastuzumab (the 2 agents together are more effective than either alone), increasing PFS by over 6 mo, with significantly higher ORRs[g]
Rituximab (Rituxan)	CD20	NHL and CLL	Response rates over 50% observed with single-agent. Even more significant responses seen in combination with chemotherapeutic agents[h]
Trastuzumab (Herceptin)	HER2	Metastatic HER2+ breast and gastric cancer	Significantly longer median time to disease progression, higher ORRs, and longer median duration of response in combination with chemotherapy in breast cancer patients[i]
Conjugated antibodies			
Ado-trastuzumab emtansine (Kadcyla)	HER2	HER2+ breast cancer	Compared to a combination of lapatinib and capecitabine, T-DM1 reduces mortality risk by 32% and increases OS by over 5 mo[j]
Brentuximab vedotin (Adcetris)	CD30	HL and systemic ALCL	ORR of 73% with median duration of 6.7 mo in patients with HL and of 86% with median duration of 12.6 mo in patients with ALCL[k]
Ibritumomab tiuxetan (Zevalin)	CD20	CD20+ NHL	ORR of 74% in patients who are refractory to rituximab and chemotherapy and 83% in patients who are rituximab-naïve but unresponsive to chemotherapy, compared with 55% for rituximab alone[l]
I-131 Tositumomab (Bexxar)	CD20	CD20+ NHL	ORR of 68% and complete response rate of 33% in patients with rituximab-refractory disease[m]

Abbreviations: ALCL, anaplastic large cell lymphoma; CLL, chronic lymphocytic leukemia; CRC, metastatic colorectal cancer; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; NSCLC, non–small-cell lung cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; T-DM1, ado-trastuzumab emtansine.

[a] Campath [package insert]. Cambridge, MA: Genzyme Corp; 2009; [b] Avastin [package insert]. San Francisco, CA: Genentech Inc; 2013; [c] Erbitux [package insert]. Princeton, NJ: Bristol-Myers Squibb Co; 2013; [d] Yervoy [package insert]. Princeton, NJ: Bristol-Myers Squibb Co; 2012; [e] Arzerra [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2011; [f] Vectibix [package insert]. Thousand Oaks, CA: Amgen Inc; 2013; [g] Perjeta [package insert]. San Francisco, CA: Genentech Inc; 2013; [h] Rituxan [package insert]. San Francisco, CA: Genentech Inc; 2012; [i] Herceptin [package insert]. San Francisco, CA: Genentech Inc; 2010; [j] Kadcyla [package insert]. San Francisco, CA: Genentech Inc; 2013; [k] Adcetris [package insert]. Bothell, WA: Seattle Genetics Inc; 2012; [l] Zevalin [package insert]. Irvine, CA: Spectrum Pharmaceuticals Inc; 2011; [m] Bexxar [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2012.

cells become cancerous they acquire certain "hallmark" abilities, one of which is the ability to stimulate angiogenesis.

Clinical validation of angiogenesis as a target for cancer therapy came in 2003 with the approval of the mAb bevacizumab, which targets the vascular endothelial growth factor (VEGF), an important driver of angiogenic pathways. VEGF and its receptor VEGFR have been a very promising area of exploration and approved agents now

TABLE 2 Small-molecule inhibitors approved by the Food and Drug Administration

Agent	Target	Indications	Advances to treatment
Axitinib (Inlyta)	VEGFR1-3, PDGFR, c-KIT	RCC	Extended PFS by 2 mo.[a] Since 2005, it is the 7th agent approved for advanced kidney cancer
Bosutinib (Bosulif)	ABL and Src	CML	Over 50% of patients previously treated with imatinib achieved a major CR of at least 18 mo[b]
Cabozantanib (Cometriq)	FLT3, KIT, MET, RET, VEGFR2	Metastatic medullary thyroid cancer	Significantly increases PFS, compared with placebo[c]
Crizotinib (Xalkori)	ALK, MET	Locally advanced or metastatic NSCLC	ORRs of 50% with a duration of over 40 weeks[d]
Dasatinib (Sprycel)	ABL and Src	CML and ALL	Patients resistant or intolerant to imatinib experienced PFS of 80% at 2 years[e]
Enzalutamide (Xtandi)	Androgen receptor	Late-stage prostate cancer	Increases OS by almost 5 mo, compared w placebo[f]
Erlotinib (Tarceva)	EGFR	NSCLC, pancreatic cancer	Improves OS and PFS in NSCLC patients both with and without *EGFR* mutations. When approved for pancreatic cancer it was the first new drug in over a decade to produce improvements in OS (23%) in these patients[g]
Everolimus (Affinitor)	mTOR	Pancreatic neuroendocrine tumor, RCC, nonresectable subependymal giant cell astrocytoma associated with tuberous sclerosis, advanced breast cancer	Most recently approved for patients with advanced HER2+ breast cancer, everolimus improves PFS by over 4 mo when combined with exemestane[h]
Gefitinib (Iressa)	EGFR	NSCLC with known benefit from gefitinib	10% improvement in response rate in NSCLC patients. However, in 2005 the FDA limited approval of gefitinib to patients who are known to benefit from gefitinib and it is no longer approved for use in new patients[i]
Imatinib (Gleevec)	KIT, PDGFR, ABL	KIT-positive GIST, various hematologic malignancies including CML	CHR in 98% of patients with CML. In 2012, imatinib was approved for extended use in the adjuvant treatment of GIST as OS is significantly increased when the drug is taken for 3 years after surgery rather than standard 1 year[j]
Lapatinib (Tykerb)	HER2, EGFR	HER2-positive breast cancer	Significant increases in PFS and TTP, respectively, in combination with letrozole in patients with hormone-positive, HER2+ breast cancer and in combination with capecitabine in patients with HER2+ breast cancer.[k] Though not yet approved for such use, has shown even greater improvement in PFS when used with trastuzumab
Nilotinib (Tasigna)	ABL	CML (Ph+)	Superior to imatinib in achieving MMRs, CCRs[l]
Pazopanib (Votrient)	VEGFR, PDGFR, KIT	RCC, advanced soft tissue sarcoma	In patients with RCC, pazopanib showed ORRs of 30%, compared with 3% for placebo[m]
Ponatinib (Iclusig)	ABL, FGFR1-3, FLT3, VEGFR2	CML, ALL	MHRs observed in half of all patients who are intolerant or resistant to other TKIs[n]
Regorafenib (Stivarga)	KIT, PDGFRβ, RAF, RET, VEGFR1-3	CRC, GIST	Most recently approved for GIST, PFS improves by almost 4 mo[o]
Sorafenib (Nexavar)	VEGFR, PDGFR, KIT, RAF	HCC, RCC	In patients with RCC, median PFS is almost doubled; in patients with HCC, TTP improves almost 3 mo[p]
Sunitinib (Sutent)	VEGFR, PDGFR, KIT, RET	GIST, pancreatic neuro-endocrine tumor, RCC	Most recently approved for pancreatic cancer, PFS almost doubles compared with placebo[q]
Temsirolimus (Torisel)	mTOR	RCC	Significant improvements in OS and PFS compared with interferon therapy[r]
Vandetanib (Caprelsa)	EGFR, RET, VEGFR2	Medullary thyroid cancer	First drug approved for this rare type of cancer; median PFS improved by more than 6 mo[s]
Vemurafenib (Zelboraf)	BRAF	Metastatic melanoma (with *BRAF V600* mutation)	First drug approved for *BRAF*-mutant cancer; 74% cut in risk of progression compared with dacarbazine, significant PFS improvement[t]
Vismodegib (Erivedge)	Hedgehog	Advanced basal cell carcinoma	First drug to be approved for advanced forms of skin cancer; more than 40% of patients achieve complete or partial responses[u]

Abbreviations: ALCL, anaplastic large cell lymphoma; ALL, acute lymphoblastic leukemia; BRAF, gene encoding B-Raf kinase; CCR, complete cytogenic responses; CHR, complete hematologic response; CLL, chronic lymphocytic leukemia; CR, cytogenetic response; CRC, colorectal cancer; EGFR, epidermal growth factor receptor; GIST, gastrointestinal stromal tumors; HCC, hepatocellular carcinoma; HER2, human epidermal growth factor receptor 2; HL, Hodgkin lymphoma; MHR, major hematologic response; MMR, major molecular responses; NHL, non-Hodgkin lymphoma; NSCLC, non–small-cell lung cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; Ph+, Philadelphia chromosome positive; RCC, renal cell carcinoma; T-DM1, ado-trastuzumab emtansine; TKI, tyrosine kinase inhibitors; TTP, time-to-progression.

[a] Inlyta [package insert]. New York, NY: Pfizer Inc; 2012; [b] Bosulif [package insert]. New York, NY: Pfizer Inc; 2012; [c] Cometriq [package insert]. San Francisco, CA: Exelixis Inc; 2012; [d] Xalkori [package insert]. New York, NY: Pfizer Inc; 2013; [e] Sprycel [package insert]. Princeton, NJ: Bristol-Myers Squibb Co; 2012; [f] Xtandi [package insert]. Northbrook, IL: Astellas Phama US Inc; 2012; [g] Tarceva [package insert]. San Francisco, CA: Genentech Inc; 2012; [h] Affinitor [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2012; [i] Iressa [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2012; [j] Gleevec [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2013; [k] Tykerb [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2012; [l] Tasigna [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2012; [m] Votrient [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2013; [n] Iclusig [package insert]. Cambridge, MA: ARIAD Pharmaceuticals Inc; 2012; [o] Stivarga [package insert]. Wayne, NJ: Bayer Healthcare Pharmaceuticals Inc; 2013; [p] Nexavar [package insert]. San Francisco, CA: Bayer Healthcare Pharmaceuticals Inc; 2012; [q] Sutent [package insert]. New York, NY: Pfizer Inc; 2012; [r] Torisel [package insert]. Philadelphia, PA: Wyeth Pharmaceuticals Inc; 2012; [s] Caprelsa [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2012; [t] Zelboraf [package insert]. San Francisco, CA: Genentech Inc; 2012; [u] Erivedge [package insert]. San Francisco, CA: Genentech Inc; 2012.

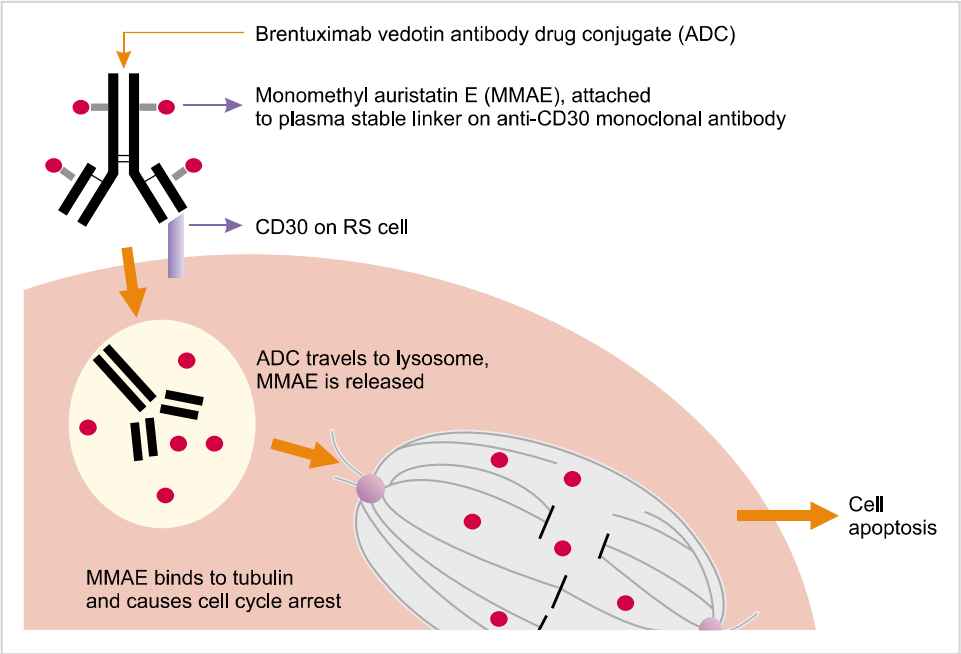

FIGURE 2 Proposed mechanism of action of brentuximab vedotin antibody drug conjugate (ADC): Depiction of CD30 ligation by ADC followed by CD30-ADC internalization, lysosomal cleavage of linker, and intracellular release of antitubulin agent MMAE leading to cell cycle arrest and apoptosis. Reproduced with permission from Korean Journal of Hematology (Korean J Hematol. 2012;47:8-16).
Abbreviation: RS, Reed-Sternberg.

include sorafenib, sunitinib, pazopanib, and, most recently, axitinib, which was approved for the treatment of renal cell carcinoma after it demonstrated a 2-month improvement in progression-free survival (PFS).[9]

Top 5 research developments

'Hallmarks' of cancer

Hanahan and Weinberg suggested that there are 6 essential alterations in cell physiology[10] that allow the transformation of a normal cell into a malignant tumor. These so-called "hallmarks" of cancer include the cells' ability to sustain their own growth, avoid cell death, divide without limit, stimulate angiogenesis, and invade and metastasize (Figure 3). The hallmarks were recently updated to reflect new research. Two new hallmarks were added (evasion of the immune system and reprogramming of cell metabolism) along with several "enabling characteristics," which must be fulfilled for a cell to begin acquiring hallmark abilities (genomic instability and tumor-promoting inflammation).

Traditionally, targeted cancer therapy was aimed at preventing the uncontrolled growth of cancer cells, but we are now beginning to branch out into targeting other hallmark abilities. Therapies that may begin to emerge in the future include those targeting the glycolytic pathway, with the aim of disrupting a cancer cell's ability to effect a metabolic change known as the Warburg effect (switching energy production from oxidative phosphorylation to glycolysis).[11]

Genome sequencing

Significant technological advances in the past several decades, such as the advent of "high throughput" and "next generation" sequencing have enabled researchers to rapidly and cost-effectively analyze entire genomes. This enables them to take the characterization of driver events of cancer to the next level and sequence the whole genome of a tumor for comparison with healthy tissue.

This technology can be used to examine a specific tumor type or subtype, the cells of the tumor microenvironment, a subset of cancer cells (ie, cancer stem cells), or the molecular signature associated with a particular tumor-related process. In the clinic, this translates into superior classification of tumors and tumor subtypes, identification of genes of diagnostic and therapeutic significance (driver events), and prediction of cancer risk and clinical outcomes. Ultimately, it may enable clinicians to really deliver on the potential of personalized medicine, so that we may see targeted therapies becoming standard of care and of benefit to all cancer patients.[8]

Tumor cell heterogeneity

We are now beginning to understand that tumors contain cells that are both phenotypically and functionally diverse and that this can have significant implications for targeted therapy. Different populations of cells within a tumor may respond differently to targeted therapies, not just because of genetic variation, but also epigenetic differences and the effects of the tumor microenvironment. The current paradigm for cancer treatment is to target underlying common features, but if each cancer is indeed unique it will require more individualized treatment.

One important population is that of cancer stem cells (CSCs), the progenitor cells from which all other cells of the tumor arise. CSCs potentially represent an important target for cancer therapy and may have implications for the application of existing targeted therapies. For example, recent research found that HER2-targeted treatments may work in HER2-negative breast cancer patients, as well as HER2-positive patients, in whom they are currently approved. A

TABLE 3 Companion diagnostics tests approved by the Food and Drug Administration[a]

Target	Trade name	Use
HER2	INFORM HER2/NEU	FISH test for HER2 positivity in breast cancer patients with localized, node-negative breast cancer. Used as a prognostic indicator and for risk stratification
	PATHVYSION HER-2 DNA Probe Kit	FISH test for HER2 positivity in breast cancer patients with stage 2, node-positive breast cancer who are being considered for trastuzumab treatment
	PATHWAY ANTI-HER-2 (4B5) Rabbit Monoclonal Antibody	Antibody for IHC detection of HER2 in breast cancer patients for whom trastuzumab treatment is being considered
	INSITE HER-2/NEU Kit	IHC assessment of HER2 expression levels in breast cancer patients for whom trastuzumab treatment is being considered
	SPOT-LIGHT HER2 CISH Kit	CISH test for quantitative assessment of *HER2* gene amplification in breast cancer patients for whom trastuzumab treatment is being considered
	Bond Oracle HER2 IHC System	IHC assessment of HER2 expression levels in breast cancer patients for whom trastuzumab treatment is being considered
	HER2 CISH PharmDx Kit	CISH test for quantitative determination of HER2 status in patients with stage 2, node-positive breast cancer
	INFORM HER2 DUAL ISH DNA Probe Cocktail	Determines *HER2* gene status by enumeration of the ratio of the *HER2* gene to Chromosome 17 in patients with breast cancer for whom trastuzumab treatment is being considered
	HERCEPTEST	Immunocytochemical assay for HER2 protein expression levels in breast cancer patients for whom trastuzumab and pertuzumab treatments are being considered
	HER2 FISH PharmDx Kit	FISH assay for determining *HER2* gene amplification in breast cancer patients for whom trastuzumab and pertuzumab treatments are being considered
EGFR	DAKO EGFR PharmDx Kit	IHC test for EGFR expression to aid in identifying colorectal cancer patients eligible for treatment with cetuximab or panitumumab
C-KIT	DAKO C-KIT PharmDx	IHC test for c-KIT expression to aid in the differential diagnosis of GIST and to identify patients who may be eligible for treatment with imatinib
ALK	VYSIS ALK Break Apart FISH Probe Kit	FISH assay for detecting rearrangements involving the *ALK* gene in patients with NSCLC and to aid in identifying patients eligible for treatment with crizotinib
BRAF V600 mutation	COBAS 4800 BRAF V600 Mutation Test	Test for the detection of the *BRAF V600E* mutation in melanoma patients, to identify those who may be eligible for treatment with vemurafenib
KRAS	Therascreen KRAS RGQ PCR Kit	Real-time qualitative PCR assay for the detection of 7 somatic mutations in the *KRAS* gene of patients with colorectal cancer, to aid identification of patients eligible for cetuximab therapy based on a 'no *KRAS* mutation detected' result

Abbreviations: ALK, anaplastic lymphoma kinase; BRAF, gene encoding B-Raf kinase; CISH, chromogenic *in situ* hybridization; EGFR, epidermal growth factor receptor; FISH, fluorescence *in situ* hybridization; GIST, gastrointestinal stromal tumors; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemical; NSCLC, non–small-cell lung cancer; PCR, polymerase chain reaction.

[a] Adapted from http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm

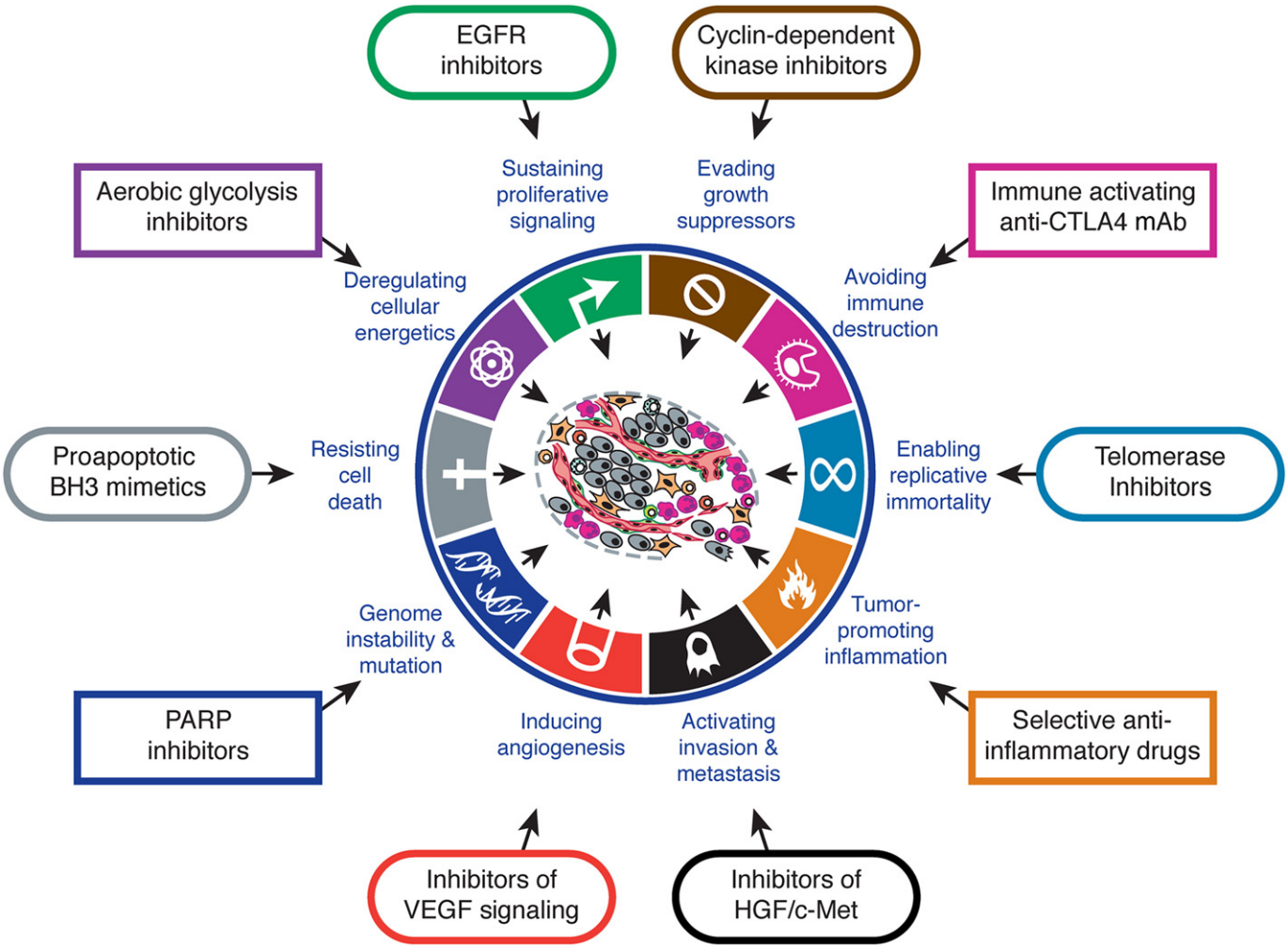

FIGURE 3 The hallmarks of cancer.[11]
Abbreviations: CTLA4, cytotoxic T-lymphocyte antigen-4; EGFR, epidermal growth factor receptor; HGF, hepatocyte growth factor; mAb, monoclonal antibody; PARP, Poly(ADP-ribose) polymerase; VEGF, vascular endothelial growth factor.

potential molecular mechanism for this finding is that HER2 is expressed by CSCs at levels that are beneath the threshold of detection for tests for HER2 positivity, but which still provide a target for HER2 therapy.[12]

Therapeutic cancer vaccines

Therapeutic cancer vaccines are designed to generate a targeted, immune-mediated antitumor response either against a patient's own cells or tumor (patient specific) or against specific tumor-associated antigens (patient nonspecific). They represent one of several immunomodulatory strategies that are being used in the fight against cancer and, as researchers gain understanding of the immune antitumor response, they are becoming an increasingly effective and important treatment modality. The first therapeutic vaccine, sipuleucel-T, was approved by the FDA in 2010 for the treatment of metastatic castration-resistant prostate cancer after it demonstrated an improvement in overall survival of over 4 months. A number of other therapeutic vaccines are in phase 3 clinical trials, including PSA-TRICOM, BiovaxID, MAGE-A3, and nelipepimut-S, for the treatment of prostate cancer, non-Hodgkin lymphoma, non–small-cell lung cancer, and breast cancer, respectively.[13]

Alternative targets

Because protein kinases play a vital role in intracellular signal transduction and are very readily "druggable," they have historically been an extremely attractive target for therapeutic intervention in cancer. Recent advances in technology, however, are making it possible to more easily target proteins besides kinases. A significant example is the tumor suppres-

sor protein, *p53*, which is mutated in more than half of all human cancers but, until recently, was not an "ideal" target for conventional methods of drug development.

Developments in drug candidate screening, chemistry and structure-based design have led to novel ways of targeting not easily druggable proteins like *p53*. For example, drugs are being developed that target vital interactions between proteins rather than the proteins themselves and researchers are also exploring the concept of synthetic lethality (the theory that combining 2 mutations that are nonlethal by themselves can lead to cell death – thus targeting a gene that is synthetic lethal to a cancer relevant mutation should specifically kill cancer cells).

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