Immunotherapy may hold the key to defeating virally associated cancers

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Infection with certain viruses has been causally linked to the development of cancer. In recent years, an improved understanding of the unique pathology and molecular underpinnings of these virally associated cancers has prompted the development of more personalized treatment strategies, with a particular focus on immunotherapy. Here, we describe some of the latest developments.

The link between viruses and cancer

Suspicions about a possible role of viral infections in the development of cancer were first aroused in the early 1900s. The seminal discovery is traced back to Peyton Rous, who showed that a malignant tumor growing in a chicken could be transferred to a healthy bird by injecting it with tumor extracts that contained no actual tumor cells.[1]

The infectious etiology of human cancer, however, remained controversial until many years later when the first cancer-causing virus, Epstein-Barr virus (EBV), was identified in cell cultures from patients with Burkitt lymphoma. Shortly afterward, the Rous sarcoma virus was unveiled as the oncogenic agent behind Rous' observations.[2]

Seven viruses have now been linked to the development of cancers and are thought to be responsible for around 12% of all cancer cases worldwide. The burden is likely to increase as technological advancements make it easier to establish a causal link between viruses and cancer development.[3]

In addition to making these links, researchers have also made significant headway in understanding how viruses cause cancer. Cancerous trans-

formation of host cells occurs in only a minority of those who are infected with oncogenic viruses and often occurs in the setting of chronic infection.

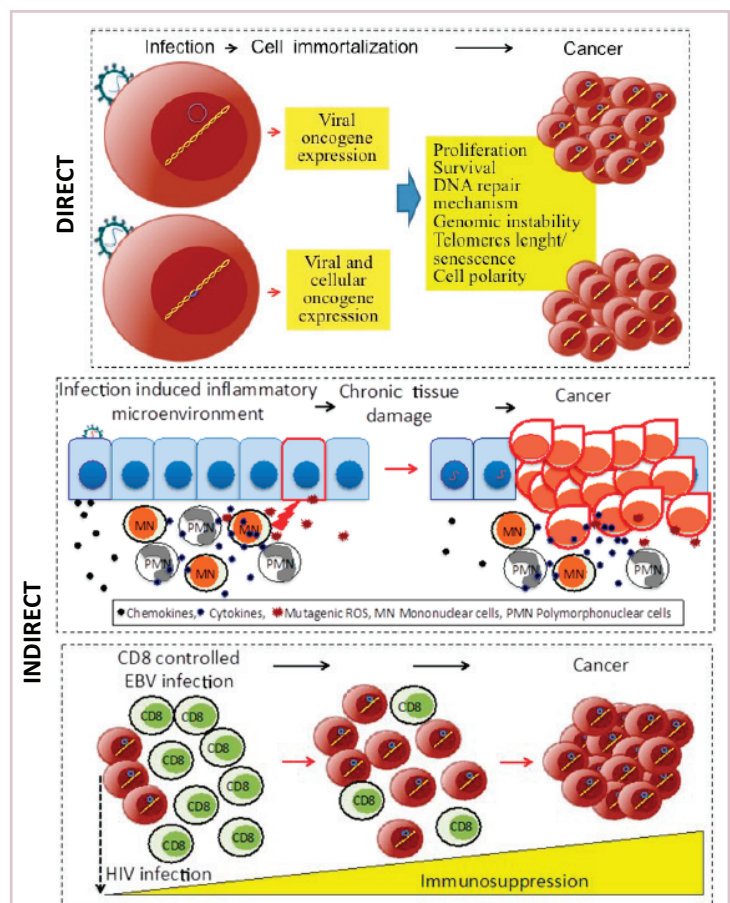Viruses can mediate carcinogenesis by direct and/or indirect mechanisms (Figure 1). Many of the

FIGURE Direct and Indirect Mechanisms of Viral Carcinogenesis. Viruses can directly mediate carcinogenesis by integration of viral oncogenic genes or by enhancement of already existing oncogenic genes into the host genome, thereby promoting many of the hallmarks of cancer (top panel). They can also indirectly promote cancer development by fostering a chronic inflammatory microenvironment and local tissue damage (middle panel) and via immunosuppression (bottom panel).

TABLE 1 The burden of virally associated cancers

Virus type	Type of virus	Associated cancer(s)	Incidence	Percentage of global cancers
Hepatitis B (HBV)	DNA	Hepatocellular carcinoma	>50% cases	4.9
Hepatitis C (HCV)	RNA	Hepatocellular carcinoma	27% cases	4.9
Human papillomavirus (HPV)	DNA	Cervical cancer Anal cancer Vulvar cancer Vaginal cancer Head and neck squamous cell carcinoma Penile cancer	>99% cases Up to 93% cases 50% cases 65% cases 45-90% cases 35%	5.2
Human T-lymphotropic virus 1 (HTLV-1)	RNA	Adult T-cell leukemia/lymphoma	<10% cases	.03
Kaposi sarcoma-associated herpes-virus/human herpesvirus 8 (KSHV/HHV-8)	DNA	Kaposi sarcoma Multicentric Castleman disease Primary effusion lymphoma	All cases	0.9
Merkel cell polyomavirus (MCV)	DNA	Merkel cell carcinoma	80% cases	Unknown
Epstein-Barr virus (EBV)	DNA	Burkitt lymphoma Nasopharyngeal Classic Hodgkin lymphoma Posttransplantation lymphoproliferative disease Diffuse large B-cell lymphoma Gastric cancer	99% cases >99% cases 40% cases Most cases 20% cases 8.7% cases	1-1.5

hallmarks of cancer, the key attributes that drive the transformation from a normal cell to a malignant one, are compatible with the virus's needs, such as needing to avoid cell death, increasing cell proliferation, and avoiding detection by the immune system.

Viruses hijack the cellular machinery to meet those needs and they can do this either by producing viral proteins that have an oncogenic effect or by integrating their genetic material into the host cell genome. When the latter occurs, the process of integration can also cause damage to the DNA, which further increases the risk of cancer-promoting changes occurring in the host genome.

Viruses can indirectly contribute to carcinogenesis by fostering a microenvironment of chronic inflammation, causing oxidative stress and local tissue damage, and by suppressing the antitumor immune response.[4,5]

Screening and prevention efforts have helped to reduce the burden of several different virally associated cancers. However, for the substantial proportion of patients who are still affected by these cancers, there is a pressing need for new therapeutic options, particularly since genome sequencing studies have revealed that these cancers can often have distinct underlying molecular mechanisms.

Vaccines lead the charge in HPV-driven cancers

German virologist Harald zur Hausen received the Nobel Prize in 2008 for his discovery of the oncogenic role of human papillomaviruses (HPVs), a large family of more than 100 DNA viruses that infect the epithelial cells of the skin and mucous membranes. They are responsible for the largest number of virally associated cancer cases globally – around 5% (Table 1).

A number of different cancer types are linked to HPV infection, but it is best known as the cause of cervical cancer. The development of diagnostic blood tests and prophylactic vaccines for prevention and early intervention in HPV infection has helped to reduce the incidence of cervical cancer. Conversely, another type of HPV-associated cancer, head and neck squamous cell carcinoma (HNSCC), has seen increased incidence in recent years.

HPVs are categorized according to their oncogenic potential as high, intermediate, or low risk. The high-risk HPV16 and HPV18 strains are most commonly associated with cancer. They are thought to cause cancer predominantly through integration into the host genome. The HPV genome is composed of 8 genes encoding proteins that regulate viral replication and assembly. The E6 and E7 genes are the most highly oncogenic; as the HPV DNA is inserted into the host genome, the transcriptional regulator of E6/E7 is lost, leading to their increased expression. These genes have significant oncogenic potential because of their interaction with 2 tumor suppressor proteins, p53 and pRb.[6,7]

The largest investment in therapeutic development for HPV-positive cancers has been in the realm of immunotherapy in an effort to boost the anti-tumor immune response. In

TABLE 2 Ongoing clinical trials in HPV-associated tumors

Drug	Developer	Mechanism of action	Stage of development/indication
Axalimogene filolisbac (AXAL/ADXS11-001)	Advaxis	Therapeutic vaccine	Phase 3 cervical cancer (AIM2CERV; NCT02853604) Phase 2 NSCLC (NCT02531854) Phase 1/2 HNSCC (NCT02291055)
TG4001	Transgene	Therapeutic vaccine	Phase 1/2 HNSCC (NCT03260023)
GX-188E	Genexine	Therapeutic vaccine	Phase 1/2 cervical cancer (NCT03444376)
VGX-3100	Inovio	Therapeutic vaccine	Phase 3 cervical cancer (REVEAL; NCT03185013) Phase 2 vulvar cancer (NCT03180684)
MEDI-0457 (INO-3112)	Inovio	Therapeutic vaccine	Phase 2 HPV+ cancers (NCT03439085) Phase 1/2 HNSCC (NCT03162224)
INO-3106	Inovio	Therapeutic vaccine	Phase 1 HPV+ cancers (NCT02241369)
TA-CIN	Cancer Research Technology	Therapeutic vaccine	Phase 1 cervical cancer (NCT02405221)
TA-HPV	Cancer Research Technology	Therapeutic vaccine	Phase 1 cervical cancer (NCT00788164)
ISA-101	Isa	Therapeutic vaccine	Phase 2 HNSCC (NCT03258008)
PepCan	University of Arkansas	Therapeutic vaccine	Phase 2 cervical cancer (NCT02481414)
Nivolumab (Opdivo)	Bristol-Myers Squibb	Immune checkpoint inhibitor	Phase 2 HNSCC (NCT03342911)
AMG319	Amgen	PI3K inhibitor	Phase 2 HNSCC (NCT02540928)
BKM120	Novartis	PI3K inhibitor	Phase 1 HNSCC (NCT02113878)
HPV-specific T cells	Baylor College of Medicine, National Cancer Institute	Adoptive cell therapy	Phase 1 HPV+ tumors (NCT02379520) Phase 1 vulvar cancers (NCT03197025)

HPV, human papillomavirus; HNSCC, head and neck squamous cell carcinoma; NSCLC, non-small cell lung cancer; PI3K, phosphatidylinositol-3-kinase

particular, there has been a focus on the development of therapeutic vaccines, designed to prime the anti-tumor immune response to recognize viral antigens. A variety of different types of vaccines are being developed, including live, attenuated and inactivated vaccines that are protein, DNA, or peptide based. Most developed to date target the E6/E7 proteins from the HPV16/18 strains (Table 2).[8,9]

Leading the pack is axalimogene filolisbac (AXAL; ADXS11-001), a live, attenuated vaccine in which the *Listeria monocytogenes* bacterium is bioengineered to secrete the HPV16 E7 protein, fused to a fragment of listeriolysin O, the main virulence factor of this bacterium.[10,11]

The vaccine showed significant promise in early-stage clinical trials, with a good safety profile and evidence of anti-tumor activity. The results of a phase 2 study (GOG/NRG 0265) were presented at the 2017 Society of Gynecology Oncology annual meeting. A total of 50 patients with recurrent metastatic cervical cancer had been treated with AXAL, all of whom had received at least 1 prior line of systemic therapy for metastatic disease. Researchers reported a 1 year survival rate of 38%, unprecedented in this patient population.[12]

In a separate phase 2 trial AXAL was evaluated as monotherapy or in combination with cisplatin in patients with previously treated cervical cancer and demonstrated a 1 year survival rate of 32%.[13] The phase 3 AIM2CERV trial of AXAL as adjuvant monotherapy, to prevent recurrence in patients with high-risk cervical cancer treated with chemoradiation is currently ongoing, as are several trials in other types of HPV-positive cancer.

Other immunotherapies are also being evaluated, including immune checkpoint inhibitors, antibodies designed to target one of the principal mechanisms of immune evasion exploited by cancer cells. The combination of immune checkpoint inhibitors with vaccines is a particularly promising strategy in HPV-associated cancers. At the European Society for Medical Oncology Congress in 2017, the results of a phase 2 trial of nivolumab in combination with ISA-101 were presented.

Among 24 patients with HPV-positive tumors, the majority oropharyngeal cancers, the combination elicited an overall response rate (ORR) of 33%, including 2 complete responses (CRs). Most adverse events (AEs) were mild to moderate in severity and included fever, injection site reactions, fatigue and nausea.[14]

TABLE 3 Ongoing clinical trials in HBV/HCV-associated tumors

Drug	Developer	Mechanism of action	Approved indication/clinical testing
Regorafenib (Stivarga)	Bayer	Multitargeted TKI	FDA approved Phase 1 + pembrolizumab (NCT03347292)
Ramucirumab (Cyramza)	Eli Lilly	VEGFR2-targeted mAb	Phase 3 (REACH-2; NCT02435433)
Sorafenib (Nexavar)	Bayer	Multitargeted TKI	FDA approved Phase 3 (NCT01730937, NCT02774187)
Lenvatinib (Lenvima)	Eisai	Multitargeted TKI	Phase 3 (NCT01761266)
Cabozantinib (Cabometyx/Cometriq)	Exelixis	Multitargeted TKI	Phase 3 (NCT01908426)
Apatinib	LSK	VEGFR2 inhibitor	Phase 3 (NCT02329860, NCT02702323)
Axitinib (Inlyta)	Pfizer	Multitargeted TKI	Phase 2 (NCT01334112)
Capmatinib (INC280)	Novartis	MET inhibitor	Phase 2 (NCT01737827, NCT02795429)
Galunisertib	Eli Lilly	TGF-betaR inhibitor	Phase 2 (NCT01246986, NCT02178358)
TRC105	Tracon	Endoglin-targeted mAb	Phase 2 (NCT02560779)
Tivozanib	Aveo Oncology	VEGFR inhibitor	Phase 2 (NCT01835223)
Vorinostat (Zolinza)	Merck	HDAC inhibitor	Phase 1 (NCT01075113)
Nivolumab (Opdivo)	Bristol-Myers Squibb	Immune checkpoint inhibitor	Phase 3 (NCT03383458, NCT02576509)
Pembrolizumab (Keytruda)	Merck	Immune checkpoint inhibitor	Phase 3 (NCT02702401, NCT03062358)
Durvalumab (Imfinzi)/ tremelimumab	AstraZeneca/ MedImmune	Immune checkpoint inhibitors	Phase 3 (NCT03298451)
Avelumab (Bavencio)	EMD Serono/Pfizer	Immune checkpoint inhibitor	Phase 2 (NCT03389126)

FDA, United States Food and Drug Administration; HBV, hepatitis B virus; HCV, hepatitis C virus; HDAC, histone deacetylase; mAb, monoclonal antibody; TGF-betaR, transforming growth factor beta receptor; TKI, tyrosine kinase inhibitor; VEGFR2, vascular endothelial growth factor receptor 2

Hepatocellular carcinoma: a tale of two viruses

The hepatitis viruses are a group of 5 unrelated viruses that causes inflammation of the liver. Hepatitis B (HBV), a DNA virus, and hepatitis C (HCV), an RNA virus, are also oncoviruses; HBV in particular is one of the main causes of hepatocellular carcinoma (HCC), the most common type of liver cancer.

The highly inflammatory environment fostered by HBV and HCV infection causes liver damage that often leads to cirrhosis. Continued infection can drive permanent damage to the hepatocytes, leading to genetic and epigenetic damage and driving oncogenesis. As an RNA virus, HCV doesn't integrate into the genome and no confirmed viral oncoproteins have been identified to date, therefore it mostly drives cancer through these indirect mechanisms, which is also reflected in the fact that HCV-associated HCC predominantly occurs against a backdrop of liver cirrhosis.

HBV does integrate into the host genome. Genome sequencing studies revealed hundreds of integration sites, but most commonly they disrupted host genes involved in telomere stability and cell cycle regulation, providing some

insight into the mechanisms by which HBV-associated HCC develops. In addition, HBV produces several oncoproteins, including HBx, which disrupts gene transcription, cell signaling pathways, cell cycle progress, apoptosis and other cellular processes.[15,16]

Multitargeted tyrosine kinase inhibitors (TKIs) have been the focal point of therapeutic development in HCC. However, following the approval of sorafenib in 2008, there was a dearth of effective new treatment options despite substantial efforts and numerous phase 3 trials. More recently, immunotherapy has also come to the forefront, especially immune checkpoint inhibitors.

Last year marked the first new drug approvals in nearly a decade – the TKI regorafenib (Stivarga) and immune checkpoint inhibitor nivolumab (Opdivo), both in the second-line setting after failure of sorafenib. Treatment options in this setting may continue to expand, with the TKIs cabozantinib and lenvatinib and the immune checkpoint inhibitor pembrolizumab and the combination of durvalumab and tremelimumab hot on their heels.[17-20] Many of these drugs are also being evaluated in the frontline setting in comparison with sorafenib (Table 3).

At the current time, the treatment strategy for patients

TABLE 4 Ongoing clinical trials in other virally associated tumors

Drug	Developer	Mechanism of action	Approved indication/Clinical testing
ATA129 (Tabelecleucel)	Atara	Adoptive cell therapy	Phase 3 EBV+ lymphoproliferative disease (NCT03394365/ALLELE, NCT03392142/MATCH)
EBVST	Tessa	Adoptive cell therapy	Phase 3 EBV+ nasopharyngeal carcinoma (NCT02578641)
CMD-003 (Baltaleucel-T)	Cell Medica	Adoptive cell therapy	Phase 2 EBV+ lymphomas (NCT02763254, NCT01948180/CITADEL)
Avelumab (Bavencio)	EMD Serono/Pfizer	Immune checkpoint inhibitor	Phase 1/2 MCV+ MCC (NCT02584829)
Pembrolizumab (Keytruda)	Merck	Immune checkpoint inhibitor	Phase 2 EBV+ gastric cancer (NCT03257163) Phase 1 KSHV+ Kaposi sarcoma (NCT02595866)
Nivolumab (Opdivo)	Bristol-Myers Squibb	Immune checkpoint inhibitor	Phase 2 EBV+ lymphoproliferative disorders and NHL (NCT03258567) Phase 2 HTLV+ T-cell lymphomas (NCT03075553) Phase 2 MCC (NCT03071406, NCT02196961) Phase 1 KSHV+ Kaposi sarcoma (NCT03316274
Talimogene laherparepvec (Imlygic; T-VEC)	Amgen	Vaccine	Phase 2 MCV+ MCC (NCT02819843, NCT02978625)
Ruxolitinib (Jakafi)	Incyte	JAK inhibitor	Phase 2 HTLV-1+ tumors (NCT01712659)
HBI-8000	Huya	HDAC inhibitor	Phase 2 HTLV-1+ tumors (NCT02955589)
Belinostat (Beleodaq)	Spectrum	HDAC inhibitor	Phase 2 HTLV-1+ tumors (NCT02737046)
Tocilizumab	Hoffman La Roche	IL-6 receptor-targeting mAb	Phase 2 KSHV+ multicentric Castleman disease (NCT01441063)
Pomalidomide (Pomalyst)	Celgene	Immunomodulatory agent	Phase 1/2 KSHV+ Kaposi sarcoma (NCT01495598)
Lenalidomide (Revlimid)	Celgene	Immunomodulatory agent	Phase 1/2 KSHV+ large cell lymphoma (NCT02911142)
Sapanisertib (MLN0128)	Millennium	mTOR inhibitor	Phase 1/2 MCV+ MCC (NCT02514824)
Ibrutinib (Imbruvica)	Pharmacyclics	BTK inhibitor	Phase 2 EBV+ DLBCL (NCT02670616)

BTK, Bruton's tyrosine kinase; DLBCL, diffuse large B cell lymphoma; EBV, Epstein-Barr virus; HDAC, histone deacetylase; HTLV-1, human T lymphotropic virus 1; JAK, Janus kinase; KSHV, Kaposi sarcoma herpesvirus; mAb, monoclonal antibody; MCC, Merkel cell carcinoma; MCV, Merkel cell polyomavirus; mTOR, mammalian target of rapamycin; NHL, non-Hodgkin lymphoma

with HCC is independent of etiology, however, there are significant ongoing efforts to try to tease out the implications of infection for treatment efficacy. A recent meta-analysis of patients treated with sorafenib in 3 randomized phase 3 trials (n = 3,526) suggested that it improved overall survival (OS) among patients who were HCV-positive, but HBV-negative.[21]

Studies of the vascular endothelial growth factor receptor 2-targeting monoclonal antibody ramucirumab, on the other hand, suggested that it may have a greater OS benefit in patients with HBV, while regorafenib seemed to have a comparable OS benefit in both subgroups.[22-25] The immune checkpoint inhibitors studied thus far seem to elicit responses irrespective of infection status.

A phase 2 trial of the immune checkpoint inhibitor tremelimumab was conducted specifically in patients with advanced HCC and chronic HCV infection. The disease control rate (DCR) was 76.4%, with 17.6% partial response (PR) rate. There was also a significant drop in viral load, suggesting that tremelimumab may have antiviral effects.[26,27,28]

Adoptive cell therapy promising in EBV-positive cancers

More than 90% of the global population is infected with EBV, making it one of the most common human viruses. It is a member of the herpesvirus family that is probably best known as the cause of infectious mononucleosis. On rare occasions, however, EBV can cause tumor development, though our understanding of its exact pathogenic role in cancer is still incomplete.

EBV is a DNA virus that doesn't tend to integrate into the host genome, but instead remains in the nucleus in the form of episomes and produces several oncoproteins, including latent membrane protein-1. It is associated with a range

of different cancer types, including Burkitt lymphoma and other B-cell malignancies. It also infects epithelial cells and can cause nasopharyngeal carcinoma and gastric cancer, however, much less is known about the molecular underpinnings of these EBV-positive cancer types.[26,27]

Gastric cancers actually comprise the largest group of EBV-associated tumors because of the global incidence of this cancer type. The Cancer Genome Atlas Research Network recently characterized gastric cancer on a molecular level and identified an EBV-positive subgroup as a distinct clinical entity with unique molecular characteristics.[29]

The focus of therapeutic development has again been on immunotherapy, however in this case the idea of collecting the patients T cells, engineering them to recognize EBV, and then reinfusing them into the patient – adoptive cell therapy – has gained the most traction (Table 4).

Two presentations at the American Society of Hematology annual meeting in 2017 detailed ongoing clinical trials of Atara Biotherapeutics' ATA129 and Cell Medica's CMD-003. ATA129 was associated with a high response rate and a low rate of serious AEs in patients with posttransplant lymphoproliferative disorder; ORR was 80% in 6 patients treated after hematopoietic stem cell transplantation, and 83% in 6 patients after solid organ transplant.[30]

CMD-003, meanwhile, demonstrated preliminary signs of activity and safety in patients with relapsed extranodal NK/T-cell lymphoma, according to early results from the phase 2 CITADEL trial. Among 6 evaluable patients, the ORR was 50% and the DCR was 67%.[31]

Newest oncovirus on the block

The most recently discovered cancer-associated virus is Merkel cell polyomavirus (MCV), a DNA virus that was identified in 2008. Like EBV, virtually the whole global adult population is infected with MCV. It is linked to the development of a highly aggressive and lethal, though rare, form of skin cancer – Merkel cell carcinoma.

MCV is found in around 80% of MCC cases and in fewer than 10% of melanomas and other skin cancers. Thus far, several direct mechanisms of oncogenesis have been described, including integration of MCV into the host genome and the production of viral oncogenes, though their precise function is as yet unclear.[32-34]

The American Cancer Society estimates that only 1500 cases of MCC are diagnosed each year in the United States.[35] Its rarity makes it difficult to conduct clinical trials with sufficient power, yet some headway has still been made.

Around half of MCCs express the programmed cell death ligand 1 (PD-L1) on their surface, making them a logical candidate for immune checkpoint inhibition. In 2017, avelumab became the first FDA-approved drug for the treatment of MCC. Approval was based on the JAVELIN Merkel 200 study in which 88 patients received avelumab. After 1 year of follow-up the ORR was 31.8%, with a CR rate of 9%.[36]

Genome sequencing studies suggest that the mutational profile of MCV-positive tumors is quite different to those that are MCV-negative, which could have therapeutic implications. To date, these implications have not been delineated, given the challenge of small patient numbers, however an ongoing phase 1/2 trial is evaluating the combination of avelumab and radiation therapy or recombinant interferon beta, with or without MCV-specific cytotoxic T cells in patients with MCC and MCV infection.

The 2 other known cancer-causing viruses are human T-lymphotropic virus 1 (HTLV-1), a retrovirus associated with adult T-cell leukemia/lymphoma (ATL) and Kaposi sarcoma herpesvirus (KSHV). The latter is the causative agent of Kaposi sarcoma, often in combination with human immunodeficiency virus (HIV), a rare skin tumor that became renowned in the 1980s as an AIDS-defining illness.

The incidence of HTLV-1- and KSHV-positive tumors is substantially lower than the other virally associated cancers and, like MCC, this makes studying them and conducting clinical trials of novel therapeutic options a challenge. Nonetheless, several trials of targeted therapies and immunotherapies are underway.

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