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Current progress in the development of prophylactic and therapeutic vaccines

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Vaccines are essential public health tools and play an important role in reducing the burden of infectious diseases in the population. Emerging infectious diseases and outbreaks pose new challenges for vaccine development, requiring the rapid design and production of safe and effective vaccines against diseases with limited resources. Here, we focus on the development of vaccines in broad fields ranging from conventional prophylactic vaccines against infectious diseases to therapeutic vaccines against chronic diseases and cancer, providing a comprehensive overview of recent advances in eight different vaccine forms (live attenuated vaccines, inactivated vaccines, polysaccharide and polysaccharide conjugate vaccines, recombinant subunit vaccines, virus-like particle and nanoparticle vaccines, polypeptide vaccines, DNA vaccines, and mRNA vaccines) and the therapeutic vaccines against five solid tumors (lung cancer, breast cancer, colorectal cancer, liver cancer and gastric cancer), three infectious diseases (human immunodeficiency virus, hepatitis B virus and human papillomavirus-induced diseases) and three common chronic diseases (hypertension, diabetes mellitus and dyslipidemia). We aim to provide new insights into vaccine technologies, platforms, applications and understanding of potential next-generation preventive and therapeutic vaccine technologies, paving the way for the vaccines design in the future.

prophylactic vaccine, therapeutic vaccine, immune response, infectious diseases, cancers, chronic diseases

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Introduction

Vaccination is the most economical and effective means to protect susceptible populations and control infectious diseases. As a result, vaccines are considered one of the ten greatest public health achievements of the 20th century (https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6019a5_addinfo.htm). The use of vaccines has enabled humankind to eradicate smallpox on a global scale, eliminate poliomyelitis in most countries, and control diphtheria, pertussis, tetanus, mumps, measles, rubella, *Haemophilus influenzae* type b, and other infectious diseases in parts of the world, with significantly reduced morbidity and mortality (Matić and Šantak, 2022; Pollard and Bijker, 2021).

However, the current COVID-19 pandemic caused by SARS-CoV-2 has resulted in more than half a billion confirmed cases and over six million deaths. Emerging infectious diseases and outbreaks pose new challenges for

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vaccine development, requiring the rapid development of safe and effective vaccines against diseases with limited resources (Lu et al., 2020). In addition, vaccine for several severe diseases caused by infectious pathogens, including human immunodeficiency virus (HIV), respiratory syncytial virus (RSV), cytomegalovirus (CMV), herpes simplex virus (HSV), and Epstein-Barr virus (EBV), have not yet been developed and require new vaccine development strategies. On the whole, vaccines enable people to live healthier and longer lives. However, as life expectancy increases, the burden of noncommunicable diseases (NCDs), such as cancer, autoimmune diseases, hypertension, atherosclerosis, and diabetes, has increased. NCDs, also known as chronic diseases, result from a combination of genetic disorders, along with physiological, environmental, and lifestyle factors and can last a long time. According to a WHO report (https://www.who.int/news-room/fact-sheets/detail/noncommunicable-diseases), 41 million people die each year from NCDs, which is equivalent to 71% of the global death toll. This shifting disease burden exacerbates the urgent need for therapies to treat NCDs.

Conventional prophylactic vaccines prevent disease through the administration of an antigen to healthy individuals to establish specific immunity, and this occurs mainly for communicable diseases. Therapeutic vaccines are used as post-exposure treatments to boost the immune system against pre-existing conditions such as chronic infections, precancerous lesions, or cancer. Therapeutic vaccines are designed to modulate the human immune system and induce cell-mediated immunity to target cells or molecules associated with NCDs rather than pathogens or pathogen-infected cells (Darrow and Kesselheim, 2015). Therapeutic vaccines differ from prophylactic vaccines in some important ways. Since prophylactic vaccines are usually given to healthy people, these people have a low tolerance for adverse events. In contrast, therapeutic vaccines are usually post-exposure treatments and are highly tolerated by patients.

The mature traditional vaccine and fast-growing novel vaccine technologies have promoted global prophylactic and therapeutic vaccine development. In recent years, advances in immunology, molecular biology, and genomics have led to more efficacious vaccine success (Pollard and Bijker, 2021). mRNA vaccines (Comirnaty, Spikevax, AWcorna) and viral vector vaccines (Convidecia, AZD1222, Ad26.COV2.S) (Baden et al., 2020; Polack et al., 2020) against the COVID-19 pandemic have been the quickest vaccines ever developed. The pneumococcal polysaccharide-protein conjugate vaccine (Prevnar13, Prevnar 20) was based on protein conjugate vaccine technology (Willson, 2020). Human papillomavirus (HPV) vaccines (Gardasil, Gardasil 9, Cervarix, Cecolin and Wozehui), designed based on genetic engineering technology, prevent HPV-related cancers through the expression of virus-like particles (VLP) (Hu et al., 2020; Willson, 2020). Meningococcal Group B vaccines (Trumenba, Bexsero) represent the "reverse vaccinology" strategy from genome to vaccine (Willson, 2020). Finally, the novel adjuvanted recombinant herpes zoster vaccine, Shingrix, broadens the immunity in immunocompromised people (Lal et al., 2015). The continuous development of vaccines has improved our understanding of immunology and the basis of immunity, with vaccines against NCDs becoming a new "hot spot" in research. Currently, there are prostate cancer vaccines (Provenge), bladder cancer vaccines (TheraCys), colon cancer vaccines (OncoVAX), melanoma vaccines (M-VAX and Melacine), renal cell cancer vaccines (Oncophage), lung cancer vaccines (Racotumomab and CIMAvaxEGF) and among others. In addition, therapeutic vaccines have also made great progress in the fields of hypertension, chronic hepatitis B, and other diseases.

This review aims to provide an overview of our current progress and understanding of state-of-the-art vaccine technologies, platforms, applications, and potential next-generation vaccine technologies. Prophylactic vaccines and therapeutic vaccines will be discussed in this review. According to the components of the vaccine, prophylactic vaccines can be divided into live-attenuated vaccines, inactivated vaccines, polysaccharide and polysaccharide-conjugate vaccines, recombinant subunit vaccines, polypeptide vaccines, DNA and mRNA vaccines. In addition, according to disease classification, therapeutic vaccines can be divided into tumor-targeted vaccines, infectious disease-targeted vaccines, and chronic disease-targeted vaccines. We believe that this review will shed insight into vaccine technology and development.

Advances in prophylactic vaccines development

Live-attenuated vaccines

Live-attenuated vaccines are created by organisms that retain their antigenicity but have been genetically engineered or attenuated (weakened) by chemical or other methods (Ghattas et al., 2021). Generally, these vaccines induce humoral and cellular immune responses with long-term persistence; however, there is still a risk of virulence reversal, which renders the vaccine unsuitable against highly pathogenic variants. In addition, attenuated vaccines have a shorter validity period, poor thermal stability, and have stringent requirements for storage and transportation; this causes a slow response in the event of a pandemic. Since attenuated vaccines can possibly revert to a virulent form, they may also induce severe diseases in immunocompromised people (Ghattas et al., 2021). Despite these issues and because the benefits outweigh the risks, live-attenuated vaccines remain a valuable platform for vaccine development. The current list

of licensed attenuated vaccines include vaccines against Smallpox (Vaccinia) (ACAM2000), Measles, Mumps, and Rubella Virus (M-M-RII), Tuberculosis (Bacillus of Calmette and Guerin (BCG)), Cholera (Vaxchora), Influenza (FluMist), Dengue (Dengvaxia; Tetravalent), Rotavirus (Rotarix), Varicella Virus, Typhoid (Vivotif), yellow fever (YF-Vax), and many others (Ghattas et al., 2021) (Table 1). According to a document released by the WHO (https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines), there are two live-attenuated COVID-19 vaccines in the clinical trial: COVI-VAC, developed by Codaenixin in partnership with Serum Institute of India, and MV-014-212, developed by Meissa Vaccines, Inc.

Research is ongoing to improve the safety of the live-attenuated vaccines and further reduce their virulence; this has been tested by increasing replication fidelity, through codon deoptimization, and via engineering of the viral genome. Vignuzzi et al. sought to exploit the observation that restricting viral population diversity through increased replication fidelity could dramatically reduce tissue tropism and virus pathogenicity (Vignuzzi et al., 2008). The results showed that poliovirus variants with reduced genetic diversity elicited protective immune responses in animal infection models. This limiting viral quasi species diversity provides a new approach to engineering stable attenuated vaccines for RNA viruses. Codon pair deoptimization (CPD) is another efficient virus attenuation strategy that utilizes suboptimal codon pairs to attenuate recoded viruses. Groenke et al. increased the number of suboptimal codon pairs and CpG dinucleotides in the recoding genome by changing the position of synchronization codons (Groenke et al., 2020). Their study on the influenza A virus showed that suboptimal codon pairs caused attenuation, whereas an increase in the proportion of CpG dinucleotides had no effect. In addition, they showed that suboptimal codon pairs could reduce the stability and translation efficiency of the mRNAs of deoptimized codon pairs. Therefore, the reduction in protein production directly leads to virus attenuation.

Recently, Trimpert et al. constructed a COVID-19 candidate live-attenuated vaccine (Trimpert et al., 2021), named sCPD9, via large-scale encoding of the SARS-CoV-2 genome (modified by the method of CPD), and assessed the immunogenicity and protective efficacy of the vaccine in Roborovski dwarf hamsters. The authors showed that a single intranasal inoculation of sCPD9 elicits cross-neutralizing antibody responses against the four SARS-CoV-2 variants of current interest: B.1.1.7 (Alpha), B.1.351 (Beta), B.1.1.28.1 (Gamma), and B.1.617.2 (Delta), protecting against COVID-19-like diseases. A live-attenuated COVID-19 vaccine, COVI-VAC (Wang et al., 2021), was developed by encoding a segment of the viral spike protein using synonymous suboptimal codon pairs. The authors found that the vaccine stimulated high levels of neutralizing antibodies in a hamster model, with the highly attenuated COVI-VAC protective at a single intranasal dose. This vaccine is now in clinical trial phase III (ISRCTN15779782).

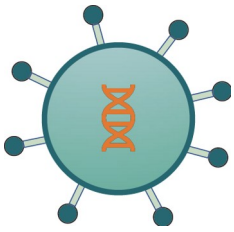
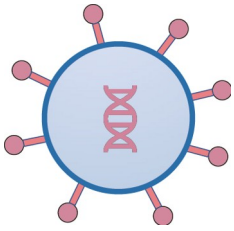
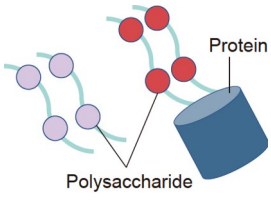
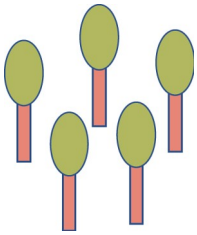
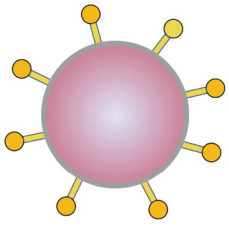
Amber (amb) mutation is a novel strategy to make safer and more effective live-attenuated vaccines. This method showed promising in generating live but replication-incompetent virus vaccines by applying genetic code expansion to the influenza virus genome. The researchers expanded the genetic code of the influenza A virus genome through transgenic cell lines containing an orthogonal translation mechanism. This approach creates premature stop codons (PTCs)—which carry viruses that are sufficiently infectious but fail to replicate in conventional cells, while produce highly reproductive and genetically stable progeny viruses in transgenic cell lines. In mouse, ferret, and guinea pig models, such live vaccines elicited robust immunity against parental and antigenically distinct strains (Si et al., 2016).

Another promising method of genetic engineering to attenuate viruses is engineering the viral genome. Researchers reported the development of a poliovirus type 2 vaccine strain (nOPV2) in which they introduced modifications to 50 untranslated regions of the Sabin2 genome to stabilize attenuation determinants. In this approach, the 2C coding region prevents recombination, and the 3D polymerase limits the adaptability of the virus. This strain is genetically more stable than the original Sabin2 strain and less likely to recover virulence. In preclinical and clinical studies, nOPV2 is immunogenic and may lead to the complete eradication of poliovirus (Yeh et al., 2020). Another group rationally designed a live-attenuated varicella vaccine candidate, v7D (Wang et al., 2022), in which the virulence factor ORF7 was deleted. The virus replicates in MRC-5 fibroblasts and human PBMC (VZV-transmitted vector) similar to a wild-type virus but is severely impaired when it infects human skin and nerve cells. Yet, v7D has comparable immunogenicity to vOka both *in vitro* and in various small animals. Finally, v7D was well tolerated and immunogenic in non-human primates. This vaccine is currently under phase II trials in China (ChiCTR1900022284). Future development of an attenuated vaccine should focus on selecting more stable virus strains and employ gene editing strategies to stabilize the attenuated factors.

Inactivated vaccines

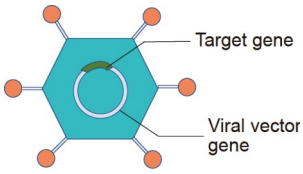
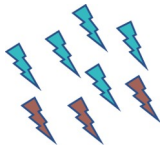
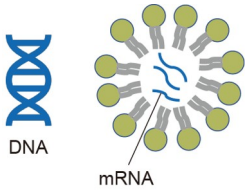
Inactivated vaccines are derived from a killed form of pathogens such as viruses or bacteria that are cultured and then inactivated by physical or chemical methods to become non-infectious or nontoxic (Sanders et al., 2014). Inactivated vaccines include the whole inactivated or fractional inactivated vaccines (Toxoid vaccines). Toxoid vaccines use inactivated toxins produced or secreted by bacteria whose

Table 1 Various types of vaccine[a)]

Vaccine type		Advantages	Disadvantages	Example of Licensed vaccines or EUA (Brand name, Developer)*
Live-attenuated vaccine		Long-lasting humoral and cellular immune responses	Inconsiderable on immunocompromised individuals; Poor thermal stability; Cold chain requirement; A risk of virulence reversal and unsuitable for highly pathogenic pathogens	Smallpox (ACAM2000, Sanofi Pasteur) Measles, mumps, rubella (M-M-RII, Merck) Tuberculosis (BCG vaccine, Organon Teknika) Cholera (Vaxchora, Emergent Travel Health) Dengue Tetravalent (DENGVAVIA, Sanofi Pasteur) Influenza (FluMist, Medimmune) Rotavirus (Rotarix, GlaxoSmithKline (GSK)) Varicella virus (VARIVAX, Merk) Typhoid (Vivotif, Berna Biotech) Yellow fever (YF-Vax, Sanofi Pasteur) Zoster (Zostavax, Merck) Hepatitis A (Haiweike, Changchun Inisitute) Japanese Encephalitis (-, Lanzhou Inisitute) Poliovirus (-, Beijing Insitute)
Inactivated vaccine		Short development cycle, relatively mature manufacture process, non-infectious virulence and high safety, temperature-resistant and can be stored for a long time	Cellular immunity is generally weak; Multiple vaccinations requirement; the virus antigen may be impaired in structure and consequent antigenicity; instability of antigen conformation and reducing the immunogenicity	Hepatitis A (Havrix; GSK; VAQTA Merck) Poliovirus (IPOL, Sanofi Pasteur) Japanese Encephalitis (IXIARO, Valneva Austria GmbH. Vienna) Diphtheria and Tetanus Toxoid (-, Sanofi Pasteur) Diphtheria and Tetanus Toxoids and Acellular Pertussis (INFANRIX, GSK) Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed and Inactivated Poliovirus (KINRIX, GSK) Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DAPTACEL, Sanofi Pasteur) Enterovirus 71 (Inlive, Sinovac) Influenza A (H1N1) 2009 Monovalent (-, CSL limited) Influenza (Fluarix Quadrivalent, GSK) Rabies (RabAvert, Novartis) Haemorrhagic Fever with Renal Syndrome (-, TOYOUVAX) Tick-borne Encephalitis (FSME-Immun, Pfizer) SARS-CoV-2 (CoronaVac, Sinovac; WIBP-CorV, Wuhan Insti. BBIBP-CorV, Beijing Institute)
Polysaccharide, Polysaccharide-protein Conjugate vaccine		Comprised of only the polysaccharide or protein, relatively mature manufacture process; conjugate vaccine facilitates TCR recognition and activation of Th responses; improve and shape titer and quality of antibodies as well as B cell memory response P	Olysaccharide vaccine show weak immunogenicity, poor persistence, and only produce T cell independent immune responses	Meningococcal Group A/C/Y/W-135 (Menomune-A/C/Y/W-135, Sanofi Pasteur) Pneumococcal Vaccine (PNEUMOVAX 23, Merck; Huiyikang, Chengdu Institute) Typhoid Vi (Typhim Vi, Sanofi Pasteur) Haemophilus B conjugte (Liquid PedvaxHIB, Merck; HIBERIX, GSK; ActHIB, Sanofi Pasteur) Pneumococcal 13-valent conjugate (Prevnar 13, Pfizer) Pneumococcal 15-valent conjugate (VAXNEUVANCE, Merck) Pneumococcal 20-valent Conjugate (PREVNAR 20, Wyeth Pharmaceuticals) Meningococcal Groups A, C, Y, W-conjugate (MenQuadfi, Sanofi Pasteur) Meningococcal Groups A, C, Y, and W-135 conjugate (MENVEO, GSK; Menactra, Sanofi Pasteur)
Recombinant Subunit vaccine		Good safety and stability, Long-lasting immunity, mature industrialization	Multiple doses required Adjuvants are required to enhance |immunogenicity	Influenza (Flublok Quadrivalent, Sanofi Pasteur) Meningococcal Group B (TRUMENBA, Wyeth Pharmaceuticals; BEXSERO, GSK) Zoster (SHINGRIX, GSK) SARS-CoV-2 (ZF2001, Zhifei; Nuvaxovid, Novavax)
Virus-like particles (VLPs), Nanoparticle vaccine		Robust immunogenicity, long-lasting immune responses, good safety, flexible antigen display and delivery	More expensive than traditional subunit vaccines, nanoparticle vaccines can trigger systemic or local inflammatory responses, some limitations in high production and storage costs	Hepatitis B (Heptavax-B, Merck; RECOMBIVAX HB, Merck; Engerix B, GSK; HBVaxPro, Merck, HEPLISAV-B, Dynavax, Fendrix, GSK; Hepavax-Gene, Crucell) Human papillomavirus (Gardasil 9; Merck; Gardasil, Merck; Cervarix, GSK; Cecolin, Wantai) Hepatitis E (Hecolin, Wantai) Malaria (Mosquirix, GSK) SARS-CoV-2 (Covifenz, Medicago)

(*To be continued on the next page*)

(*Continued*)

Vaccine type		Advantages	Disadvantages	Example of Licensed vaccines or EUA (Brand name, Developer)*
Viral vector-based vaccine		Accept the insertion of large gene fragments, induces robust humoral and cell-mediated immunity, respond to an epidemic or pandemic rapidly	Pre-existing immunity, possible reversion to virulence	Ebola (Ad5, CanSino; Ervebo; Merck; Zabdeno, Janseen; Mvabea, Janssen) SARS-CoV-2 (Convidecia, Cansino; AZD1222, AstraZenec; Ad26.COV2.S, Janssen; Covishield, Serum Institute of India; Sputnik V, Gamaleya Research Institute of Russia)
Peptide vaccine		No risk of mutation or reversal	Insufficient immunogenicity and require multiple immunizations	In clinical
DNA and mRNA vaccine		mRNA vaccine induces robust humoral and cell-mediated immunity; sustained and higher antigen expression level, rapid development, cost-effective and large-scale production compared with traditional vaccines	DNA vaccines are limited by weaker immunogenicity and require larger doses, safety and duration of antibody response require longer-term data for a comprehensive understanding	SARS-CoV-2 (ZyCoV-D, Zydus Cadila; Comirnaty, BioNTech/Pfizer; Spikevax, Moderna; AWcorna, W alvax)

a) * Data from FDA, EMA, NMPA, and Health Canada.

toxicity has been suppressed but maintained the immunogenicity (Ghattas et al., 2021). Compared with attenuated vaccines and genetically engineered vaccines, inactivated vaccines have the advantages of a short development cycle, a relatively mature manufacturing process, non-infectious virulence, and high safety. The production cost of inactivated vaccines is generally low, and because they are temperature-resistant, they can be stored for a long time. The inactivated vaccine usually induces a humoral immune response, whereas cellular immunity is weak. Multiple vaccinations are often required to generate protective immunity and thus reduce vaccine compliance. In the process of inactivation, the virus antigen may be impaired in structure and consequent antigenicity, resulting in the instability of antigen conformation and reducing the immunogenicity of the vaccine. There are many approved inactivated vaccines: representative examples include hepatitis A virus vaccine (HAVRIX and VAQTA), poliovirus (IPOL) vaccine, Japanese encephalitis virus (IXIARO) vaccine, Diphtheria and Tetanus Toxoids and Acellular Pertussis (INFANRIX) vaccine, Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed and Inactivated Poliovirus Vaccine (KINRIX) vaccine, Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DAPTACEL) vaccine, influenza vaccine (Fluarix Quadrivalent), human rabies vaccine (RabAvertandImovax), Enterovirus 71 (Inlive), Haemorrhagic Fever with Renal Syndrome vaccine, Tick-borne Encephalitis vaccine (FSME-Immun), and COVID-19 vaccine (CoronaVac, WIBP-CorV, BBIBP-Cor) (Table 1). At the time of writing, 11 inactivated vaccines against the COVID-19 disease have been approved for conditional or emergency use worldwide (including five vaccines from China).

From other pathogen studies, a Zika virus inactivated vaccine candidate (PIZV) (Baldwin et al., 2018) has been developed. After two immunization doses, the aluminum-adjuvanted candidate PIZV was shown to be highly immunogenic in both CD-1 and AG129 mice, thus supporting the progression of a PIZV candidate to clinical development (NCT03343626).

Historically, outbreaks of human hand, foot, and mouth disease (HFMD) were mainly caused by enterovirus 71 and coxsackievirus A16. More recently, coxsackievirus A6 and A10 have been associated with an increase in sporadic HFMD cases and outbreaks worldwide. In a study, coxsackievirus A6, A10, and A16 (CA6, CA10, and CA16) were inactivated by formalin or b-propiolactone (BPL) under different conditions, and examined for immune efficacy. The authors found the immune efficacy of CA10 and CA16 after BPL inactivation (BI) to be better than that after formalin treatment (Lim et al., 2018). In addition, the bi-trivalent treatment induced sufficient neutralizing antibodies and cell-mediated immune responses, indicating BI-CA6, CA10, and CA16 as potential multivalent vaccine candidates. Inactivated vaccine platforms are relatively mature, highly safe, and could be used to respond quickly to emerging pathogens, thus vital for responding to outbreaks.

Polysaccharide and polysaccharide-protein conjugate vaccines

Polysaccharide vaccines are made from carbohydrate-based polymers such as teichoic acid or peptidoglycan, which are derived from the capsular structure of bacterial pathogens. Several vaccines against bacterial capsular polysaccharides, such as Meningococcal Group A/C/Y/W-135 vaccine (Menomune-A/C/Y/W-135), Pneumococcal vaccine (Pneumovax 23), and Typhoid Vi Polysaccharide vaccine (Typhim Vi) (Table 1), have been approved to protect against invasive meningococcal and typhoid disease (Ghattas et al., 2021). However, since polysaccharides are not processed and displayed on the major histocompatibility complex (MHC) molecules like proteins, polysaccharide vaccines commonly show weak immunogenicity, poor persistence, and only produce T cell-independent immune responses (Ghattas et al., 2021; Lesinski and Westerink, 2001). Without the involvement of T cells, these vaccines do not induce a memory immune response or affinity maturation, and the induced antibodies—mainly IgM and IgG 2—are not suitable activators of complement, resulting in ineffective and temporary immune protection.

Polysaccharide-conjugate vaccines can overcome the shortcomings of polysaccharide vaccines. Polysaccharide-conjugate vaccines are prepared by covalently linking the capsular polysaccharides of pathogens to protein carriers, such as diphtheria toxoid (DT), tetanus toxoid (TT), modified diphtheria toxin termed CRM_{197}, meningococcal outer membrane protein complex (OMPC), or H. influenzae protein D HiD (Anish et al., 2021). Protein carriers and polysaccharides appear simultaneously on MHC-II, leading to T cell receptor (TCR) recognition and activation of Th responses. Interactions between Th and B cells would improve and shape the titer and quality of antibodies and the B cell memory response. Covalent conjugate methods include standard chemical cross-linking and bioconjugate technology (Anish et al., 2021; Rappuoli et al., 2019). The currently approved polysaccharide conjugate vaccines typically are produced via the chemistry approach, including the Pneumococcal 13-valent, 15-valent, and 20-valent conjugate vaccines (Prevnar 13, Vaxneuvance, Prevnar 20), Haemophilus B conjugate vaccine (Liquid PedvaxHIB, HIBERIX, ActHIB), and two Meningococcal conjugate vaccines (Groups A, C, Y, W, MenQuadfi; Groups A, C, Y, and W-135, MENVEO, Menactra)(Table 1), among others. Recently, Enotarpi et al. reported the induction of protective antibodies against Neisseria meningitidis serogroup A with MenA, a stabilized glycomimetic conjugate vaccine (Enotarpi et al., 2020). The group generated a series of non-acetylated carbaMenA oligomers, which are proven to be more stable than capsular polysaccharides (CPS), and showed that thatrandom O-acetylation of the octamer (DP8) improved the inhibition of anti-MenA CPS antibody binding and, after conjugation to CRM_{197}, elicited anti-MenA protective murine antibodies. This method can be used for generating a stabilized neoglycoconjugate vaccine.

Bioconjugation technology allows polysaccharides and carrier protein biosynthesis inside a microbe, most often *E. coli*. This is followed by *in vivo* coupling of the proteins via a specific oligosaccharide transferase from the N-linked protein glycosylation system. Biosynthesis has been favored in recent years because of its economy, rapidity, and efficiency. The first polysaccharide conjugate vaccine candidate produced by this technology is the *Shigella dysenteriae* polysaccharide conjugate vaccine (GVXN SD133) (Hatz et al., 2015), developed by GlycoVaxyn AG in Switzerland, which has completed phase I clinical trials (NCT01069471). The study demonstrated a good safety profile of the GVXN SD133 vaccine, eliciting a significant humoral response to Shigella O1 polysaccharide at all doses tested. The protein carrier also produced functional antibodies, proving the advantages of this new technology in preserving carbohydrates and binding protein epitopes. Another bioconjugate vaccine against *Shigella flexneri* 2a (Flexyn2a) (Riddle Mark et al., 2016) elicited statistically significant *S. flexneri* 2a lipopolysaccharide (LPS)-specific humoral responses in all groups post-vaccination at all time points in phase I study (NCT02388009). The results showed Flexyn2a has a satisfactory safety profile, generating robust humoral responses. This vaccine is currently under phase IIb (NCT02646371). Overall, the polysaccharide-conjugate vaccine platform has shown more potential than other platforms and offers solutions to the pressing problems and challenges associated with bacterial vaccine pressing through the gradual use of biosynthesis technology.

Recombinant subunit vaccines

The recombinant subunit vaccines use a genetic engineering approach to express pathogen-specific genes in a suitable host cell such as *E. coli*, yeast, insect cells, or mammalian cells, among others. The recombinant subunit vaccine tends to have good safety and stability. However, because exogenous proteins usually show MHC class II responses and generally do not produce strong T cell responses, adjuvant stimulation and multiple vaccinations are required to enhance immunogenicity, and this may not be suitable for respiratory mucosal immunization. The currently licensed human recombinant subunit protein vaccines include influenza vaccine (FluBlok), herpes zoster vaccine (Shingrix), meningococcal serogroup B (Trumenba, Bexsero) vaccine, and COVID-19 vaccine (ZF2001, Nuvaxovid) (Table 1).

In recent years, with the advances in theories and technologies in reverse vaccinology, structural biology, genomics, and proteomics, recombinant subunit vaccine

immunogens have gradually moved towards a new stage of rational design. The process of reverse vaccinology is developing vaccines using a bottom-up approach from the genome to the vaccine. The MenB vaccine (Bexsero), approved in 2013, is a classic case of reverse vaccinology (Pizza et al., 2000). It is based on whole-genome prediction and screening of critical protective or virulent antigens of pathogenic microorganisms followed by the development of new vaccines; such examples include three antigens: Neisseria heparin binding antigen (NHBA), factor H binding protein (fHbp), and Neisseria adhesin A (NadA). Shingrix, a recombinant subunit adjuvant vaccine developed by GlaxoSmithKline, is composed of the glycoprotein gE recombinant protein of varicella-zoster virus supplemented with a new adjuvant, $AS01_B$. Overall vaccine efficacy against herpes zoster was 97.2% in older adults (≥50 years of age) (Lal et al., 2015). The success of Shingrix emphasizes the vital role of adjuvants in vaccine development. NVX-CoV2373 (Nuvaxovid) is a recombinant protein vaccine containing the S-trimer expressed by insect cells and the Matrix-M adjuvant. Recent clinical results show a vaccine efficacy of 92.6% against any variant of concern or interest (Dunkle et al., 2021). Tuberculosis subunit vaccine M72/AS01E (GlaxoSmithKline) contains two M72 recombinant fusion immunogens (MTB32A and MTB39A) combined with the adjuvant system $AS01_E$, and provides ~50% protection against disease progression to active pulmonary tuberculosis for about 3 years in M. tuberculosis-infected, HIV-negative adults (Tait et al., 2019). In addition, another recombinant subunit tuberculosis vaccine (GamTBvac) is shown to consist of two mycobacterial antigen fusions (Ag85A and ESAT6-CFP10) with a dextran-binding domain immobilized on dextran and mixed with an adjuvant consisting of DEAE-dextran core, and CpG oligodeoxynucleotides (TLR9 agonists). The results in phase II have shown promising safety and tolerability, with the induction of an antigen-specific interferon-gamma response, Th1 cytokine-expressing CD4+ T cells, and IgG responses (Tkachuk et al., 2020).

Structural biology also facilitates rational design of the vaccine. The RSV surface fusion (F) protein exists in two conformations: pre-fusion (pre-F) and post-fusion (post-F) conformations. Based on the high-resolution complex structure of pre-F and antibodies, the F protein was modified to become stabilized in a pre-fusion state (DS-Cav1). Clinical phase I showed a more than 10-fold increase in the neutralizing activity of serum antibodies against prefusion-specific surface RSV F (Crank et al., 2019). Others designed and obtained a stable RBD-sc-dimer vaccine molecule, also based on structural interrogation. The N602 residue at the C-terminus of the RBD was designed in tandem with the N-terminus of another RBD, which improved the stability of the RBD dimer and the neutralizing antibody response (Dai et al., 2020). According to an official report, the phase III clinical data of the vaccine showed that the vaccine's protective efficacy against COVID-19 of any severity in people aged 18 years and over was 81.43% (NCT04646590). These results represent clinical evidence of the utility of structure-based vaccine design, heralding the dawn of a new era of precision vaccinology.

The recombinant subunit vaccine platform has technical advantages, such as safety and efficiency, and good stability, and a mature industry. However, safe and effective adjuvants are crucial to improving vaccine efficacy. New technologies of structural biology, reverse vaccinology, and novel adjuvants will facilitate the design of recombinant protein vaccines.

Virus-like particle and nanoparticle vaccines

Virus-like particles (VLPs) are nano-sized (20–200 nm) particles formed by the self-assembly of viral structural proteins, and their structure and immunogenicity are similar to those of natural viruses. VLPs do not contain viral genetic material, and hence, they can mimic the viral antigenicity without being pathogenic. VLPs have a highly repeated antigenic epitope array conducive to being phagocytosed by dendritic cells (DCs) and presented to MHC class I and class II molecules (Qian et al., 2020). They can activate the body to induce strong cellular and humoral immune responses, making it an ideal platform for vaccine development. Currently approved VLPs vaccines include hepatitis B (Heptavax-B, Engerix-B, Recombivax HB, HBVaxPro, Heplisav-B, Fendrix, Hepavax-Gene), HPV vaccine (Cervarix, Gardasil, Gardasil 9, Cecolin and Wozehui), hepatitis E vaccine (Hecolin), malaria vaccine (Mosquirix) and COVID-19 vaccine (Covifenz) (Table 1). In addition, a variety of VLP-based prophylactic vaccines have entered the clinical trial stage, primarily against norovirus, rotavirus, BK polyomavirus, rabies, RSV, HIV, influenza virus, among others.

The vaccine against malaria remains a big challenge. Scientists from GSK used a truncated circumsporozoite protein (CSP) combined with hepatitis B surface antigen (HBsAg) to generate protein named RTS. RTS was then co-expressed in yeast cells with another free HBsAg to generate RTS,S VLPs. However, although a three-dose vaccination with RTS,S/AS01 was initially protective against clinical malaria, vaccine efficacy waned over time and was less than effective in higher-than-average exposures to malaria parasites (Olotu et al., 2016). However, this development of the RTS,S vaccine has greatly improved our chances of achieving the long-term goal of developing an effective and safe malaria vaccine. More recently, the chimeric design of VLPs has been proposed to protect against multi-type pathogens. The authors replaced the HPV L1 loop region with the phylogenetically closely related loop region. The triple-

type chimera of HPV33/58/52 VLPs induced neutralization titers comparable to a mixture of the three wild-type VLPs in mice and non-human primates (Li et al., 2018). The authors are currently developing seven type-cross vaccines against 20 HPV variants based on this strategy (Qian et al., 2022; Yu et al., 2022). A plant-based VLPs vaccine against COVID-19 developed by Medicago Inc. was recently authorized for use in Canada (Ward et al., 2021). The vaccine contains VLPs of the SARS-CoV-2 spike (S) protein (original strain) along with the AS03 adjuvant, and shown 71% efficacy in protecting trial participants aged 18 to 64 years (https://www.canada.ca/en/health-canada/services/drugs-health-products/covid19-industry/drugs-vaccines-treatments/vaccines/medicago.html).

Nanoparticle vaccines (NPVs) use nanomaterials as carriers, linkers, or immunomodulators to link specific antigens and adjuvants by physical or chemical methods. Such nanocarrier-based delivery systems can protect the vaccine from premature degradation, improve its stability, and facilitate immunogen delivery to antigen-presenting cells (APCs), especially DCs (Diaz-Arévalo and Zeng, 2020). In addition, nanoparticles provide a suitable vaccine administration route and enhance antigen uptake with a slow-release profile, thus generating strong humoral, cellular, and mucosal immune responses. Nanoparticles can be derived from liposomes, VLPs, and metal or nonmetal inorganic, polymeric, and lipids. But as with other vaccine candidates, the production of NPVs is fraught with many difficulties and challenges. For example, some NPVs can trigger systemic or local inflammatory responses, whereas some nanomaterials will accumulate in cells, resulting in its long-term retention in the body, possibly leading to vascular thrombosis. In addition, there are still some limitations in terms of the high production and storage costs (Diaz-Arévalo and Zeng, 2020; Kheirollahpour et al., 2020).

Self-assembled protein scaffolds are also widely used in vaccine development; examples include I53-50, ferritin, mi3, and IMX313 particles. I53-50 is a two-component protein designed by computational engineering that self-assembles into an icosahedral nanoparticle. This system has been used for the development of vaccines against RSV (Marcandalli et al., 2019), influenza virus (Boyoglu-Barnum et al., 2021), and HIV (Brouwer et al., 2019), with these I53-50 vaccine candidates inducing a strong antibody response in animal models. In COVID-19 vaccine development, a multivalent SARS-CoV-2 spike receptor-binding domain nanoparticle (RBD-NP) vaccine was shown to be protective in mice after a single immunization. This RBD-NP vaccine elicits a diverse polyclonal antibody response in non-human primates (Walls et al., 2021) and is thus currently undergoing clinical trials (NCT04742738, NCT05007951). Another study presented a vaccine that displays multiple copies of the SARS-CoV-2 spike protein to induce a strong neutralizing antibody response, thus offering protection against high-dose SARS-CoV-2 challenge (Brouwer et al., 2021).

Ferritin is a natural protein cage comprising a 24-mer structure with eight threefold axes that can be used to display trimeric antigens, such as influenza hemagglutinin (HA) (Kanekiyo et al., 2013) or HIV Env protein (Jardine et al., 2013). A ferritin-based vaccine candidate is currently in phase I clinical trial (NCT04645147) against EBV, the cause of infectious mononucleosis, various cancers and autoimmune diseases. Several COVID-19 vaccines have also been designed to use ferritin to display the RBD or Spike trimer to form nanoparticles, and both vaccine candidates exhibited an elevated antibody response in preclinical studies (Joyce et al., 2021; Saunders et al., 2021).

Finally, mi3 NP, a mutated form of rationally designed i301 nano-cage, shows higher yield, homogeneity, and stability than the original form. RBD-based mi3 vaccines can induce neutralizing antibodies against SARS-CoV-2 variants and SARS-CoV (Halfmann et al., 2021). mi3 has been used to develop vaccines for influenza, classic swine fever, and malaria (Kim et al., 2022).

Displaying antigens to a scaffold can be achieved by genetic fusion, tag/catcher assembly, or chemical cross-linking. The major challenge associated with protein-based nanoparticle vaccines is to maintain the structural conformation of the antigen when fused to or displayed on a scaffold (Rodrigues et al., 2021). Nanoparticle vaccines are an exciting platform for flexible antigen display and hold great promise in vaccine development.

Viral vector-based vaccines

Viral vector-based vaccines use attenuated virus vaccine strains or non-replicating viruses as vectors to effectively deliver antigen gene codes to the nuclei of host cells to induce immune responses. The viral genome can stably accept the insertion of large gene fragments and express specific antigens so that a variety of vaccines can be developed using viral vector technology. The antigens can be precisely synthesized, modified, and targeted to specific cells in the host. Viral vectors induce body responses similar to those in response to natural infection, resulting in robust humoral and cellular immune responses. The major concern of viral-based vaccine is the pre-existing immunity against the vector, which attenuates both antibody elicitation and T-cell responses by the vaccine. Currently, many viral vectors, such as human and chimpanzee adenovirus (Ad, and ChAd), vesicular stomatitis virus (VSV), modified vaccinia virus Ankara (MVA), measles virus (MV), poxvirus, Newcastle disease virus (NDV) and other viruses have been used as vectors for vaccine development. The approved viral vector-based vaccines are Ebola virus vaccines and COVID-19 vaccines.

The first licensed Ebola virus vaccine, developed by CanSino Biotechnology, Inc., is based on an adenovirus (Ad5) vector, approved by National Medical Products Administration (NMPA) (Table 1). Others include the replication-competent VSV-based Ebola vaccine, ERVEBO, developed by Merck and approved by the Food and Drug Administration (FDA); an adenovirus Ad26 encoding Zaire Ebola virus glycoprotein, Zabdeno, developed by Janssen-Cilag International N.V. (Janssen); Mvabea, an MVA encoding for the glycoproteins of Zaire Ebola virus, Sudan Ebola virus and Marburg virus, and a nucleoprotein of the Tai Forest Ebola virus developed by Janssen. To date, there are five approved viral vector-based COVID-19 vaccines: adenovirus vector-based Ad5, developed by CanSino; AZD1222 (Vaxzevria) based on recombinant ChAdOx1 adenoviral vector (ChAd) platform, developed by AstraZeneca; Covishield (ChAdOx1_nCoV-19), developed by the Serum Institute of India Pvt. Ltd; Ad26.CoV2.S vaccine, developed by Janssen; and Sputnik V, based on the Ad26 and Ad5 vectors, developed by the Gamaleya Research Institute of Russia.

The China Center for Disease Control and Prevention (China CDC) has developed an HIV vaccine (DNA/rTV) based on DNA vaccine in combination with a replication-competent Tiantan vaccinia (rTV) vaccine containing *gag*, *pol*, and *env* genes. This vaccine protects against viral acquisition in rhesus macaques following homologous and heterologous challenge. The DNA/rTV vaccines are safe and induce an immunogenic response in phase I (ChiCTR-PRC-10001287) (Liu et al., 2015). In November 2021, a phase II clinical trial (ChiCTR1900021422) using the DNA/rTV vaccine was completed. Researchers have also constructed a COVID-19 vaccine with replication-competent recombinant viruses (rVSV-SARS-CoV-2) containing the spike protein. Results showed that the neutralizing antibody levels elicited by rVSV-SARS-CoV-2 vaccine in macaques by intranasal (i.n.) administration were 8-fold higher than that achieved via the intramuscular (i.m.) injection route (Li et al., 2021). Similarly, a mycobacterium tuberculosis vaccine, based on the NS1-del-based attenuated influenza virus vector, has also entered into phase I clinical trial (NCT03017378). Xiamen University, the University of Hong Kong, and the Beijing Wantai Biological Pharmacy developed an attenuated influenza virus-based COVID-19 vaccine, DelNS1-2019-nCoV-RBD-OPT1 (Intranasal flu-based-RBD), which is presently in phase III clinical trial (ChiCTR2100051391).

Viral vectors-based vaccines are increasingly used in the production of prophylactic vaccines because of the versatility of their manufacturing platforms and to the response time during an epidemic or pandemic. However, rare risk events remain a significant issue that need to be addressed to fully exploit the potential of this platform in the future, which is of great significance in infectious diseases and cancer.

Peptide vaccines

The immune system responds to an antigen, and usually focuses on a few amino acids (aa) or peptides, mainly B- and T-cell epitopes. Peptide vaccines are designed to identify peptide sequences on pathogens that induce a protective immune response, with these peptide sequences then used to fully synthesize vaccine substances. Because they are synthetic, there is no risk of mutation or reversal, and peptide antigens can be rapidly modified to produce specific responses (Malonis et al., 2020). However, this approach is still a practical and theoretical difficulty. Peptide vaccines often have insufficient immunogenicity by themselves, and require multiple immunizations to be effective. Immunogenicity can be enhanced by fusing the epitope peptide to a carrier protein, chemically linking the epitope peptide with a carrier protein, or artificially synthesizing repeating sequences of the related peptide. Epitopes are not usually simple sequences of amino acids; however, structural epitopes—with precise conformation—can sometimes be necessary and sufficient for antibody binding (Malonis et al., 2020). Therefore, peptide presentation in a conformation-dependent manner is an essential consideration for peptide vaccine design. Advanced peptide vaccines are currently in clinical trials, including those for influenza virus, Hepatitis C virus, HIV-1, malaria, and Alzheimer's disease vaccines.

Recently, the University Hospital Tubingen developed a peptide-based COVID-19 vaccine candidate, named CoVac-1, consisting of SARS-CoV-2 T cell epitopes derived from multiple viral proteins: spike, nucleocapsid, membrane, envelope, and open reading frame 8 (ORF8). This was in combination with the Toll-like receptor 1/2 agonist, XS15, emulsified in Montanide ISA51 VG (Heitmann et al., 2022). In phase I, open-label trial (NCT04546841), CoVac-1 has shown a favorable safety profile, and SARS-CoV-2-specific T cell responses targeting multiple vaccine peptides were induced in all participants, mediated by multifunctional T helper 1 CD4+ and CD8+ T cells. These findings demonstrated that CoVac-1 induced a broad, potent, and variant of concern-independent T cell response.

A malaria vaccine, PEV3B, contains two polypeptides from *Plasmodium falciparum* apical membrane antigen 1 (AMA-1) and circums porozoite protein (CSP). Clinical trial phases Ia (NCT00400101) (Okitsu et al., 2007) and Ib (NCT00513669) (Cech et al., 2011) demonstrated the safety and immunogenicity of the virosome-formulated PEV3B. Indeed, the AMA-1 and CSP peptide antigen-specific IgG titers were significantly higher than those in the control group at most time points. These findings provide a solid basis for further developing multivalent virion peptide vaccines for malaria.

A novel universal flu vaccine, Multimeric-001 (M-001), developed by BiondVax Pharmaceuticals Ltd. and containing

conserved epitopes from the HA, NP, and M1 proteins of influenza type A and type B strains, was designed to protect against multi-strains and multi-season influenza virus strains (Atsmon et al., 2012). Seven completed clinical trials have shown the vaccine to be safe, well-tolerated, and immunogenic to a broad range of flu strains. However, in October 2020, the phase Ⅲ clinical trial (NCT03450915) of M-001 did not show a significant difference between the placebo and vaccinated groups in reduction of flu illness. In HIV vaccine studies, a fusion peptide (FP) covalently linked to lysine residues in keyhole limpet hemocyanin (KLH), named FP-KLH, was designed as a boost after prime immunization with the Env trimer. This combination immunization scheme elicited monoclonal antibodies in mice that neutralized up to 31% of cross-clade of 208 HIV-1 strains (Xu et al., 2018). Immunization of guinea pigs and rhesus monkeys induced similar broad fusion peptide-directed neutralization responses, suggesting that the HIV-1 fusion peptide is a target for vaccines to elicit broadly neutralizing antibodies.

The development of peptide vaccines has attracted interest as an approach for various therapeutic areas, including cancer, Alzheimer's disease, and Hepatitis C virus (Malonis et al., 2020). Despite this, peptide vaccines still have challenges, including weak immunogenicity and inconsistent immune responses, which should be further improved and developed in combination with epitope design, vector optimization, and the inclusion of new adjuvants.

DNA and mRNA vaccine

Nucleic acid vaccines consist of DNA vaccines and mRNA vaccines. DNA vaccines use bacterial plasmids that encode proteins of interest under mammalian promoters, then drive the expression of antigens in the host cell. DNA vaccines can induce humoral and cellular immunity with long-term immune responses and are easy to manufacture and scale up. DNA vaccines against infectious and non-infectious diseases such as influenza, hepatitis B, HIV, malaria, SARS-CoV-2, and cancer have been tested in a few hundreds of human clinical trials (Gebre et al., 2021). Recently, India has approved the first DNA vaccine for human emergency use in 2022. The ZyCoV-D vaccine, developed by Zydus Cadila, adopted a non-replicating and non-integrating plasmid DNA carrying the genes of SARS-CoV-2. ZyCoV-D uses the needle-free system, where immunization is delivered into the skin in a narrow stream of fluid that significantly reduces side effects. In the interim report of the phase 3 clinical trial, the efficacy of ZyCoV-D vaccine reached about 66.6%. The occurrence of solicited adverse events was similar between the treatment groups. Overall, ZyCoV-D vaccine was verified to be efficacious, safe, and immunogenic in a phase Ⅲ trial (Khobragade et al., 2022). However, the immunogenicity of many DNA vaccines is lower than other vaccine platform, and the clinical results are disappointing as compared with the results seen in other mammalian animals. Also, safety issues, such as the integration of plasmid DNA into genomic DNA. DNA vaccine integration has been extensively investigated in the past, but no evidence shows integration occurring. DNA vaccines are limited by their weaker immunogenicity and require the administration of much larger doses. Furthermore, their effective delivery is still a question for future study (Gebre et al., 2021; Ghattas et al., 2021).

The mRNA vaccine works by introducing messenger RNA (mRNA) corresponding to the specific protein of the pathogen into the host cell (Gebre et al., 2021). mRNA vaccines mainly include traditional non-replicating mRNA and self-amplifying mRNA (SAM). The licensed COVID-19 vaccines, BNT162b2 and mRNA-1273, are both non-replicating mRNA vaccines. Self-amplifying RNA (SAM) has complete genes encoding for the RNA replication factors. Compared with traditional mRNA, SAM has a more sustained and higher antigen expression level. The dose required for the SAM vaccine is also much lower than that for conventional mRNA vaccines. Non-replicating and SAM vaccines express high levels of heterologous genes when introduced into the cytoplasm. mRNA vaccines can activate the innate immune system and exert an inherent adjuvant effect. mRNA vaccines are immunogenic; are recognized by pattern-recognition receptors (PRRs), such as TLR3 and TLR7/8; produce cytokines at the inoculation site; and recruit and drive the activation and maturation of innate immune cells, such as DC cells and macrophages(Chen et al., 2017; Gebre et al., 2021; Karikó et al., 2005; Karikó et al., 2004). For adaptive immunity, the translation process of mRNA is completed in the cytoplasm to generate the target antigen, which is then efficiently processed into polypeptides and presented to MHC-I molecules eliciting a cytotoxic T lymphocyte (CTL) response. The translated antigen is then secreted and presented on MHC-II proteins to helper T cells (Th) to elicit a CD4+ T cell response, which stimulates B cells to produce neutralizing antibodies and activate phagocytes through inflammatory cytokines (Liang et al., 2017; Lindgren et al., 2017). Similar to DNA vaccines, to overcome the lipid bilayer and transfer mRNA vaccines into the cytoplasm, various delivery approaches for mRNA vaccines have been developed, including gene gun, electroporation, lipid nanoparticles (LNPs), and others (Gebre et al., 2021).

The COVID-19 mRNA vaccine Comirnaty (BioNTech/Pfizer) was the first mRNA drug approved for humans by the FDA in August 2021; the Spikevax (Moderna) vaccine was also authorized for use in the USA in January 2022 and later in other countries (Table 1). Comirnaty and SpikeVax are LNP-formulated, nucleoside-modified mRNA vaccines that encode a prefusion stabilized form of the S protein of SARS-

CoV-2. In a study of 43,548 participants, BNT162b2 was 95% effective in preventing COVID-19 after two vaccine doses (Polack et al., 2020). The rate of serious adverse events was low and similar between the vaccine and placebo groups. In a phase III clinical trial involving 30,420 volunteers, the mRNA-1273 vaccine was 94.1% effective at preventing COVID-19, and, again, serious adverse events were rare (Baden et al., 2020). Another mRNA vaccine (CVnCoV), developed by CureVac, has progressed to clinical phase IIb/III. However, the efficacy of CVnCoV for symptomatic COVID-19 is 48.2% (Kremsner et al., 2022), and this trial was suspended following the emergence of SARS-CoV-2 variants. Another mRNA vaccine, ARCoV (Zhang et al., 2020), developed by Walvax Biotechnology of China, has approved by Indoneisa drug agency for emergency use in September 2022. ARCoV is thermostable and can be stored at room temperature for at least one week. ARCoV was shown to be safe and well-tolerated in phase I clinical studies and could induce robust humoral and cellular immune responses (Chen et al., 2022a), supporting a further large-scale clinical study and human use.

At present, there are more than 25 mRNA vaccine candidates against SARS-CoV-2 in clinical trials. In addition, there are many clinical trials of mRNA vaccines against other infectious diseases, including Zika virus (NCT04064905), influenza virus (NCT03345043, NCT03345043), CMV (NCT04232280, NCT03382405, NCT03382405), RSV (NCT04528719), Chikungunya virus (NCT03829384, NCT03325075), and Rabies (NCT02241135, NCT04062669).

Circular mRNA (circRNA) is a class of noncoding single-stranded RNA that can achieve protein expression by adding an internal ribosome entry site (IRES) and/or by incorporating specific nucleoside modifications to the 5′UTR. This novel platform has been shown to produce robust and stable translation in eukaryotic cells due to the extended half-life of transcripts (Kristensen et al., 2019). Recently, Qu et al. reported a SARS-CoV-2 Omicron circRNA vaccine, which induced potent humoral and cellular immune responses and enable effective protein against SARS-CoV-2 in mice and monkeys (Qu et al., 2022).

Compared with traditional vaccines, mRNA vaccines have an immune response mechanism similar to that of live viruses, no risk of infection or integration into the host genome, are more stable and capable of efficiently expressing antigenic proteins, and are produced through a rapid and cost-effective, large-scale production process. In theory, the development of mRNA vaccines only needs to replace the antigen sequence on a mature technology platform; thus, it offers a considerable advantage in preventing and controlling emerging infectious diseases. However, mRNA vaccines still have some challenges in translation efficiency and stability (Gebre et al., 2021; Ghattas et al., 2021). In addition, understanding the safety and duration of the antibody response require longer-term data. Overall, mRNA technology offers an exciting and promising avenue for vaccines, therapeutics, and beyond.

Current and future prophylactic vaccine market in China

China is one of the rare countries capable of supplying adequate vaccines by their industrial infrastructure. In recent years, China has made a tremendous effort on vaccine research and development and made significant progress, and her vaccine market is gradually becoming prosperous. According to the information about NMPA-approved drugs, there are 94 kinds of prophylactic vaccines in China's market, which afford the prevention against 38 types of diseases (Table 2). Among them, 80 vaccines are produced domestically and 11 are supplied from foreign countries; domestic vaccines dominate the market as the mainstay, while the supply of several strategic vaccines such as DPaT/IPV/Hib combined vaccine (Diphtheria, tetanus, pertussis, poliomyelitis, and Haemophilus type b), pentavalent rotavirus vaccine, HPV quadrivalent-, nine-valent- vaccine, and zoster vaccine still relies on the outside manufacturer. Recently, the approval of the domestic HPV vaccine and pneumonia vaccine exemplified China's great potential in vaccine development and manufacturing sectors. And China has developed new vaccines such as the hand-foot-mouth vaccine (EV71), hepatitis E vaccine, and Ebola vaccine. These achievements have laid a solid foundation for the rapid deployment of multi-technical vaccine breakthroughs after the emergence of SARS-CoV-2. The vaccines against infectious diseases currently available in China's market include ones against influenza, varicella, meningococcal meningitis, hepatitis A, hepatitis B, hepatitis E, rabies, diphtheria, pertussis, tetanus, haemophilus influenzae type b, poliomyelitis, tuberculosis, cholera, rotavirus, furunculosis, tracheitis, hand-foot-mouth disease, tetanus, typhoid, para-typhoid, yellow fever, leptospira, tick-borne encephalitis, Japanese encephalitis, measles, mumps, rubella, plague, pneumococcal pneumonia, anthrax, brucellosis, COVID-19, cervical cancer, bacillary dysentery, ebola hemorrhagic fever, haemorrhagic fever with renal syndrome, zoster. However, there is still a lack of vaccines against several diseases in China compared with the global market, such as dengue, meningococcal group B, and malaria. Meanwhile, it should also be noted that most vaccines in China are currently based on traditional vaccine platforms such as inactivated or live-attenuated, genetically engineered vaccines. The development of third-generation vaccine technologies such as viral vectors and nucleic acid vaccines is just beginning, and no nucleic acid vaccines are yet on China's market.

There is a dearth of vaccines for important diseases, such as HIV, RSV, Zika, and CMV vaccines, which have not yet

been successfully developed and marketed globally. In addition, other subtypes or mutant escape strains of major infectious disease pathogens have evolved. Thus, many challenges come, such as insufficient coverage of existing vaccines, such as COVID-19, influenza, tuberculosis vaccines, etc. Furthermore, some existing infectious disease vaccines have a poor preventive effect on several certain types, such as group B meningococcal vaccine, human papillomavirus vaccine, enterovirus EVD68, superbug vaccine, etc. In addition, China cannot independently afford the demand for vaccines for high-risk or special populations, such as the zoster vaccine for the elderly population. Finally, the combined vaccine is the primary line that can protect against several diseases and allow people to get protection with fewer shots. In the future, the development of a new generation of vaccine technologies should be strengthened, such as viral vector vaccines and nucleic acid vaccines.

Advances in therapeutic vaccines development

Unlike prophylactic vaccines, therapeutic vaccines refer to biological products that induce specific or non-specific immune responses to treat disease progression in patients already infected with pathogenic organisms or suffering from a particular disease. Thus, the primary aims of therapeutic vaccines are to induce tumor regression, eradicate minimal residual disease, establish lasting anti-tumor memory and avoid non-specific or adverse reactions (Saxena et al., 2021).

Therapeutic vaccines are mainly divided into four categories: peptide/protein-based vaccines, cell-based vaccines, DNA- or RNA-based vaccines and viral vector-based vaccines. According to disease classification, therapeutic vaccines can be divided into tumor-targeted vaccines, infectious disease-targeted vaccines, and chronic disease-targeted vaccines. The first FDA-approved cancer vaccine, Sipuleucel-T (Provenge, commercialized by Dendreon, Inc.), is currently used in the treatment of metastatic castration-resistant prostate cancer (Gardner et al., 2012; Kantoff et al., 2010). Provenge is an autologous, dendritic cell-based vaccine loaded with a prostatic acid phosphatase (PAP) antigen fused to granulocyte-macrophage colony-stimulating factor (GM-CSF); this vaccine, for the first time, realizes the idea of using a patient's own immune cells to attack cancer cells (Antonarakis et al., 2018). To date, more than 30,000 male patients have been treated with Provenge, which has been clinically shown to prolong the lives of men with advanced disease (Dores et al., 2019; Higano et al., 2019). The approval of Provenge was significantly encouraging within the field of therapeutic vaccines, and highlighted the fact that anticancer vaccines can work, thereby providing incentive for further investment in cancer vaccine development.

Therapeutic vaccines for cancer

Therapeutic vaccines for lung cancer

Lung cancer (LC), the most frequently diagnosed cancer and the main cause of cancer-related deaths, inflicts a heavy burden on public health worldwide due to a dismal prognosis and poor clinical outcomes, with a 5-year survival of 19% (Siegel et al., 2020); indeed, lung cancer accounts for 11.4% of total cases of cancer and is responsible for 18.0% of total cancer deaths around the globe (Hirsch et al., 2017; Sung et al., 2021). LC is classified into two main histological types: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). Traditional anti-cancer therapies (surgery, radiotherapy, and chemotherapy) have limited effectiveness in curbing progression (Freeman-Keller et al., 2015), and thus, research into the design of a therapeutic vaccine for LC is in full swing across the globe (Table 3). In 2008, Cuba developed the world's first effective therapeutic vaccine CIMAvax EGF for NSCLC, which was later approved in Cuba, Peru, and Venezuela for the treatment of advanced-stage (stages IIIB and IV) NSCLC after first-line chemotherapy (Gonzalez et al., 2003). CIMAvax EGF is composed of human recombinant epidermal growth factor (EGF) covalently combined with Neisseria meningitidis recombinant P64K protein (Neninger Vinageras et al., 2008). EGF regulates cell growth and division, with EGF overexpression in NSCLC patients associated with uncontrolled cell growth and division (Merlo et al., 2011). CIMAvax EGF slows the uncontrolled growth of cancer cells by stimulating the immune system to produce antibodies that specifically target EGF and inhibit its binding to its cognate receptors on cancer cells (González et al., 1998; Ramos et al., 2006). Phases II and III clinical trials have shown CIMAvax EGF to be well tolerated and extend patient survival, particularly those under the age of 60 years; the median overall survival (OS) for vaccinated and unvaccinated patients was 18.53 months and 7.55 months, respectively (Neninger Vinageras et al., 2008; Rodriguez et al., 2011).

Another vaccine, Vaxira, is an immunotherapeutic agent consisting of the murine gamma-type anti-idiotype monoclonal antibody Racotumomab and aluminum hydroxide (Sanchez et al., 2018). Racotumomab specifically induces an antibody response against Neu-glycolyl GM3 ganglioside (NeuGcGM3), which is overexpressed in several solid tumors (Gajdosik, 2014; Marquina et al., 1996; van Cruijsen et al., 2009). It is currently being evaluated for a number of cancer indications, including melanoma, breast and lung cancers (Alfonso et al., 2002; Díaz et al., 2003; Hernández et al., 2008; Neninger et al., 2007). Clinical trial results of Vaxira in the treatment of NSCLC showed a median survival time of 8.23 months, slightly higher than that of the control group of 6.8 months; the median progression-free survival time of the Vaxira treatment group was 5.33 months and the

Table 2 Current Licensed vaccines ma rket in China[a)]

Diseases	Vaccines	Platforms	Developers
Influenza	Influenza Vaccine (Split Virion), Inactivated, Quadrivalent	Inactivated	Hualan Bio/Shenzhen Sanofi/Changchun Institute/Sinovac (Beijing)/Shanghai Institute/ GDK Bio/Wuhan Institute
	Influenza Vaccine (Split Virion), Inactivated, Quadrivalent		Adimmune Corporation[b)]
	Influenza Vaccine (Split Virion), Inactivated	Inactivated	Shenzhen Sanofi/Lanzhou institute/CUROVAX/ Shanghai Institute/ AIM Bio/Zhejiang TOYOU-VAX Bio/Changchun Institute/Sinovac (Beijing)/ Dalian Aleph Biomed
	Influenza Vaccine (Split Virion), Inactivated		Adimmune Corporation[b)]
	Influenza Vaccine (Whole Virion), Inactivated	Inactivated	Lanzhou Institute/Beijing Institute
	Subunit Influenza Vaccine	Inactivated	Zhongyianke Bio
	Influenza Vaccine, Live, Nasal, Freeze-dried	Live-attenuated	Changchun BCHT Bio
	H1N1 Influenza A Vaccine (Split Virion), Inactivated	Inactivated	Hualan Bio/Changchun Institute/Shanghai Institute/Dalian Aleph Biomed/Beijing Institute/ Sicovac (Beijing)/Lanzhou Institute
	Pandemic Influenza Vaccine (Inactivated adjuvanted)	Inactivated	Sinovac (Beijing)
Varicella	Varicella Vaccine, Live	Live-attenuated	Sinovac (Dalian)/Shanghai Bio/Beijing Institute/ Chengdu Institute/Changchun Keygen Bio/ Changchun BCHT Bio/ROBIO
Meningococcal meningitis	Group ACYW135 Meningococca1 Polysaccharide Vaccine	Polysaccharide	Hualan Bio/AIM Bio/Chengdu KangHua Bio/ ZFSW Bio/ Walvax Biotech
	Group A and C Meningococcal Polysaccharide Vaccine	Polysaccharide	Hualan Bio/ ZFSW Bio/ Walvax Biotech/ Lanzhou Institute/ Zhejiang TOYOUVAX BIO
	Group A Meningococcal Polysaccharide Vaccine	Polysaccharide	Lanzhou Institute/Wuhan Institute/Chengdu Institute
	Group A plus Group C Meningococcal Conjugate Vaccine	Conjugate	Beijing Sanroad Bio/ROYAl BIO-PHAR/ZFSW Bio/OLYMVAX/ Walvax Biotech/ CanSinoBIO
Hepatitis A and B	Hepatitis A and B Combined Vaccine	Inactivated	Sinovac (Beijing)
Hepatitis A	Hepatitis A (Live)Vaccine, Freeze-dried	Live-attenuated	Changchun Insitute/Zhejiang Pukang Bio/ Institute of Medical Biology, Chinese Academy of Medical Sciences
	Hepatitis A Vaccine (Human Diploid Cell), Inactivated	Inactivated	AIM Bio/Sinovac (Beijing)
	Hepatitis A Vaccine (Human Diploid Cell) (VAQTA)	Inactivated	Merck Sharp & Dohme Corp.[b)]
Hepatitis B	Recombinant Hepatitis B Vaccine (Hansenula Polymorpha)	Virus-like particles	Hualan Bio/AIM Bio
	Recombinant Hepatitis B Vaccine (Saccharomyces cerevisiae)	Virus-like particles	Kangtai Bio/Beijing Institute
	Recombinant Hepatitis B Vaccine (CHO Cell)	Virus-like particles	Jiantan Biotech/Lanzhou Institute/Beijing Yadong
	Recombinant Hepatitis B Vaccine (Saccharomyces cerevisiae), Engerix B	Virus-like particles	GlaxoSmithKline Biologicals[b)]
Hepatitis E	Hepatitis E Vaccine (*E.coli*)	Virus-like particles	INNOVAX
Rabies	Rabies Vaccine (Hamster Kidney Cell) for Human Use	Inactivated	Aimei Hissen Vaccine (Dalian)/Henan Grand Bio/Yatai Bio-Phar/Lanzhou Institute/Zhongke Bio
	Rabies Vaccine (Hamester Kidney Cell) for Human Use, Freeze-dried	Inactivated	Lanzhou Institute
	Rabies Vaccine (Vero cell) for Human Use	Inactivated	Liaoning Chengda/Huikang/Dalian Aleph Biomed/Wuhan Institute
	Rabies Vaccine (Vero cell) for Human Use, Freeze-dried	Inactivated	Changchun Institute/Ningbo Rongan Bio/Shan-dong Yidu Biotech/Guangzhou Nuocheng Bio/ Changchun Zhuoyi Bio/Wuhan Institute/Yisheng Bio/Liaoning Chengda
	Rabies Vaccine (Human diploid cell) for Human Use, Freeze-dried	Inactivated	Chengdu Kanghua Bio

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Diseases	Vaccines	Platforms	Developers
Diphtheria, Tetanus and Pertussis, Haemophilus Influenzae Type b, Poliomyelitis	Diphtheria, Tetanus and Pertussis Combined Vaccine, Adsorbed	Inactivated	Lanzhou Institute/Wuhan Institute/Chengdu Institute
	Diphtheria, Tetanus and Acellular Pertussis Combined Vaccine, Adsorbed	Combined	Wuhan Institute/Walvax Biotech/Beijing Institute/Lanzhou Institute/Minhai Biotech/ Chengdu Institute
	Diphtheria, Tetanus, Acellular Pertussis and Haemophilus Influenzae Type b Combined Vaccine	Combined	Minhai Biotech
	Diphtheria Vaccine, Adsorbed	Inactivated	Chengdu Institute/Beijing Institute/Wuhan Institute/Lanzhou Institute
	Diphtheria and Tetanus Combined Vaccine, Adsorbed	Inactivated	Lanzhou Institute/Wuhan Institute/Beijing Institute
	Haemophilus Influenzae Type b Conjugate Vaccine	Conjugate	Walvax Biotech/OLYMVAX/Chengdu Institute/ZFSW Bio/Minhai Bio
	Haemophilus Influenzae Type b Conjugate Vaccine (Act-HIB)	Conjugate	SANOFI PASTEUR[b)]
	Diphtheria Vaccine for Adults and Adolescents, Adsorbed	Inactivated	Beijing Institute
	Diphtheria, Tetanus, Pertussis (Acellular, component), poliomyelitis (inactivated) vaccine and Haemophilus type b conjugate vaccine, adsorbed (PENTAXIM)	Combined	SANOFI PASTEUR[b)]
	Inactivated Poliomyelitis Vaccine Made From Sabin Strains (Vero cell)	Inactivated	Beijing Institute/Institute of Medical Biology, Chinese Academy of Medical Sciences/Sinovac (Beijing)
	Poliomyelitis Vaccine in Dragee Candy (Human Diploid Cell), Live	Live-attenuated	Institute of Medical Biology, Chinese Academy of Medical Sciences/Sinovac (Beijing)/Bejing Institute
	Poliomyelitis (Live) Vaccine (Human Diploid Cell), Oral	Live-attenuated	Beijing Institute
	Poliomyelitis (Live) Vaccine Type Ⅰ Type Ⅲ (Human Diploid Cell), Oral	Live-attenuated	Beijing Institute/Institute of Medical Biology, Chinese Academy of Medical Sciences
	Poliomyelitis Vaccine Type I Type III in Dragee Candy (Human Diploid Cell), Live	Live-attenuated	Institute of Medical Biology, Chinese Academy of Medical Sciences
	Adsorbed Diphtheria Tetanus Pertussis and r-Hepatitis B Combined Vaccine	Combined	Wuhan Institute
	Pertussis Vaccine	Inactivated	Lanzhou Institute
	Poliomyelitis Vaccine (Imovax Polio)	Inactivated	SANOFI PASTEUR[b)]
Tuberculosis	BCG Vaccine	Live-attenuated	Shanghai Institute/Chengdu Institute/Shanxi Phar
	Mycobacterium Vaccae for Injection	Inactivated	Zhifei Bio-PHAR
Rotavirus enteritis	Rotavirus (Live) Vaccine, Oral	Live-attenuated	Lanzhou Institute
	Reassortant Rotavirus Vaccine, Live, Oral, Pentavalent (Vero Cell) (ROTATEQ)	Live-attenuated	Merck Sharp & Dohme Corp.[b)]
Furunculosis	Furunculosis Vaccine	Inactivated	Wuhan Institute
Tracheitis	Tracheitis Vaccine	Inactivated	Wuhan Institute
Hand-foot-mouth disease	Enterovirus 71 Vaccine (Vero Cell), Inactivated	Inactivated	Wuhan Institute/Sinovac (Beijing)
	Enterovirus Type 71 Vaccine, Inactivated (Human Diploid cell)	Inactivated	Institute of Medical Biology, Chinese Academy of Medical Sciences
Tetanus	Tetanus Vaccine, Adsorbed	Inactivated	Wuhan Institute/Lanzhou Institute/OLYMVAX
Typhoid and Para-typhoid	Vi Polysaccharide Typhoid Vaccine	Polysaccharide	Chengdu Institute/Wuhan Institute/Lanzhou Institute/ZFSW Bio
	Typhoid and Para-typhoid A & B Combined Vaccine	Inactivated	Lanzhou Institute
Yellow Fever	Yellow Fever Vaccine, Live	Live-attenuated	Beijing Institute
Leptospira	Leptospira Vaccine	Inactivated	Wuhan Institute
Tick-borne Encephalitis	Tick-borne Encephalitis Vaccine, Inactivated	Inactivated	Changchun Institute

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Diseases	Vaccines	Platforms	Developers
Japanese Encephalitis	Japanese Encephalitis Vaccine, Live	Live-attenuated	Lanzhou Institute/Chengdu Institute/Wuhan Institute/
	Inactivated Japanese Encephalitis Vaccine for Humanuse (Vero cell)	Inactivated	Liaoning Chengda
	Inactivated Japanese Encephalitis Vaccine for Humanuse, freeze-dried (Vero cell)	Inactivated	Liaoning Chengda
	Japanese Encephalitis Purified Vaccine (PHK cell)	Inactivated	Lanzhou Institute
Measles, Mumps and Rubella	Measles, Mumps and Rubella Combined Vaccine, Live	Combined	Shanghai Institute/Beijing Institute
	Measles and Rubella Combined Vaccine, Live	Combined	Beijing Institute
	Measles and Mumps Combined Vaccine, Live	Combined	Wuhan Institute/Shanghai Institute
	Rubella Vaccine (Rabbit Kidney Cell), Live	Live-attenuated	Lanzhou Institute
	Rubella Vaccine (Human Diploid Cell), Live	Live-attenuated	Beijing Institute/Shanghai Institute
	Mumps Vaccine, Live	Live-attenuated	Sinovac (Dalian)/Beijing Institute/Wuhan Institute/Shanghai Institute/AIM Bio
	Measles Vaccine, Live	Live-attenuated	Wuhan Institute/Lanzhou Institute/Changchun Keygen Bio/Beijing Institute/Shanghai Institute
Plague	Plague Vaccine (Live) for Percutaneous Scarification	Live-attenuated	Lanzhou Institute
Pneumococcal pneumonia	23-valent Pneumococcal Polysaccharide Vaccine	Polysaccharide	Sinovac (Beijing)/Chengdu Institute/Minhai Biotech/Walvax Biotech
	23-valent Pneumococcal Polysaccharide Vaccine (Pneumovax)	Polysaccharide	Merck Sharp & Dohme Corp.[b)]
	13-Valent Pneumococcal Polysaccharide Conjugate Vaccine	Conjugate	Walvax Biotech
	13-valent Pneumococcal Polysaccharide Conjugate Vaccine (TT/DT)	Conjugate	Minhai Bio
	13-Valent Pneumococcal Polysaccharide Conjugate Vaccine (Prevenar13)	Conjugate	Pfizer Ireland Pharmaceuticals[b)]
Anthrax	Anthrax Vaccine (Live) for Percutaneous Scarification	Live-attenuated	Lanzhou Institute
Brucellosis	Brucellosis Vaccine (Live) for Percutaneous Scarification	Live-attenuated	Lanzhou Institute
COVID-19	COVID-19 Vaccine (Vero Cell), Inactivated	Inactivated	Wuhan Institute/Sinovac (Beijing)/Beijing Institute
	Recombinant COVID-19 Vaccine (CHO Cell)	Protein subunit	Zhifei Bio-PHAR
	Recombinant COVID-19 Vaccine (Adenovirus Type 5 Vector)	Virus-Vector	CanSinoBIO
Cervical cancer	Recombinant Human Papillomavirus Bivalent (Types 16, 18) Vaccine (*Escherichia coli*)	Virus-like particles	INNOVAX
	Recombinant Human Papillomavirus Bivalent (Types 16, 18) Vaccine (Pichia pastoris)	Virus-like particles	Zerun BIO
	Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed (CERVARIX)	Virus-like particles	GlaxoSmithKline Biologicals[b)]
	Recombinant Human Papillomavirus 9-Valent (Types 6, 11, 16, 18, 31, 33, 45, 52, 58) Vaccine (GARDASIL 9)	Virus-like particles	Merck Sharp & Dohme Corp[b)]
	Recombinant Human Papillomavirus Quadrivalent (Types 6, 11, 16, 18) Vaccine (GARDASIL)	Virus-like particles	Merck Sharp & Dohme Corp[b)]
Bacillary dysentery	Oral Bivalent Live Vaccine of S.flexneriza-S.sonnei	Live-attenuated	Lanzhou Institute
Ebola hemorrhagic fever	Recombinant Ebola Virus Disease Vaccine (Adenovirus Type 5 Vector)	Virus-Vector	CanSinoBIO
Cholera	Recombinant B-subunit/Whole Cell Cholera Vaccine (Enteric-coated Capsule)	Combined	Shanghai United Cell Bio
Haemorrhagic Fever with Renal Syndrome	Haemorrhagic Fever with Renal Syndrome Bivalent Vaccine (Hamster Kidney Cell), Inactivated	Inactivated	Changchun Institute
	Haemorrhagic Fever with Renal Syndrome Bivalent Vaccine (Gerbil Kidney Cell), Inactivated	Inactivated	Zhejiang TOYOUVAX BIO
Zoster	Recombinant Zoster Vaccine (CHO Cell)	Recombinant subunit	GlaxoSmithKline Biologicals[b)]

a) Data summarized from NMPA on September 15th, 2022. b) Imported vaccines.

control group was 3.9 months, demonstrating the superiority of Vaxira over a placebo (Alfonso et al., 2014). Based on the promising results from a phase II/III study, racotumomab was launched in 2013 in Cuba and Argentina as an intradermal injection for the treatment of patients with advanced stage NSCLC.

Tedopi is a neo-epitope-based vaccine with modified neoepitopes restricted to HLA-A2+ that targets five tumor-associated antigens frequently expressed in lung cancer: CEA, HER2, MAGE2, MAGE3 and P53 (Felip et al., 2019). In a phase II trial, Tedopi showed an OS of 17.3 months with a manageable safety profile in pre-treated advanced NSCLC patients (Barve et al., 2008). ATALANTE-1—a randomized, open-label, 2-Step, phase Ⅲ study—compared the efficacy of Tedopi with standard treatment (SoC) in HLA-A2+ NSCLC patients in 2nd or 3rd line treatment after progression of their disease on ICI (Giaccone et al., 2020). Tedopi works by stimulating killer T-cells, enabling them to spot and eliminate cancerous cells, which is a key process in treating disease. The results showed that, among 63 patients in the Tedopi group, 29 patients survived for at least 12 months, with a 12-months survival rate of 46%, much higher than the prespecified 25%. One patient is a 54-year-old patient with advanced LC. After five injections of Tedopi, the tumor shrank rapidly (from 39 to 23 mm). At the time of this report, the patient's survival period has exceeded 20.6 months, and it is still under observation. Now, due to its excellent clinical data, Tedopi has been granted orphan drug designation by the US FDA for the treatment of HLA-A2-positive NSCLC.

Therapeutic vaccines for breast cancer

Breast cancer (BC) is the second-most frequently diagnosed malignancy worldwide, accounting for over 2.26 million cases each year. It is also the leading cause of cancer-associated death in women (Jemal et al., 2007). To date, as of June 23rd, 2021), a total of 44 ongoing (i.e., active, not recruiting; recruiting; not yet recruiting) clinical trials are currently investigating therapeutic vaccines for BC (Corti et al., 2022). As for the vaccine platform, the majority of BC vaccines are peptide-based (N=20, 45.5%), whereas around 10 (22.7%) of the clinical trials are testing cell-based BC vaccines; new technologies such as viral-vectored vaccines account for six (13.6%) of the clinical trials, whereas gene-based BC vaccines are being assessed in 8 (18.2%) clinical trials (Corti et al., 2022).

Human epidermal growth factor receptor-2 (HER2), an ideal BC vaccine target, is a cell-surface receptor protein with tyrosine kinase activity, expressed in up to 75% of BC. HER2 plays an extremely important role in cell growth, survival and differentiation. The peptide-based vaccines targeting HER2 could induce durable specific cellular and humoral immune responses to inhibit the growth of HER2-positive tumor cells, showing high immunogenicity, strong specificity, and good safety (Slamon et al., 1989; Tovey et al., 2006). In a phase II clinical trial (NCT00524277), the HER2-derived peptide-vaccine, GP2, a subdominant epitope from the transmembrane domain (TMD) of HER2, was combined with GM-CSF, an FDA-approved immune adjuvant. This combination stimulated the proliferation of antigen-presenting cells (such as DCs, etc.) and further induced CD8+ cytotoxic T lymphocytes (CTLs) to recognize and destroy HER2/neu-expressing cancer cells (Mittendorf et al., 2016). In addition, the GP2 vaccine was well tolerated with no serious adverse effects (Carmichael et al., 2010), and BC patients treated with the GP2 vaccine after surgery along with Herceptin had a disease-free survival rate of 100% after a median follow-up of 5 years. Furthermore, the BC recurrence rate was 0% as compared with 89.4% for those who received GM-CSF alone. E75 (HER2/neu 369–377, KIFGSLAFL)-based vaccination is the most widely investigated strategy for the treatment of BC patients (Clifton et al., 2016). However, the current results show that the E75 vaccine only offers significant clinical benefit for patients with triple-negative BC and who express HLA-A24 when the treatment is combined with trastuzumab (Clifton et al., 2020); further evaluation of these effects are warranted. Other peptide-based vaccines are also in clinical trials (Table 3): AE37 (HER2/Neu 776–790, GVGSPYVSRLLGICL; in phase II clinical trial) (Mittendorf et al., 2016), TPIV100 (a multi-epitope-based vaccine targeting HER2 using sargramostim as an adjuvant; in phase II clinical trial), MVF-HER-2 (aa597–626; in phase I clinical trial) and MVF-HER-2 (aa266–296; in phase I clinical trial) (MVF-HER2 is a combination of two chimeric trastuzumab-like (MVF-HER-2, aa597–626) and pertuzumab-like (MVF-HER-2, aa266–296) HER2 B-cell peptide-based vaccines). Besides, cell-based therapeutic vaccines are patient-specific and require a safe approach for personalized vaccine development (Arab et al., 2020). Multiple cell-based vaccines targeting HER2 in BC are currently in development (Table 3): DC cells (NCT02061423, NCT04348747), PBMC cells (APC8024), and allogeneic cells (NCT00847171) have been used as immunogens for immunization. Preliminary results show that these vaccines are well-tolerated and provided specific anti-HER2 cellular immune responses (Emens et al., 2009; Park et al., 2007).

Presently, there is consideration of the various approaches used to increase the efficacy of BC therapeutic vaccines: this includes a selection of suitable cell subsets, selection of adjuvants, and different engineering methods (like VLP-based or gene-based-vaccines). However, the clinical benefits of these optimizations remain to be validated (Corti et al., 2022).

Therapeutic vaccines for colorectal cancer

Colorectal cancer (CRC) is the third-most common cancer in

the world, second only to LC and BC, with an incidence of 10.0% and a mortality rate of 9.4% of all cancers (Sung et al., 2021). The standard treatments for CRC are surgery, chemotherapy and radiotherapy, which may be used in combination (Yoshino et al., 2018). However, these treatments have many side effects, and many patients succumb to relapse even after a series of treatments (González-Perera et al., 2017; Ogura et al., 2019). Thus, it is crucial to develop alternative, effective treatments for this patient group. Although, there is no FDA-approved vaccine for CRC, numerous vaccines have been evaluated for treating CRC, including autologous, DC, peptide, and viral vector-based vaccines (Wrobel and Ahmed, 2019). OncoVAX, an autologous colon cancer vaccine mixed with live *Bacillus Calmette Guérin* (BCG), is used as an adjuvant treatment for patients after CRC resection (Khan et al., 2020). Phase III clinical trial (NCT02448173) results show that OncoVAX has no significant effect on patients with stage III colon cancer, but during a median follow-up period of 5.8 years. OncoVAX significantly prolonged the recurrence-free period for patients with stage II CRC, and reduces the overall recurrence risk rate and death risk(Uyl-de Groot et al., 2005; Vermorken et al., 1999). As an active-specific immunotherapeutic (ASI), OncoVAX enhances the immunogenicity of a patient's tumor cells with the assistance of an immunomodulatory adjuvant (BCG) to stimulate the patient's immune response against autologous (patient-specific) tumor cells. ASI-based treatment procedures generally assume the presence of different tumor antigens on the patient's tumor cells and that these antigens are absent or at lower concentrations in normal cells (Uyl-de Groot et al., 2005).

A recent study reported an adenovirus-based vaccine for the treatment of CRC and achieved positive results in a phase I clinical trial (NCT01972737). They found that the CRC antigen guanylyl cyclase C (GUCY2C) could evoke antigen-specific CD8+, but not CD4+, T-cell responses that deliver anti-tumor immunity without autoimmunity in mice (Gong et al., 2011; Snook et al., 2014). The Ad5-GUCY2C-PADRE vaccine, which consists of human serotype 5 adenovirus (Ad5) (as a vector), PADRE (a CD4+ T cell epitope active in the context of most human HLA molecules), and GUCY2C (Alexander et al., 1994; Snook et al., 2014) has also been tested: in a phase I/II clinical trial, 10 CRC patients were vaccinated and followed up over a period 6 months. The authors found that Ad5-GUCY2C-PADRE safely generated antigen-specific cytotoxic CD8+ cells, but not autoimmune CD4+ T cells, without serious adverse reactions (Snook et al., 2019).

At the 2020 American Society of Clinical Oncology (ASCO) Congress in the United States, the Mayo Clinic reported a new therapeutic vaccine, PolyPEPI1018, designed specifically for MSS-type CRC, which can effectively delay tumor progression. PolyPEPI1018 is a polypeptide vaccine consisting of six synthetic peptides. These peptides comprise 12 unique immunogenic epitopes derived from 7 conserved cancer testis antigens (CTAs) (TSP50, EpCAM, Survivin, CAGE1, SPAG9, MAGE-A8, FBXO39) that are frequently expressed in mCRC. This vaccine was optimized to induce long-lasting CRC specific T cell responses. In the OBERTO clinical phase I/II trial (NCT03391232), a total of 11 patients were vaccinated with PolyPEPI1018: 3 patients had further tumor progression, 5 patients had stable disease, 3 patients had partial tumor remission, and 2 patients had tumors that shrank to an acceptable extent with surgery. Remarkably, no viable tumor cells were found in the primary tumor after surgery, indicating that the tumor cells were killed. Therefore, these preliminarily findings suggest that PolyPEPI1018 has early clinical activity against MSS mCRC tumors and can effectively delay tumor progression (Fan et al., 2021; Hubbard et al., 2020). Therefore, further study is warranted to investigate the efficacy of PolyPEPI1018. Besides, multiple trials aiming to find the right antigenic stimulants are under investigation.

Therapeutic vaccines for liver cancer

Liver cancer is one of the most common cancers worldwide, with an incidence of 4.7% and a mortality rate of 8.3% of all cancers (Sung et al., 2021). Hepatocellular carcinoma (HCC) is the most frequently occurring type of primary liver cancer and most frequently develops on a background of chronic liver disease caused by alcohol abuse, or metabolic syndrome, or infection with hepatitis B (HBV) or hepatitis C (HCV) viruses. Indeed, HBV and HCV infections are considered major risk factors for HCC. Although various therapies are available for HCC, and the application of prophylactic vaccines, including the HBV vaccine, has been reported to decrease the prevalence of HCC (Qian et al., 2020); albeit a change in the overall survival for patients is still far from satisfactory and there is a great unmet need for more efficient therapies. The carcinoembryonic antigen glypican-3 (GPC3) is specifically overexpressed in 80% HCC but not in normal tissues and is therefore considered an ideal target for antigen-specific immunotherapy. Indeed, Nobuhiro et al., have found that GPC3 peptide can induce the immune response in mice to produce specific cytotoxic T lymphocytes (CTL) and anti-tumor activity without driving an autoimmune phenomenon (Tsuchiya et al., 2017b). Hence, most peptide-based HCC vaccines are mainly targeting the GPC3 antigen (Shimizu et al., 2019; Tsuchiya et al., 2017a).

In a phase II clinical case-control study (UMIN-CTR, UMIN000002614), disease-free survival (DFS), OS and CTL induction were compared in vaccinated and unvaccinated patients. The study confirmed that 80% of the patients relapsed regardless of administration of the GPC3

Table 3 Therapeutic vaccines for different diseases on the market or in clinical development[a)]

Disease categories	Diseases	Vaccine name	Vaccine type	Antigen	Clinical trial phase	Clinical trial number or Reference
Cancer	Prostate cancer	Provenge	DC-based	PAP	Licensed	58
	Lung cancer	CIMAvax EGF	Protein-based	EGF-P64K	Licensed (In Cuba, Peru, and Venezuela)	(Gonzalez et al., 2003)
	Lung cancer	Tedopi	Neo-epitopes-based	Epitopesfrom CEA, HER2, MAGE2, MAGE3 and P53	III	NCT02654587
	Breast cancer	GP2 peptide- GM-CSFVaccine	Peptide-based	GP2 peptide	II	NCT00524277
	Breast cancer	AE37	Peptide-based	HER2/Neu 776_790 (GVGSPYVSRLLGICL)	II	NCT04024800
	Breast cancer	TPIV100	Peptide-based	Multi-epitope-based vaccine targeting HER2	II	NCT04197687
	Breast cancer	MVF-HER-2	Peptide-based	HER-2 (597–626 and 266–296)	I	NCT01376505
	Breast cancer	MVF-HER-2(628-647)-CRL 1005 Vaccine	Peptide-based	HER2 (628–647)	I	NCT00017537
	Breast cancer	HER-2 pulsed Dendritic Cell Vaccine	DC-based	HER-2 pulsed DC	I	NCT02061423
	Breast cancer	Anti-HER2/HER3 Dendritic Cell Vaccine	DC-based	HER2/HER3 DC	II	NCT04348747
	Breast cancer	Allogeneic GM-CSF-secreting vaccine	Allogeneic cell-based	Allogeneic cell	II	NCT00847171
	Breast cancer	MV-s-NAP	Viral-based	NAP	I	NCT04521764
	Colorectal cancer	OncoVAX	Cell-based	Autologous tumour cell-BCG vaccine	III	NCT02448173
	Colorectal cancer	Ad5-hGCC-PADRE	VLP-based (Ad5)	hGCC(GUCY2C)-PADRE	I	NCT01972737
	Colorectal cancer	PolyPEPI1018	Peptide-based	TSP50, EpCAM, Survivin, CAGE1, SPAG9, MAGE-A8, FBXO39	I/II	NCT03391232
	Hepatocellular carcinoma	GPC3 peptide vaccine	Peptide-based	GPC3	II	UMIN000002614
	Hepatocellular carcinoma	ONO-7268MX1	Peptide-based	Glypican-3, WD-repeat-containing protein and nei endonuclease VIII-like three epitopes	I	JapicCTI-121933
	Hepatocellular carcinoma	ONO-7268MX2	Peptide-based	Glypican-3, WD-repeat-containing protein and nei endonuclease VIII-like three epitopes	I	JapicCTI- 142477
	Hepatocellular carcinoma	IMA970A	Peptide-based	16 TUMAPs	I/II	NCT03203005
	Hepatocellular peptides vaccine	Peptide-based	AFP-derived peptides	I	UMI-N000003514	
	Hepatocellular carcinoma	PPV-DC-CTL	Peptide-based	PPV peptides	I/II	(Shen et al., 2017)
	Hepatocellular carcinoma	Neoantigen long peptide vaccine	Peptide-based	Neoantigen long peptide	I	ChiCTR1900020990
	Gastric cancer	VEGFR1-1084 and VEGFR2-169	Peptide-based	VEGFR1-1084 peptide (SYGVLLWEIF),VEGFR2-169 peptide (RFVPDGNRI)	I/II	(Masuzawa et al., 2012)
	Gastric cancer	OTSGC-A24	Peptide-based	FOXM1, DEPDC1, KIF20A, URLC10 and VEGFR1	I/Ib	NCT01227772
	Gastric cancer	mRNA-4650	mRNA-based	20 different mRNA encoding defined neoantigens, mutations in driver genes, and HLA-I–predicted epitopes	I/II	NCT03480152
	Gastric cancer	IMU-131/HER-Vaxx	Peptide-based	The extracellular domain of HER2/neu	Ib	NCT02795988

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(*Continued*)

Disease categories	Diseases	Vaccine name	Vaccine type	Antigen	Clinical trial phase	Clinical trial number or Reference
Virus-induced infectious disease	Chronic hepatitis B	NASVAC	Protein-based	HBsAg and HBcAg	III	NCT01374308
	Chronic hepatitis B	YIC	Protein-based	HBsAg-HBIG	III	(Xu et al., 2013)
	Chronic hepatitis B	GS-4774	Protein-based	HBsAg, HBcAg and HBxAg	II	NCT02174276
	Chronic hepatitis B	εPA-44	Liposome-based nanoparticle lipopeptide vaccine	HBcAg, tetanus toxoid and HBsAg-peptide	III	ChiCTR2100043708
	Chronic hepatitis B	INO-1800 and INO-9112	DNA-based	HBsAg and human interleukin 12 DNA	I	NCT02431312
	Cervical precancer	VGX-3100	DNA-based	HPV16 E6/E7 andHPV18 E6/E7	II	NCT03603808
	Cervical cancer	pgDE7h	DNA-based	HPV16 E7-HSV1 Gd and Gemcitabine	Pre	(Ramos da Silva et al., 2021)
	Cervical cancer	GX-188E	DNA-based	HPV16 E6/E7,HPV18 E6/E7	II	NCT03444376
	Cervical cancer	TVGV1	Protein-based	HPV16 E7	IIa	NCT02576561
	CIN	PDS0101	Protein-based	MUC1	I	NCT02065973
	Cervical cancer	PDS0101 with chemotherapy and radiation therapy	Combination therapy	MUC1	IIa	NCT04580771
	OPSCC	PDS0101 and Pembrolizumab	Combination therapy	MUC1 and Pembrolizumab	II	NCT05232851
	HNSCC	PDS0101 and Pembrolizumab	Combination therapy	MUC1 and Pembrolizumab	II	NCT04260126
	AIDS	ICVAX	DNA-based	PD1 domain-Gag-p41	Pre	(Chen et al., 2022b)
	AIDS	GTU-MultiHIV B clade&HIV-LIPO-5	DNA-based and polypeptide-based	MultiHIV B clade fusion protein and Gag, Pol, and Nef peptides	II	NCT01492985
	AIDS	AGS-004	DC-based	Autologous dendritic cells and autologous HIV antigen-encoding RNA	IIb	NCT00672191
	AIDS	DCV3	MD-DC-based	Autologous inactivated HIV virus and IFNα-2a	I	NCT02767193
	AIDS	HIV-1 Tat	Protein-based	HIV-1 Tat	II	NCT00751595
	AIDS	Tat Oyi	Protein-based	HIV-1 Tat	II	NCT01793818
	AIDS	DCV3 vaccine + IFNα-2a	DC-based	Monocyte-derived DC	IIa	NCT02767193
	AIDS	IR103 REMUNE	Protein-based	Inactivated HIV-1 Antigen	III	NCT02366026
	AIDS	MVA HIV-B	VLP-based (MVA)	HIV-B antigen	II	NCT04120415
	AIDS	Ad5-gag	VLP-based (AAV)	Gag	I	NCT02762045
Chronic disease	Hypertension	CYT006-AngQb	VLP-based (Qβ)	Ang II	IIa	NCT00500786
	Hypertension	AGMG0201	DNA-based	Ang II	I/IIa	ACTR-N12617001192370
	Diabetes mellitus	CYT013-IL1bQb	VLP-based (Qβ)	IL-1β	I	NCT00924105
	Dyslipidemia	AT04A & AT06A	Peptide-based	PCSK9	I	NCT02508896

a) DC, Dendritic cell; PAP, prostatic acid phosphatase; EGF, epidermal growth factor; HER2, human epidermal growth factor receptor-2; MVA, modified vaccinia virus Ankara; GM-CSF, granulocyte-macrophage colony-stimulating factor; NAP, helicobacter pylori neutrophil activating protein; BCG, bacillus calmette-guérin; hGcc, human guanylyl cyclase C; GPC3, carcinoembryonic antigen glypican-3; TUMAPs, tumor-associated peptides; AFP, alpha-feto-protein; PPV, personalized peptide vaccination; CLT, cytotoxic lymphocytes; VEGFR, vascular endothelial growth factor receptor; HbsAg, hepatitis B surface antigen; HbcAg, hepatitis B core antigen; HbxAg, hepatitis B X antigen; HBIG, hepatitis B immune globule(antibody); HPV, human papillomavirus; CIN, cervical intraepithelial neoplasia; MUC1, Mucin 1; HSV-1, herpes simplex virus type 1; gD, glycoprotein D; AIDS, acquired immune deficiency syndrome; HIV, human immunodeficiency virus; IFNα-2a, interferon alpha 2a; AAV, adeno-associated virus; OPSCC, oropharynx cancer; HNSCC, head and neck squamous cell carcinoma; TT, tetanus toxoid; KLH, keyhole limpet hemocyanin; PSCK9, proprotein convertase subtilisin/kexin type9.

peptide vaccine. However, postoperative adjuvant vaccination may reduce the 1-year recurrence rate by approximately 15% and the 5-year and 8-year survival rates were improved by approximately 10% and 30%, respectively. Furthermore, patients who were positive for GPC3 IHC staining were more likely to have induced CTLs, and 60% of patients survived beyond 5 years (Taniguchi et al., 2020). Another two peptide cocktail vaccines (ONO-7268MX1 [JapicCTI-

121933] and ONO-7268MX2 [JapicCTI-142477]) containing GPC3, WD-repeat-containing protein up-regulated in HCC (WDRPUH) and nei endonuclease VIII-like three epitopes (NEIL3) were evaluated in advanced HCC in two phase I studies. In addition to GPC3, WDRPUH and NEIL3 were also identified as potential immunotherapeutic targets in HCC. Among them, WDRPUH with growth-promoting activity, the suppression of WDRPUH could retard the growth of cancer cells, while NEIL3, as a tumor antigen, its encoding gene shows high-frequency loss of heterozygosity in HCC, suggesting that it may be a potential tumor suppressor gene, playing a role in DNA repair (Ikeda et al., 2021). HCC patients treated with both ONO-7268MX1 and ONO-7268MX2 showed good tolerability along with induced CTL responses. Some patients also showed long-term disease control, and stable disease was reported in nine and five patients with a disease control rate of 52.9% and 35.7%, for ONO-7268MX1 and ONO-7268MX2, respectively (Ikeda et al., 2021). These results imply the potential usefulness of these vaccines for the treatment of HCC.

In addition to GPC3, other peptide-based vaccines are also being validated in clinical studies. IMA970A is a peptide-based HCC vaccine composed of 16 newly discovered tumor-associated peptides (TUMAPs) that are overexpressed in tumor tissues of HCC patients. IMA970A is delivered along with the immunostimulatory agent, CV8102, which can induce a balanced Th1/Th2 immune response. Of these TUMAPs, 7 are restricted to HLA-A*02, 5 to HLA-A*24, and 4 to HLA class II. Patients with very-early, early, and intermediate-stage HCC were enrolled to receive a single pre-vaccination infusion of low-dose cyclophosphamide followed by 9 intradermal vaccinations. Preliminary results show a favorable safety profile for the vaccine, but immunogenicity data have not yet been published (NCT03203005) (Buonaguro et al., 2020). Besides, alpha-fetoprotein (AFP), the most widely used serum marker for HCC, improves prognosis and can be used to monitor response to therapy; the safety and efficacy of AFP-derived peptide vaccines have also been validated in clinical trials (Nakagawa et al., 2017).

Another form of therapeutic vaccine for HCC is based on a personalized peptide vaccine. In 2017, a phase I/II study assessed the efficacy and safety of a new modality for the treatment of advanced HCC: cellular immune therapy based on personalized peptide vaccination (PPV-DC-CTL) in combination with radiotherapy. The results showed that the vaccine was well tolerated and caused no serious side effects, and the 9 patients in the study had good disease control, with a response rate (RR) of 33% and a disease control rate (DCR) of 66% (Shen et al., 2017). The therapeutic effect was significantly better than that reported for transcatheter arterial chemoembolization (TACE), sorafenib and chemotherapy, separately (Qin et al., 2013). Another form of personalized peptide vaccine is to use non-synonymous mutated epitope peptides derived only from malignant tumor cells as antigens (named neoantigens); these peptides are expressed in tumors together with the MHC (Wang et al., 2019; Yarchoan et al., 2017) and are therefore specifically recognized by T cells to trigger a strong anti-tumor immune response (Keskin et al., 2019). Recently, Liu's team found the personalized neoantigen vaccine strategy to be safe, feasible and efficient in preventing postoperative recurrence of HCC, and also useful in monitoring the progression of HCC through the corresponding neoantigen mutations in ctDNA; indeed, this provides reliable information for personalized medicine among patients with HCC. In a phase I clinical trial (ChiCTR1900020990), 10 patients with HCC and vascular invasion underwent radical surgical resection and prophylactic TACE within 2 months after diagnosis of HCC. Non-synonymous somatic single nucleotide variants were identified by whole-exome sequencing of tumor and peritumoral tissues. For the vaccine, 6–20 somatic point mutations or RNA-edited neoantigen long peptide (27aa) was used and mixed with the ploy:IC adjuvant as a therapy for anti-HCC recurrence. The results showed that no obvious treatment-related adverse events: Neoantigen vaccination could effectively induce and activate specific immune responses in patients with HCC and vascular infiltration, and correspondingly prolong recurrence-free survival for these patients. The median RFS of patients was 7.4 months, confirming the safety and feasibility of personalized neoantigen vaccines for preventing postoperative recurrence in patients with HCC (Cai et al., 2021). In conclusion, we discussed several examples of positive results covering peptide vaccines for cancer treatment, suggesting that induction of CTLs in humans is promising. But so far, no complete and definitive recovery case has been observed. It is necessary to further design and screen effective peptide sequences with high immunogenicity, with supplementation of high-efficiency adjuvants, or combination with other immunotherapies to achieve better tumor regression.

Therapeutic vaccines for gastric cancer

There has been a push to investigate the role of cancer vaccines in various tumor groups, including gastrointestinal cancers. Gastric cancer (GC) is the fifth-largest cancer in the world, with an incidence of 5.6% and a mortality rate of 7.7% of all cancers in 2020. Most patients with GC are found in the advanced stage, and the 5-year OS for patients with unresectable lesions due to locally advanced disease or metastatic spread ranges from only 5% to 15% (Al-Batran and Ajani, 2010). In recent years, great progress has been made in the treatment of GC with immune checkpoint inhibitors, but therapeutic vaccines for GC are still in the clinical stage (Table 3) (Kang et al., 2017; Muro et al., 2016). Therefore, many studies are exploring the potential use of a combination

of immune checkpoint inhibitors with chemotherapy and other drugs or vaccines. For example, in a previous study, patients with advanced GC were treated with a combination of human leukocyte antigen (HLA)-A24-restricted human vascular endothelial growth factor receptor 1 (VEGFR1)-1084 and VEGFR2-169 polypeptide vaccines with S-1 plus cisplatin, and the median survival time reached 14.2 months (Masuzawa et al., 2012). Another option, Gastrin-17-diphtheria toxoid immunogen (G17DT; Gastrimmune), an anti-gastrin 17 immunogen, has been confirmed that could raise high-affinity neutralizing antibodies against gastrin 17 that could block gastrin-stimulated growth and inhibit gastrin from interacting with the CCK-2 receptor. G17DT has now been used for both passive and active immunotherapy in many tumor treatments, including primary and metastatic disease (Watson and Gilliam, 2001). Indeed, the authors confirmed that, when combined with 5-fluorouracil plus cisplatin, G17DT could stimulate an immune response in the body, and those with an immune response concomitant with a longer survival (Gilliam et al., 2004).

As mentioned above, tumor-specific antigens are potential targets for immunotherapy. Four cancer-specific antigens—FOXM1, DEPDC1, KIF20A and URLC10—have been identified through studies comparing the differential protein expression between GC samples and normal tissues; these four antigens were also up-regulated in lung, esophageal, bladder cancer and other cancers (Kanehira et al., 2007; Sundar et al., 2018; Teh et al., 2010).

Angiogenesis is a key mechanism of tumor progression, and vascular epithelial growth factor (VEGF) is the most potent and specific known promoter of angiogenesis, and, therefore, it is used as a target in many vaccines (Roberts et al., 2004). OTSGC-A24 is an HLA-A*24:02-binding peptide vaccine cocktail that targets FOXM1, DEPDC1, KIF20A, URLC10 and VEGFR1. In a phase I/Ib clinical trial (NCT01227772), significant CTL responses were observed in 24 patients with advanced GC with the HLA-A*24:02 haplotype, with patients showing an OS of 5.7 months (Sundar et al., 2018).

In addition to tumor antigens, neoantigens or T cells that recognize neoantigens are present in most cancers and provide a specific and highly immunogenic target for personalized vaccine design. A phase I/II clinical trial (NCT03480152) evaluated an mRNA vaccine called mRNA-4650, which consisted of up to 20 different mRNAs that encoded for defined neoantigens, mutations in driver genes, and HLA-I–predicted epitopes in patients. Among patients with metastatic gastrointestinal cancer, the vaccine was shown to be safe and elicited mutation-specific T-cell responses against predicted neo-epitopes that were not detected prior to vaccination (Cafri et al., 2020). However, no objective clinical response has been observed, and the vaccine may be considered in combination only with other immunotherapies to enhance the therapeutic effect.

Recently, Ursula Wiedermann's team developed a therapeutic B-cell epitope vaccine (IMU-131/HER-Vaxx) and validated its immunogenicity and efficacy in patients with HER2/neu-overexpressing gastroesophageal adenocarcinomas (GEA) in a phase Ib clinical trial (NCT02795988). IMU-131/HER-Vaxx consists of three fused B-cell epitopes (P4, P6, and P7) from the extracellular domain of HER2/neu coupled to CRM_{197} and adjuvanted with Montanide. Antibodies against the IMU-131 peptides inhibit intracellular signaling by binding to three separate regions of the HER2 receptor and engaging the dimerization loop of the HER2 receptor to prevent the dimerization of the two. This blockade of the HER2 signaling pathway is supposed to be more effective than that with trastuzumab alone. In contrast, CRM_{197} (CRM; cross-linked material), an enzymatically inactive and non-toxoid form of diphtheria toxin, has been successfully used as a chaperone in various vaccines, which can rapidly activate CD4+ T cells with a heterogeneous Th1 and Th2 cytokine profile for activating B cells and regulating the quantity of the induced antibodies. In most of the 14 vaccinated GEA patients, HER2-specific antibodies and T cell responses were detected, and IMU-131 showed good tolerability and safety (Tobias et al., 2017; Wiedermann et al., 2021).

Therapeutic vaccines for virus-induced infectious disease

Therapeutic vaccines for hepatitis B virus

Hepatitis B virus (HBV) belongs to the *Hepadnaviridae* family and is a partially double-stranded enveloped DNA virus (Rajoriya et al., 2017). As mentioned above, HBV infection is one of the important factors leading to HCC, but not all HBV infections progress to cancer. On the contrary, chronic hepatitis B (CHB) caused by HBV has a wider impact on public health. Despite decades of aggressive vaccination, 2 billion people worldwide have hepatitis B serologic profiles, of which 250 million have chronic hepatitis B (Karayiannis, 2017). Currently, there are only two approved drugs for CHB: nucleotide analogs and pegylated interferon (IFN), both of which are effective at inhibiting viral replication but not effective in clearing the viral genome or serum from infected hepatocyte HBV surface antigens (HBsAg) (Horng et al., 2020). Therefore, there is an urgent need to explore new therapeutic approaches. Currently, 2 therapeutic vaccines (NASVAC and YIC) have completed phase III clinical trials. In addition, 3 vaccines have completed phase II clinical trials, of which 2 (GS-4774 and HB02 VAC-ADN) did not reach the primary endpoint, and 1 (εPA-44) reached the treatment endpoint and entered phase III clinical trials. Three more therapeutic vaccines (CVI-HBV-002, VBI-2601 and HepTcell) are in phase II clinical trials, and many are in phase I clinical trials (Table 3).

The HBV capsid is mainly composed of HBsAg, HBcAg, HBeAg and HbxAg (Rajoriya et al., 2017). At present, most HBV therapeutic vaccines focus on HBsAg and HBcAg as the main immunogens. In a phase III clinical trial, naïve patients with CHB were treated with NASVAC, a therapeutic vaccine containing HBsAg and HBcAg. The authors found that 85% of the 80 patients vaccinated with NASVAC had elevated alanine aminotransferase (ALT) levels and had cleared HbeAg (Al Mahtab et al., 2018). Another phase III clinical trial evaluated an alum-adjuvanted therapeutic hepatitis B vaccine (YIC) composed of antigen (HBsAg)-antibody (HBIG [hepatitis B immune globule]) immunogenic complexes. This study aimed to eliminate immune tolerance by altering the processes and presence of HBV antigens in patients. Unfortunately, phase III results for the vaccine failed to meet the clinical endpoint of achieving HBeAg seroconversion in patients (Xu et al., 2013).

One phase II trial (NCT02174276) evaluated the efficacy of the GS-4774 vaccine consisting of HBs, HBc, and HBx fusion antigens. The results showed that, while GS-4774 was safe and had a strong immune-stimulating effect on CD8+ T cells, and it failed to reduce HBsAg levels in patients (Boni et al., 2019). There are plans to explore this drug's efficacy in combination with other antiviral drugs.

A recent study reported the potential role of HBxAg alone as the primary immunogen. HBxAg induced systemic HBx-specific CD4+ and CD8+ T cell responses in HBV-bearing mice and showed marked HBs and HBV-DNA depletion, with protection that lasted for at least 30 days (Horng et al., 2020). Although this study is only in the preclinical stage, the HBV clearance effect demonstrated by the vaccine makes its future development hopeful. Another currently promising vaccine is the *de novo*-designed liposome-based nanoparticle lipopeptide vaccine, εPA-44 (NCT00869778). In HLA-A2-positive patients with progressive CHB, a finite concentration of 900 μg of εPA-44 resulted in a significantly higher HBeAg seroconversion rate than did the placebo along with a sustained off-treatment effect (Wei et al., 2022). A phase III clinical trial is ongoing (ChiCTR2100043708).

Other CHB therapeutic vaccines based on viral vectors or genomes are also ongoing. A phase I clinical trial (NCT02431312) has evaluated the safety, tolerability, and immunogenicity of the INO-1800 (DNA plasmids encoding HBsAg and HBcAg) alone or in combination with INO-9112 (DNA plasmid encoding human interleukin 12) vaccine. Preliminary immunological data has shown that patients treated with INO-1800 could generate T cells that recognized the core components of HBV and cleared HBV from the liver by the way of interferon gamma release. Moreover, INO-1800 can activate and expand CD8+ killer T cells; although other clinical data have not yet been published (https://clinicaltrials.gov). In another phase I/II clinical trial, a DNA-based vaccine called ANRS HB02 VAC-AND, encoding HBsAg, induced a sustained HBV-specific CD4+ T cell response in CHB patients treated with NAs, but most patients experienced virological rebound after discontinuation of NAs(Fontaine et al., 2011).

Therapeutic vaccine for human papillomavirus

Cervical cancer is the fourth-most prevalent cancer in women, and mainly caused by persistent infection with high-risk human papillomavirus (HR-HPV). According to the WHO, in 2020, about 604,127 women were newly diagnosed with cervical cancer worldwide, with 341,831 deaths. Although a variety of preventive vaccines are available, the prevalence and mortality of cervical cancer remains high, and there is no approved non-surgical treatment. Therefore, research on HPV therapeutic vaccines is necessary. Unlike preventive vaccines that focus on the HPV L1 protein, therapeutic vaccines mainly target the HPV early proteins E5, E6 and E7, which are highly expressed in tumor cells. a variety of different forms of vaccines have entered clinical trials based on the E6/E7 protein (Table 3), with data indicating good development potential. Indeed, five different DNA therapeutic vaccines (GX-188E, VGX-3100, pNGVL4a-CRT/E7 (detox), pNGVL4a-Sig/E7 (detox)/HSP70, MEDI0457) are shown to be well tolerated and clinically effective (Akhatova et al., 2021). Among them, the VGX-3100 vaccine has entered phase III clinical trials.

VGX-3100 is the first immunotherapy targeting HPV-related cervical precancer. It contains the E6 and E7 DNA of HPV16 and 18, and was injected intramuscularly using the CELLECTRA 5PSP electroporation technique. The results showed that VGX-3100 could elicit a systemic immune response, with histopathological regression in 49.5% of the three-dose vaccine recipients, and an HPV clearance rate of 40.2%, which was higher than that of placebo recipients (30.6% and 15.4%). A phase III trial (REVEAL) is currently underway to confirm the efficacy, safety and tolerability of VGX-3100 in women with HPV16/18-positive high-grade squamous lesion (CIN2/3) (Trimble et al., 2015).

Given the limited results associated with complete remission for monotherapy vaccine treatments for cervical cancer, combination therapy using vaccines and immunotherapy agents may provide a more robust immunological response. Another DNA-based vaccine pgDE7h (encoding HPV16 E7 fused to the herpes simplex virus type 1 (HSV-1) glycoprotein D (gD)) was found to have a synergistic antitumor effect when combined with Gemcitabine (Gem), a nucleoside analogue used in the clinic for a wide range of tumors. This combination induced tumor-specific cytotoxic CD8+ T cells and eradicated existing tumors (Ramos da Silva et al., 2021). In addition, one study found that pembrolizumab combined with the GX-188E (a DNA-based vaccine engineered to express E6 and E7 proteins of HPV16 and HPV18 fused to extracellular domain of Flt3L and the signa sequence of

tissue plasminogen activator) offers a new possible regimen for CIN3 patients (Choi et al., 2020).

Protein-based vaccines are processed by antigen-presenting cells (APCs), which results in the presentation of antigens via HLA class I and class II for the generation of CD8+ and CD4+ T-cell responses without type restriction (Smalley Rumfield et al., 2020b). TVGV1 is a fusion protein-based vaccine comprising two antigens, *Pseudomonas aeruginosa* exotoxin and KDEL endoplasmic reticulum retention signal fused to HPV16 E7, and adjuvanted with CpG ODN or GPI-0100. This vaccine has been shown to induce T cell responses and provide potent inhibition of HPV16-transformed B6 tumors (Da Silva et al., 2019). A phase IIa clinical trial is currently underway in women with high-grade HPV cervical infection (NCT02576561).

There are also several polypeptide-based vaccines that use non-E6/E7 proteins as immunogens. PDS0101 is a non-MHC-restricted vaccine based on the tumor-associated antigen MUC1, which is highly expressed in tumors. This vaccine uses R-1,2-dioleoyl-3-trimethyl-ammonium-propane (R-DOTAP) (a liposomal carrier that activates TLR7) as the adjuvant (Smalley Rumfield et al., 2020a). PDS0101 was found to be safe and tolerated in a phase I dose-escalation trial (NCT02065973). Vaccination resulted in resolution of CIN in a non-MHC-restricted manner in all patients. Several phase II trials combining PDS0101 with other immunomodulatory therapies have been initiated (Table 3).

Therapeutic vaccines for human immunodeficiency virus

Despite 40 years of intensive research since the first clinical observations of AIDS and the subsequent isolation of the etiologic retrovirus HIV in the early 1980s, the HIV/AIDS epidemic remains a major global health threat to humans. Indeed, as of 2020, 38 million people are still living with HIV (Jin et al., 2020). Current treatment strategies for HIV/AIDS include the use of antiretroviral therapy (ART), which has helped transform AIDS from a life-threatening illness to a manageable chronic disease, and has significantly increased the life expectancy of HIV-infected persons. However, the presence of viral reservoirs formed by latently infected cells results in patients having to undergo life-long maintenance therapy (Espinar-Buitrago and Muñoz-Fernández, 2022). In the absence of effective eradication strategies for HIV-1, HIV research efforts are focused on developing cures.

The SARS-CoV-2 pandemic introduced the world to an effective form of vaccine based on mRNA encapsulated in lipid nanoparticles (LNPs). ICVAX, a PD1-based DNA vaccine against HIV-1, encodes a recombinant antigen consisting of the human soluble PD1 domain fused with two mosaic Gag-p41 antigens, and can induce broad and polyfunctional T cell responses against different HIV-1 subtypes; these findings highlight the great potential to translate PD1-based DNA vaccine approaches for clinical use (Chen et al., 2022b). A phase II clinical trial (NCT01492985) evaluated the therapeutic effect of a DNA-based vaccine (GTU-MultiHIV B clade) combined with a polypeptide-based vaccine (HIV-LIPO-5), and found that the primary-booster immunization of the DNA and LIPO-5 vaccines elicited a wider range of pluripotent T cells than the vaccine alone, but failed to control viremia following interruption of antiretroviral therapy, suggesting the importance of combining vaccine strategies with other immunization-based interventions (Lévy et al., 2021). Other vaccine formats, such as AGS-004, which consists of mature autologous dendritic cells and in vitro-transcribed autologous HIV antigen-encoding RNA, are being validated in Phase IIb clinical trial. Compared with the placebo group, AGS-004 elicited strong and polyfunctional HIV-specific T-cell responses. However, an antiviral effect was not detectable (Gay et al., 2018). Another study combined a monocyte-derived dendritic cell (MD-DC)-based vaccine (loaded with high doses of HIV-1 heat-inactivated autoantigen) with pegylated interferon alpha 2a (IFNα-2a) in chronic HIV-1 patients with suboptimal results (Leal et al., 2021). Overall, there is a long way to go to develop a vaccine against HIV.

Therapeutic vaccines for chronic disease

Cardiovascular disease (CVD) is the main chronic disease leading to death worldwide, and hypertension, dyslipidemia and diabetes are the main causes of CVD (Fukami et al., 2021). Vaccine research for hypertension, dyslipidemia, and diabetes has spanned more than 60 years. With gradual improvements in various vaccine construction models, many therapeutic vaccines are currently in clinical trial, but no vaccine has been launched due to poor treatment compliance.

Therapeutic vaccines for hypertension

The renin-angiotensin system (RAS), including renin, angiotensin I (Ang I), angiotensin II (Ang II), and AT1R, is the primary target of therapeutic vaccines for hypertension. The earliest hypertensive vaccines targeted renin. However, they were eventually terminated due to damage to the kidneys (Page et al., 1941). Subsequently, the efficacy of AngI-targeted hypertension vaccines, such as PMD2850 and PMD3117, was also verified in a number of clinical trials, but all ended in failure (Brown et al., 2004; Downham et al., 2003). Ang II is another main target of many hypertension vaccines, such as the CYT006-AngQb developed by Cytos in Switzerland in 2007 (a vaccine composed of Ang II-conjugated bacteriophage Qβ (AngQb) VLP). The vaccine was well tolerated and induced anti-Ang II antibodies in all subjects, with a half-life of approximately 4 months (Tissot et al., 2008). Also based on Ang II, Koriyama et al. constructed the Ang II DNA vaccine encoding the fusion protein

of Ang II and HBcAg, which can effectively reduce blood pressure for at least 6 months (Koriyama et al., 2015). In 2022, a placebo-controlled dose-escalation study was conducted to investigate the safety, tolerability, and immune responses generated in response to a modified Ang II DNA vaccine (AGMG0201). The results showed that AGMG0201 was well tolerated and could also induce anti-angiotensin II antibodies (Nakagami et al., 2022).

In addition to the RAS-targeting vaccine, Liao's team has developed a hypotensive vaccine (ADRQβ-004) targeting the sympathetic nervous system (SNS) α1D-adrenoceptor, which exhibited good blood pressure reduction in rats and could effectively prevent vascular structural remodeling, cardiac hypertrophy and fibrosis, as well as renal injury in hypertensive animals (Li et al., 2019). Wu et al. designed the epitope CE12 derived from human L-type calcium channel (CaV 1.2) and bound it to Qβ VLPs and HBcAg VLPs, respectively, to test the efficacy of the epitope in hypertensive animals. Both Qβ-CE12 and HBcAg-CE12-CQ10 vaccines effectively reduced blood pressure in hypertensive rodents, and HBcAg-CE12-CQ10 also ameliorated L-NAME-induced kidney injury (Wu et al., 2020). Dai et al. developed a vaccine, ETRQβ-002, against endothelin-1 (ET-1) type A receptor (ETAR), and confirmed that the vaccine can significantly reduce the pulmonary hypertension caused by monocrotaline (MCT)- and Sugen/hypoxia in rats; it also ameliorated any pathological remodeling of the pulmonary arterioles (Dai et al., 2019). In summary, vaccines targeting Ang II and AT1R of RAS, α1DAR kidney and LCaCd of SNS, and ETAR constitute a series of candidates for therapeutic vaccines for hypertension, and sets the foundation for continued research for combined treatment of hypertension vaccines.

Therapeutic vaccines for Diabetes mellitus

Diabetes mellitus (DM), a metabolic disease characterized by hyperglycemia, is a highly prevalent chronic condition in adults worldwide. Globally, an estimated 382 million people are living with DM, and this number is expected to reach nearly 600 million by 2035 (Verstraeten et al., 2020). DM can be divided into type 1 and type 2 DM according to the pathogenesis of the disease. DM type 1 is an autoimmune disease in which autoimmune T cells attack insulin-producing β cells. Glutamate decarboxylase (GAD) is a major target of the autoimmune response in DM type 1; albeit several clinical trials of GAD-based vaccines have yielded conflicting results (Lu et al., 2018). Surprisingly, Bacillus Calmette-Guérin (BCG) vaccine was administered to patients with DM type 1. An 8-year follow-up clinical trial showed that the BCG vaccine offered long-term effects: it was well tolerated, and led to the stable reduction of epigenetic changes in blood glucose and Treg signature genes in patients with DM (Kühtreiber et al., 2018). In 2017, the D41-IA2(5)-P2-1 vaccine designed by Li et al. was considered as a promising treatment for DM type 1. D41-IA2(5)-P2-1 consists of a peptide of DPP4, an anti-diabetic B epitope of Insulinoma antigen-2 (IA-2), and a Th2 epitope (P2: IPALDSLTPANED) of P277 peptide from human heat shock protein 60 (HSP60), which can significantly control hyperglycemia (Li et al., 2017a). Similar to D41-IA2(5)-P2-1, a U-IA-2(5)-P2-1 (UIP-1) chimeric vaccine, designed by Li Z et al., could also successfully increase insulin levels and decrease blood glucose levels in mice after immunization (Li et al., 2017b).

Although the pathological mechanism of DM type 2 is unclear, there are 4 known targets: adipose tissue antigen, somatostatin, glucose-dependent insulin denaturing polypeptide (GIP) and ghrelin (Monteiro, 2014). Interleukin-1β (IL-1β) is a major pro-inflammatory substrate in the pathogenesis of DM type 2, and there is evidence to suggest that reducing IL-1β activity may serve as a new therapeutic strategy for DM type 2. The vaccine hIL1bQb, consisting of full-length, recombinant IL-1β coupled to Qβ VLPs, was tested in a preclinical and clinical, randomized, placebo-controlled, double-blind study in patients with type 2 DM. The results showed the Hil1bQb vaccine targeting IL-1β to be safe and well tolerated, with neutralizing IL-1β-specific antibody responses detectable after six injections with doses of 900 μg in these patients (Cavelti-Weder et al., 2016). At present, the pathogenesis of DM and the key targets of glucose metabolism are still unclear. Further exploration in the field of diabetes vaccines is expected to offer new solutions.

Therapeutic vaccines for dyslipidemia

Dyslipidemia is a key risk factor for CVD and is typically characterized by high low-density lipoprotein (LDL) cholesterol, low high-density lipoprotein (HDL) cholesterol, or hypertriglyceridemia (Fukami et al., 2021). The proprotein convertase subtilisin/kexin type 9 (PCSK9) regulates LDL receptor expression through receptor internalization and subsequent lysosomal degradation and is a known anti-hyperlipidemic drug or vaccine target. To date, the most advanced methods to inhibit PCSK9 are monoclonal antibodies (mAbs), such as the well-known alirocumab and evolocumab, which were approved by the FDA in 2015, and provided solid clinical evidence for the development of PCSK9 vaccines (Jones, 2015; Robinson et al., 2015). AT04A and AT06A are two AFFITOPE peptide vaccine candidates that treat hypercholesterolemia by inducing PCSK9-specific antibodies. The results of a phase I clinical trial (NCT02508896) showed that both AT04A and AT06 were safe and immunogenic, but only AT04A exhibited significant LDLc-lowering activity (Zeitlinger et al., 2021).

There are other vaccines targeting PCSK9; for example, the Qβ VLP-based vaccine PCSK9Qβ-003. This vaccine can significantly reduce total cholesterol and PCSK9 expression

in Balb/c mice and LDLR$^{+/-}$ mice, and also up-regulate liver LDLR, SREBP-2, Hepatocyte nuclear factor-1α (HNF-1α) and HMG CoA reductase levels (Pan et al., 2017). Besides, a vaccine consisting of a short peptide of PCSK-9 fusion to KLH elicited significant long-acting antibody responses against PCSK9 in male apolipoprotein E (ApoE)-deficient mice (Kawakami et al., 2018). An immunogenic peptide, called immunogenic fusion PCSK9-tetanus (IFPT), was conjugated to the surface of nanoliposomes using DSPE-PEG-maleimide lipid (L-IFPT) and adsorbed to Alhydrogel (L-IFPTA+); this vaccine candidate induced a high IgG antibody response to the PCSK9 peptide and reduced plasma concentrations by up to 58.5% in hypercholesterolemic mice (Momtazi-Borojeni et al., 2019).

Recently, angiopoietin-like protein (ANGPTL) 3 has received attention as a novel target for LDL-C- and TG-lowering strategies. Anti-ANGPTL3 antibodies, antisense oligonucleotides and small-interfering RNAs targeting ANGPTL3 have been developed as targeted ANGPTL3 inhibitors and are in clinical trial (NCT03409744, NCT03452228, NCT03747224). Fukami et al. designed 3 epitope peptide-based vaccines targeting ANGPTL3 (E1-E3), of which the E3 (32EPKSRFAMLD41) peptide did not induce cytotoxicity and significantly reduced circulating levels of triglycerides, LDL-C, and small dense (sd)-LDL-C in ob/ob mice; it also decreased obesity-induced fatty liver disease (Fukami et al., 2021). In addition to the targets of PCSK9 and ANGPTL3, it is also necessary to study other target vaccines related to cholesterol and triglyceride metabolism, such as ApoB-100, to accelerate the promotion of vaccines that effectively inhibit dyslipidemia.

Conclusions and future perspectives

Vaccines are essential public health tools and play important roles in reducing the burden of infectious diseases in the population. Over the past 20 years, the types of diseases that can be effectively prevented by vaccines have continued to increase to more than 40. Indeed, the emergence of the preventive effect of the HPV vaccine on related malignant tumors and the launch of the therapeutic vaccine for prostate cancer marked a further expansion of the utility of vaccines from traditional prevention to treatment. However, still unclear are the key pathogenic factors and potential interventions for many major infectious diseases, particularly those caused by complex pathogenic infections (AIDS and tuberculosis), and chronic diseases represented by tumors and metabolic disease. The development of vaccines against these diseases is world-class. For sudden major infectious diseases such as SARS-CoV-1 and SARS-CoV-2, weak immune responses or unexpected immune responses (such as antibody-mediated infection enhancement, ADE) are difficult problems to solve in innovative vaccine research. Therefore, the development of a new generation of more efficient vaccines requires efforts in four directions, as explored below.

(i) Adjuvant: There are several important factors to consider related to adjuvants. There needs to be control and improvement of the physicochemical properties of adjuvants, optimization of the production processes, and in-depth research analysis as to the mechanism of action of adjuvants to fully understand their impact on the immune system. It is also important that we continue to explore the optimal combination(s) of adjuvants and tumor antigens to enhance vaccine immunogenicity, and work to design novel complex adjuvants that target subunit antigens, proteins or peptides of different pathogens; this will be aided by the production of chemical and new synthetic material technologies to enhance the targeted delivery of antigens to immune cells (next point), and overcome the inhibition of antigen presentation by the tumor immunosuppressive microenvironment. It may also help to activate tumor-specific T cells in a state of immune exhaustion and senescence, and promote the formation of memory T cells.

(ii) Delivery system: The ultimate goal of a drug/vaccine delivery system is to deliver cargo to a target site(s) with predetermined release kinetics and duration of effect. No single tool is suitable for all forms of treatment, with different vaccine formats each having their advantages and disadvantages that require optimization for delivery and treatment. Indeed, it is necessary to understand differences in drug absorption, distribution, metabolism and elimination between humans and animals, and explore the best combination of different vaccine antigens or drugs and delivery systems. The COVID-19 pandemic reminds us that the future is uncertain, and we need to continuously develop novel delivery systems to adapt to the trend of diversified and precise vaccine development. It is also pertinent to pay attention to the efficiency and targeting of delivery systems, and more attention should be paid to the safety and clinical translation feasibility of the delivery system itself.

(iii) Discovery and screening of neoantigens: Combined with clinical and laboratory research results, it will be vital to comprehensively employ and assess multi-omics data and other automated high-throughput functional screening tools to vigorously develop new theories and technologies for unique or general vaccine target screening and discovery in various fields. Furthermore, through next-generation sequencing and bioinformatics technologies, it will be necessary to design more efficient prediction algorithms to improve the odds of finding effective tumor antigens as vaccine targets.

(iv) Combination therapy: Because of the heterogeneous and complex immunosuppressive microenvironment of tumors, single-agent immunotherapy often fails to provide

good outcomes, generally leading to low response rates or secondary resistance. Therefore, immunotherapy often tends to be used in combination with different treatment methods. Immunotherapies, such as immune checkpoint inhibitors (ICI) and adoptive cell therapy (ACT), have revolutionized cancer treatment, especially for metastatic cancers. Indeed, this has been seen through the combination of multiple tumor targets in the design tumor vaccines, and in the supplemental use of immunotherapy to diversify tumor treatments. Indeed, fostering such strengths and avoiding weaknesses can significantly improve the treatment for patients with cancer.

Vaccination has historically proven to provide health and well-being, and new technologies offer new possibilities to address challenges where traditional approaches have failed. However, there is limited data available on the safety of new technologies, and consideration is needed in terms of the feasibility of vaccine production and transformation, and the complexity of human immune responses. New technologies and strategies will help address complex or severe diseases facing humanity now or in the future, and this knowledge will be important for the design of effective vaccines.

Data Availability Statement: All relevant data are within the manuscript.

Compliance and ethics *The author(s) declare that they have no conflict of interest.*

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