The Explosion of Therapeutic Modalities: Small Molecules, Biologics, and Everything in Between

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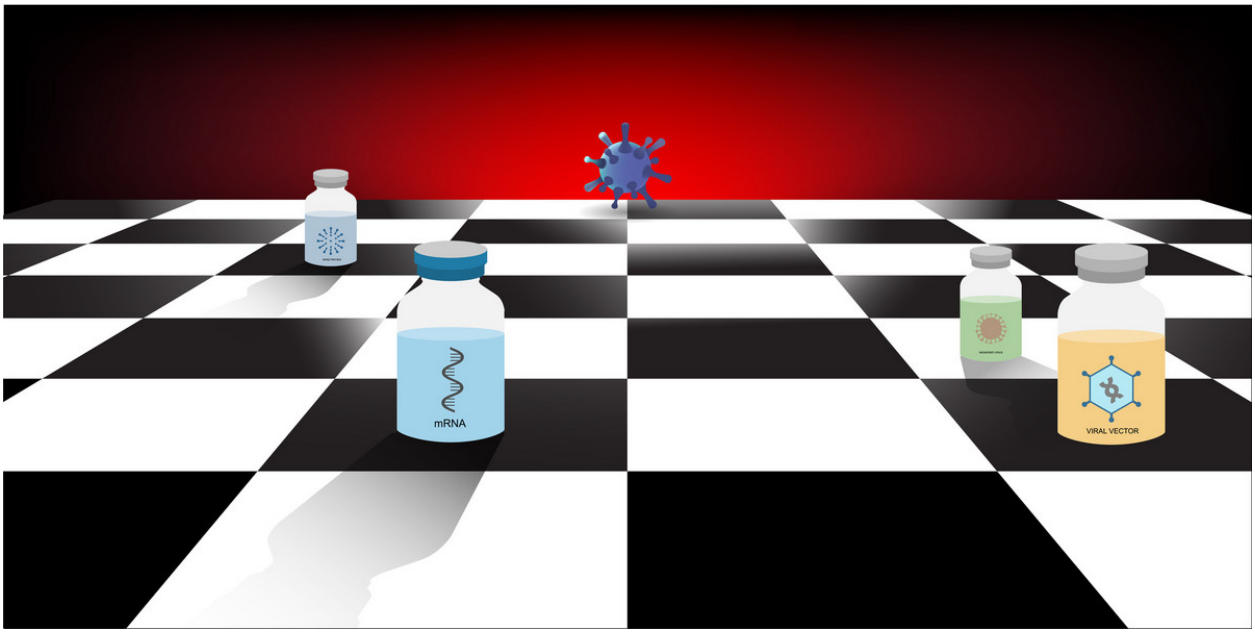
Since the early days of the pharmaceutical industry, small molecules have been the most extensively used group of drugs. Nowadays, up to 90% of the on-the-market therapeutics are small molecules, which can be explained by some of their unique features. Firstly, their size permits easy ingestion and distribution all over the body with a bloodstream allowing a convenient, non-invasive oral route of administration. Small molecules efficiently penetrate cell membranes to reach intracellular targets, exhibit a variety of action mechanisms due to their physicochemical properties and provide direct interaction with a target.

However, small molecules are rather promiscuous, usually bind to various off-target sites, rendering side effects or toxicity. Furthermore, small molecules are prone to drug-drug interactions that can occur due to the presence of concomitant drugs that affect their transport, metabolism, or elimination pathways. Finally, small molecules can't usually target protein-protein interactions -- one of the most important aspects of biological machinery.

According to scientists from Vanderbilt University, 3,000 out of 20,000 proteins of the human proteome are considered “druggable” and only half of all genes involved in disease pathogenesis can be influenced.



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Luckily, many issues that can't be addressed with small molecules are tackled with larger moieties – biologics, which are produced by living organisms or contain compounds of living organisms. The group is broad and includes proteins, antibodies, hormones, modified RNA molecules, cell and gene therapies, etc. Active biologics development started at the end of the 20th century and revolutionized the healthcare world, as they managed to meet medical conditions previously considered untreatable.

The major explosion of innovative biological modalities took place in the first two decades of the 21st century. New treatments include various types of antibodies and antibody-drug conjugates, BITE (Bispecific T cell Engager) molecules designed to treat cancer, CAR-T and TCR-T cells – a new step in immunotherapies evolution, and oncolytic viruses. Fusion proteins, peptides, and peptibodies (proteins fused to antibodies) form a separate group of therapeutics. Modified RNA molecules, antisense nucleotides, and iRNAs are becoming more and more popular with their ability to control protein expression. In this review, we discuss in detail some of the most promising pharmaceutical modalities that were developed recently.

Antibody-drug conjugates

Antibody-drug conjugates (ADCs) are a novel class of biological drugs designed to selectively deliver cytotoxic drugs to a variety of cancer cells. ADCs consist of cytotoxic drugs attached to monoclonal antibodies through a linker. The unique nature of monoclonal antibodies enables targeted localization of ADCs to tumor cells, protecting unmodified healthy tissues. ADCs binding to the cell surface of a cancer cell results in internalization of the conjugates and activation of cytotoxic drugs, leading to rapid cell death. ADCs are considered highly potent anti-cancer treatments; however, remarkably challenging synthesis of ADCs significantly slows down their wide use.

The clinical applications of ADCs are accelerating rapidly. Seagen and Astellas recently announced the full FDA approval to Padcev, an ADC used for the treatment of adult patients with advanced bladder cancer and cancers of the urinary tract. In addition, Seagen partnered with a leading China-based biotech company RemeGen to develop and commercialize Disitamab vedotin, an ADC targeting HER2 protein in urothelial, gastric and breast cancer cells. Last year, RemeGen carried out one of the world's largest IPOs in the biotech industry, raising more than $500 million on the Hong Kong stock exchange.

Another company pioneering the development of ADCs, Orum Therapeutics, announced a $54 million financing to advance their leading therapeutic candidates into the clinic. The company has developed a new class of ADCs activating the ubiquitin pathway to degrade target proteins within hematological cancer cells and solid tumors, expecting initial clinical testing in 2022.

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Peptide-drug conjugates (PDCs)

PDCs are an emerging class of targeted therapeutics that deliver cytotoxins to the selected receptors of diseased tissues. PDCs structure includes three vital components - a homing peptide, a linker, and a cytotoxic payload. PDCs mechanism of action is similar to that of ADCs; however, PDCs feature lower immunogenicity, enhanced tissue penetration due to their low molecular weight, and can be easily synthesized on large scale. Small molecular weight also causes one of the main drawbacks of PDCs - poor circulation stability leading to limited therapeutic effect. Different peptide modifications and nanoparticles are being studied to enhance the stability of PDCs.

In December 2020, a Japan-based bio-venture company PeptiDream entered a partnership with Takeda to develop PDCs for the treatment of neuromuscular and neurodegenerative diseases, with PeptiDream

expecting to receive up to $3.5 billion as upfront and milestones payments. The research is mainly focused on designing PDCs that would be able to successfully deliver drug payloads through the blood-brain barrier. Moreover, Peptidream entered a collaboration with Alnylam Pharmaceuticals worth $2.2 billion to develop peptide-siRNA conjugates for targeted delivery of RNAi to a wide range of cell types and tissues.

A US-based company Cybrexa Therapeutics designed a PDC tumor targeting platform for the next-generation cancer therapies. The company's lead therapeutic candidate, CBX-12, targeting advanced solid tumors, recently entered Phase 1/2 trial. In 2021, Cybrexa Therapeutics raised over $25 million to advance its groundbreaking cancer research.

BiTE (Bispecific T-cell Engagers)

BiTE has become a promising strategy to harness the power of the immune system to target cancer cells. BiTE technology is developed to overcome tumors' ability to suppress immune surveillance by activating the host's T cells. BiTE molecules consist of two artificial monoclonal antibodies, with one engineered to bind antigens on tumor cells and the other to bind proteins found on the surface of T cells. As a result of bispecific monoclonal binding, T cells are recruited to cancer cells, which triggers T cell cytotoxic potential and leads to tumor eradication.

One of the world's largest biotech companies, Amgen, is a pioneer in BiTE research and has recently announced the acquisition of Teneobio for $900 million to further expand their current T-cell engagers library. Teneobio has developed a technology to generate multi-specific antibodies that can rapidly identify multiple targets. Amgen is planning to implement this technology for the design of multi-specific therapeutics which could significantly advance antibody-based drugs.

In 2020, a Netherlands-based biotech company Lava Therapeutics raised $83 million to fund the advancement of their novel immuno-oncology programs. The company's lead BiTE candidates targeting myeloma and leukemia showed promising results in preclinical studies and has recently entered Phase 1/2a clinical trial.

Another company pushing the rapid development of the BiTE technology, Janux Therapeutics, recently announced $125 million round to advance their T-cell engagers platform. The Janux BiTE development pipeline targets multiple types of cancer, and the advancement of the Company's first candidate into the

clinic is expected in the first half of 2022.

CAR-T Therapy

CAR-T Cell Therapy is a modern, personalized approach to treating cancer. This technology is based on the modification of the patient's immune cells (T-cells) outside of the body to express a chimeric antigen receptor (CAR). Modified cells are infused into the host to attack and eradicate the malignant tumors.

In August 2021, AdAlta and Carina Biotech entered a collaboration agreement to develop next-generation i-body enabled CAR-T cells. Clinical-stage company AdAlta is using its proprietary i-body technology platform to address challenging drug targets, with an initial focus on treating fibrotic diseases. Carina Biotech is researching and developing CAR-T technology and other adoptive cell therapies to treat different types of solid cancers. Until now, certain types of blood cancers have been the primary target of CAR-T therapy, but the future collaboration promises to broaden the range of treatable cancers.

Century Therapeutics is another biotechnology company that is developing Induced Pluripotent Stem Cells (iPSC)-derived CAR-T and CAR-NK (Natural Killers) cell therapies. Their technology promotes longer cell persistence, providing a therapeutic response. During the last financing round in March 2021, Century Therapeutics raised $160 million to advance the company’s pipeline of (iPSC)-derived cell therapies for cancer.

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TCR-T Therapy

Similar to CAR-T, T cell receptor immunotherapy (TCR-T) is a powerful cancer therapy strategy. Both technologies attach new receptors on the lymphocyte membrane, enabling them to attack different forms of cancer. A great advantage of TCR technology is the possibility to detect cancerous targets hidden inside cells, while CAR-T therapy is limited to scanning malignant proteins on the cell surface.

Swedish biotechnology company Anocca is using the potential of T-cell immunotherapy to fight cancer. In July 2021, Anocca closed a $47 million Series B financing to further advance the TCR-T technology and progress cellular therapy into Phase I/IIa clinical trials. T-knife Therapeutics company is also developing

cutting-edge T-cell receptors technologies to treat solid cancer. Lately, the $110 million Series B funding was successfully completed. The company plans to use its funding to increase manufacturing capacity, expand the research team and advance the T-cell receptor therapy pipeline.

Moreover, several other companies such as Kite Pharma, JunoTherapeutics, Adaptimmune Therapeutics are also engaged in the development of TCR-T immunotherapy, anticipating the use of the therapy for cancer treatment shortly.

Messenger RNA therapeutics and RNA aptamers

Modern technologies enabled the development of RNA-based therapies to treat a wide range of diseases. Nowadays, two major approaches exist in the RNA therapy branch: the use of mRNA and RNA aptamers. Messenger RNA (mRNA) is a direct template for the realization of genetic information into protein building blocks and control of protein synthesis. RNA aptamers are single-stranded oligonucleotides that can specifically bind certain target molecules.

In August 2021, Sanofi entered into an agreement to acquire Translate Bio, a clinical-stage mRNA therapeutics company, for $3.2 billion. As part of this collaboration, two clinical trials of mRNA vaccines are ongoing: the COVID-19 vaccine study and the seasonal flu vaccine mRNA trial. In addition, German-based biotech leader BioNTech is designing new RiboMab and RiboCytokine platforms for mRNA-based therapeutics.

Clinical stage biopharmaceutical company AptaTargets is developing therapeutic applications based on aptamer technology. Recent studies report the development of a new candidate ApTOLL aptomer used to protect patients from the harmful effects of acute ischemic stroke. The company just closed a second financing round, securing $5.9 million of investments.

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Targeting nucleic acids: ASOs and RNAi

Direct messenger RNA binding has become a new therapeutic approach to controlling protein synthesis and regulating the course of certain diseases. Currently, there are two directions in this area: antisense

oligonucleotides (ASOs) and therapy based on RNA interference (RNAi).

ASOs are single-stranded nucleic acids that are complementary to the target RNA Sequence. ASOs can regulate mRNA expression through several mechanisms, including induction of RNase H endonuclease activity to reduce the translation of the target gene, steric hindrance of ribosomal activity and others. By 2021, only a few ASO-based drugs have been approved by the FDA, including therapeutic agents for Duchenne muscular dystrophy, Batten disease Cytomegalovirus retinitis and other rare pathologies.

In RNAi-based therapy, the target mRNA undergoes enzymatic cleavage, reducing the level of expression of the corresponding protein. Suppression of gene expression using RNA interference is a natural process in the life of cells, therefore, the introduction of synthetic RNAi is a predictable process.

In July 2021, Vico Therapeutics, a Netherlands-based biotech company, announced that the FDA had granted orphan drug designation to Vico Therapeutics' VO659, an investigational antisense oligonucleotide gene-silencing therapy for Huntington's disease. In addition, the company has raised $31 million in Series A funding to further develop its leading antisense oligonucleotide platform.

American clinical-stage company Arrowhead Pharmaceuticals is focusing on developing medicines that treat intractable diseases by silencing the genes that cause them using RNAi therapy. In July 2021, the FDA gave Breakthrough Therapy designation (BTD) for the company's second-generation investigational RNAi therapeutic.

Over the last 5 years, only 11 new medical entities based on nucleic acids have been approved by the FDA. All of them are focused on rare diseases, and the majority are owned by three companies – Alnylam Pharmaceuticals, Ionis Pharmaceuticals and Sarepta Therapeutics.

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Next-generation vaccines

Nucleic acid vaccines are revolutionizing the world of medicine. DNA and mRNA-based vaccines trigger an immune response by directing cells in the body to generate proteins that mimic disease antigens. Foreign proteins are recognized by the immune system, which stimulates humoral and cell-mediated immunity. mRNA vaccines function by activating the cell's translation machinery right after mRNA molecules enter the cell, whereas DNA molecules must cross the nuclear barrier before initiating antigen

production. It is possible that future mRNA vaccines will be able to provide immunity against multiple diseases simultaneously reducing the number of necessary immunizations.

Messenger RNA vaccines showed to be a crucial turning point in the global fight against SARS-CoV-2. In August 2021, FDA announced it had approved the first COVID-19 vaccine, Pfizer-BioNTech mRNA vaccine. Moreover, the DNA-based vaccine against Covid-19 was developed by an Indian pharmaceutical company Zydus Cadila and recently authorized by the Indian government. ZyCoV-D is a needle-free three-dose vaccine and is delivered intradermally over a period of 56 days.

Pennsylvania-based biotechnology company INOVIO launched Phase 2 trial to evaluate the vaccine against the Middle East Respiratory Syndrome (MERS). The vaccine is DNA-based and has the potential to become the first vaccine against MERS.

Another class of up-and-coming vaccines is cancer vaccines. Cancer vaccines activate the body's immune system to fight cancer. Genentech and BioNTech have been working together to develop individualized cancer vaccines by identifying neoantigens for each patient and generating vaccines against them. Through this collaboration, BioNTech received more than $300 million in upfront and near-term milestones.

Oncolytic virus therapies

Oncolytic viruses are a new powerful therapeutic tool developed against cancer. Oncolytic viruses (OVs) are genetically engineered viruses that can selectively replicate only in cancer cells, resulting in the death of abnormal cells. Tumors have an immunosuppressive effect, thus the immune system is not able to provide a defence response to eliminate tumorigenic cells. Cancer cells affected by the oncolytic viruses lose their immune tolerance and get exposed to innate and adaptive immunity, which promotes the native immune response.

In October 2015, FDA approved the first oncolytic virus therapy T-VEC for the treatment of advanced melanoma. The drug was initially developed by BioVex, but the development was taken over by Amgen that acquired BioVex in 2011. 3-year follow-up data showed that T-VEC safely extended recurrence-free survival (RFS) in patients with resectable melanoma.

In August 2021, ImmVira, the biotechnology company focused on the development of new generation oncolytic viruses as potential cancer therapeutics, obtained approval from National Medical Products

Administration (NMPA) to carry out clinical trials of the leading MVR-T3011 IV oncolytic virus therapy program. One of the key ImmVira's goals during the development was to advance oncolytic herpes virus technology, so the drug can be applied intravenously -- and the company successfully accomplished it, conducting the first trial in the world with intravenous administration of the candidate.

Protein degraders

Protein degraders (PDs) have emerged as a novel and innovative therapeutic modality that destroys rather than inhibits protein targets. PDs exploit the natural mechanism human cells use to degrade proteins by recruiting components of the Ubiquitin-proteasome system (UPS) to the target protein. Small molecule drugs called PROTACs (PROteolysis TArgeting Chimeras) consist of two covalently linked protein-binding molecules: one engineered to bind a protein targeted for degradation and another capable of recruiting an E3 ubiquitin ligase that places ubiquitin chains on the target.

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In the last year, Big Pharma has sprung up to develop these next-generation drugs. Pharmaceutical giants, such as Lilly, Pfizer, and Bayer are generously investing in the current PDs trend. More specifically, Lilly has agreed to pay $1.6 billion in milestone payments to partner with Lycia Therapeutics and use their platform to discover new PDs. Pfizer has promised $1 billion to Arvinas to commercialize one of the most advanced protein degraders in the clinic, ARV-471, a degrader of the oestrogen receptor that drives most forms of breast cancer. Bayer has also shown a growing interest in protein degradation and announced the acquisition of Vividion Therapeutics for $1.5 billion. Bayer will utilize Vividion's discovery platform to design therapeutics for traditionally undruggable targets.

The Asian market of targeted protein degradation can be represented by Ranok Therapeutics – an emerging biopharmaceutical company based in Hangzhou, China. In August 2021, the company secured $40 million round to advance their Chaperone-mediated Protein Degradation Platform (CHAMP) into clinical trials in the near future.

A Hong Kong-based company Insilico Medicine entered an R&D collaboration with Arvinas. This strategic partnership will include the design of transformative treatment modalities PROTACs by exploiting Insilico Medicine's AI-assisted systems.

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