The information and statistics set out in this section and other sections of this prospectus were extracted from different official government publications, available sources from public market research and other sources from independent suppliers, and from the independent industry report prepared by the CIC. We engaged the CIC to prepare the CIC Report, an independent industry report, in connection with the Global Offering. The information from official government sources has not been independently verified by us, the Sole Sponsor, Joint Representatives, Joint Global Coordinators, Joint Bookrunners, any of the Underwriters, any of their respective directors and advisers, or any other persons or parties involved in the Global Offering, and no representation is given as to its accuracy. Accordingly the information from official government sources contained herein may not be accurate and should not be unduly relied upon.

RNA-based therapeutics comprise a rapidly expanding category of drugs that have the potential to change the standard of care for many diseases and actualize personalized medicine. According to The Limitless Future of RNA Therapeutics, published in Frontiers in Bioengineering and Biotechnology, these drugs are cost effective to manufacture, relatively simple to manufacture and can target previously undruggable pathways. RNA-based therapeutics can be classified by the mechanism of activity, including RNA interference (RNAi) therapeutics, messenger RNA (mRNA) therapeutics, antisense oligonucleotides (ASO), small activating RNA (saRNA) therapeutics, clustered regularly interspaced short palindromic repeats (CRISPR) therapeutics, and others. RNA-based therapeutics may work by loss of function (e.g., gene silencing) or gain of function (e.g., introducing an exogenous protein or replacing a faulty protein). Our target market is global with our current focus specifically on the U.S. and China markets, which are supported by our research and development facilities and manufacturing capabilities in both countries. We mainly focus on the research and development of therapeutics in the fields of oncology, fibrosis, antiviral and products that leverage liver targeted drug delivery. Our initial focus is on oncology and fibrosis products, as well as antiviral products and products that leverage liver targeted drug delivery.

Source of Information and Key Assumptions

We commissioned China Insights Consultancy ("CIC") to conduct a research and analysis of, and to produce a report on the RNAi therapeutics and mRNA vaccine market in the U.S. and China. CIC is an independent investment consulting company that provides industry consultancy services, commercial due diligence and strategic consulting services to companies in various industries. We have agreed to pay a total fee of US$100,000 for the preparation and use of the Industry Report on the RNAi Therapeutics and mRNA Vaccine Market in the U.S. and China (the "CIC Report"), which is dated as of July 13, 2021. Figures and statistics provided in this prospectus and attributed to CIC or the CIC Report have been extracted from the CIC Report and published with the consent of CIC.

The market projections described here are based on the following key assumptions: (1) the overall social, economic and political environment around the globe and in China is expected to remain stable during the forecast period; (2) global and China's economic and industrial development is likely to maintain a steady growth trend over the next decade; (3) increasing prevalence, supportive government programs and policies, increasing amount of research and development expenditures, increasing patient affordability, etc.; and, (4) there is no extreme force majeure or industry regulation in which the market may be affected dramatically or fundamentally.

China Insights Consultancy undertook both primary and secondary research using a variety of resources. Primary research involved interviewing key industry experts and leading industry participants, while secondary research involved analyzing data from various publicly available data sources, including the U.S. Food and Drug Administration; National Institutes of Health; U.S. National Library of Medicine, International Monetary Fund, National Bureau of Statistics of China, National Health Commission of the People's Republic of China, National Medical Products Administration, company reports, China Insights Consultancy's own internal database, etc.

All statistics are reliable and based on information available as of the date of this report. Other sources of information, including governments, industry associations, or marketplace participants, may have provided some of the information on which the analysis or its data is based.

1. Calculation of treatment market size in China and the U.S.: Treatment Market size = (Number of target patients) * (Treatment rate) * (Average annual cost per patient)

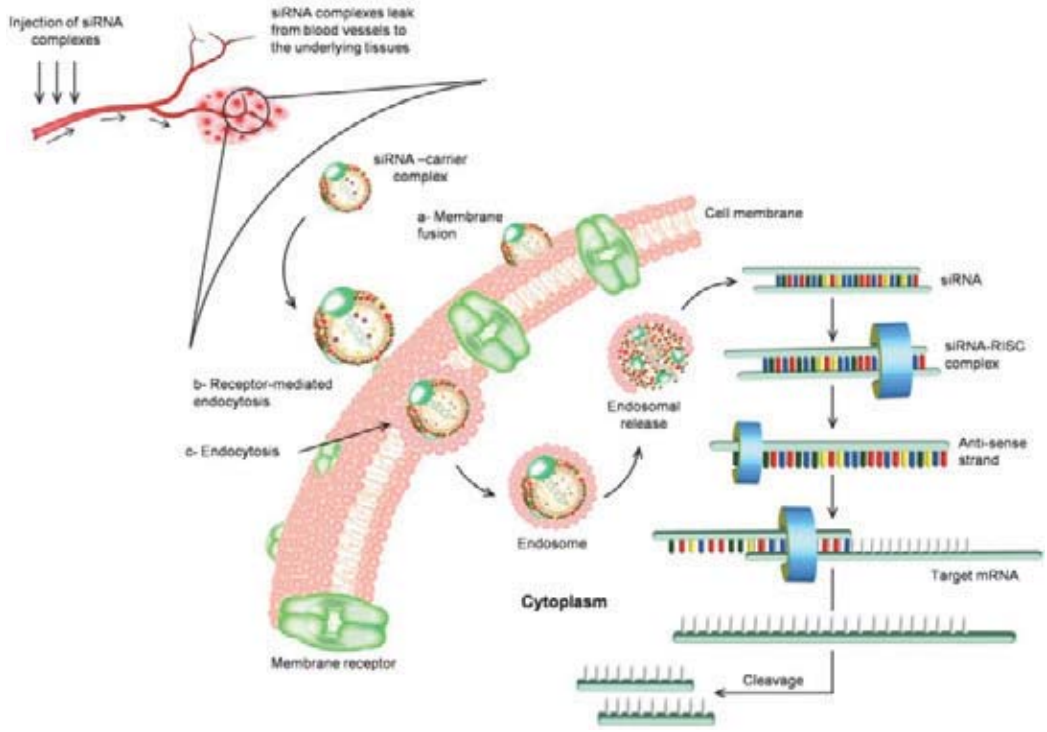
2. Calculation of pharmaceuticals market size in China and the U.S.: Pharmaceuticals Market Size = (Number of target patients for pharmaceutical treatment) * (Average annual cost of available pharmaceuticals)

RNAi therapeutics market

The development of novel pharmaceutical therapies is very time consuming. RNAi technology is based on a relatively new mechanism of action discovered by two U.S. scientists in 1998 who later received the 2006 Nobel prize in Physiology and Medicine for their discovery. The US FDA approved the first RNAi-based drug in 2018 (Patisiran, manufactured by Alnylam) after 20 years of development efforts and technology advancements, which is very much similar to the timeline for the first approved antibody drug. In contrast, in the last three years, there have been three more RNAi-based drugs approved by regulatory authorities (Givosiran and Lumasiran, approved by US FDA and manufactured by Alnylam, and Inclisiran, approved by EMA and manufactured by Novartis under license from Alnylam) demonstrating an acceleration of RNAi-based drug development. We can expect a fast growth of approved RNAi-based drugs in the near future; indeed, there are currently more than 50 on-going clinical studies, approximately one third of which are in the later stage of development.

RNA interference (RNAi) is a conserved biological response to double-stranded RNA that mediates resistance to both endogenous parasitic and exogenous pathogenic nucleic acids, and regulates the expression of protein-coding genes. RNAi therapeutics comprise a new class of drug molecules that can be used to treat disease by silencing the expression of specific genes. RNAi molecules are typically further classified into three types: small interfering RNAs (siRNAs), microRNAs (miRNAs) and short hairpin RNAs (shRNAs). siRNAs are artificially synthesized, 19-25 nucleotide long, double-stranded RNA molecules. siRNAs can be designed to inhibit specific disease-causing proteins by designing the sequence of the siRNA to achieve complementarity to a short region of the mRNA transcribed from the gene encoding the protein of interest. Once siRNAs are transfected into cells, they are recognized by the cells' enzymatic machinery involved in RNAi. The siRNAs are loaded into the RNA-Induced Silencing Complex (RISC), where the "passenger" strand is released, activating RISC. The remaining single-stranded "guide" RNA molecule loaded in RISC can then elicit gene silencing by binding, through perfect complementarity, to a single target mRNA sequence, thereby targeting it for cleavage and degradation. The result is inhibition of the production of the protein encoded by the mRNA and thus treatment of the disease caused by the protein. siRNA has high specificity of targeting and strong silencing effect. miRNAs and shRNAs utilize the same pathway but are first processed into short double-stranded RNAs before loading into RISC.

Mechanism of RNAi therapeutics



Source: Draz, M. et al. Theranostics, 2014:4(9), 872–892.

RNAi therapeutics potentially offer applications for a broad variety of diseases with a long acting duration within the human body, and the development of new therapies requires shorter time to completion. RNAi therapeutics treat diseases by targeting the specific disease-causing genes that were once considered undruggable.

Since the 2006 Nobel prize in Physiology and Medicine was awarded to biologists Andrew Fire and Craig Mello for the discovery of the process of RNA interference, there have been great strides in technologies based on RNA interferences as well as the applications for those technologies. The following summarizes key advances:

- **2007 to 2010, the surge of research**: A surge of interest was seen in researchers who sought to use RNA interference as a technique for basic science and the development of therapeutics.

- **2011 to 2014, hurdles and challenges in development of RNAi drugs**: Low efficacy and severe side effects are the main problems in developing RNAi-based drugs. One of the first treatment to make it to a Phase III clinical trial – an RNAi therapeutic for macular degeneration from the OPKO Health – was shut down in 2009. By 2010, pharmaceutical companies began to turn away from this technique, with large companies such as Roche, Pfizer, and Merck shutting down their RNAi research programs.

- **2015 to 2017, the rebound**: Development in RNAi technologies began to rebound due to progress in developing delivery platforms – LNP-based delivery platform and GalNAc-based delivery platform. Alnylam conducted several clinical trials with RNAi-based drugs encapsuled by LNPs, which addressed the degradation issue of naked siRNA. In addition, GalNAc-siRNA conjugates also showed efficacy and low toxicity in clinical trials. Other delivery platforms, such as the PNP delivery platform, also showed great potential with its distinct advantages in high delivery efficiency and low toxicity.

- **2018, first siRNA drug using an LNP-based delivery platform approved (Patisiran)**: Alnylam achieved the first siRNA drug approval by U.S. FDA for Patisiran for the treatment of ATTR.

- **2019, first siRNA drug using a GalNAc-based delivery platform approved (Givosiran)**: Alnylam achieved the first GalNAc-siRNA drug approval by FDA for Givosiran for the treatment of acute hepatic porphyria.

- **2020, more siRNA drugs are approved (Inclisiran, Lumasiran)**: Novartis received approval from European Commission for Inclisiran, which uses a GalNAc-based delivery platform.

- **2021, a new boom of siRNA drug development**: As of Latest Practicable Date, there are over 50 on-going clinical trials of siRNA therapeutics in the U.S., and six trials in China.

The main issues affecting the safety and efficacy of RNAi therapeutics are stability, cellular uptake, endosomal escape, and pharmacokinetics. In recent years, the technological advancements of nanotechnology-based siRNA delivery technologies, chemical modification, and others, have significantly increased the efficacy and reduced the off-target effect of RNAi therapeutics. For instance, for the LNP delivery platform, according to Lorenzer et al., the evolution of lipid structures and particle composition has resulted in improved in-vitro and in-vivo efficacy. RNAi therapeutics have the following advantages, compared with other therapeutics, such as small molecules and antibodies:

- **Wider selection of druggable targets:** Due to RNAi therapeutics' capability to regulate the expression of various proteins, both extracellular and intracellular, by targeting mRNA and other targetable RNA in the cytoplasm and preventing disease-associated proteins from being made, RNAi therapeutics have potential to expand the range of 'druggable' targets, thereby providing unprecedented opportunities for clinical translation.

- **Precise and personalized therapeutics:** RNAi therapeutics function through base-pair binding with the mRNA target to cause degradation of that target, yielding high efficacy and specificity, with low off-target rate, resulting in potent, targeted gene silencing.

- **Favorable safety:** RNAi therapeutics leverage a natural biological process for gene silencing, and risk of cytotoxicity and immunogenicity are significantly reduced with chemical modifications and/or drug formulation technology improvements. Chemical modification to the RNA can enhance nuclease and siRNA stability and potency, pharmacodynamic, as well as pharmacokinetic. Therefore, modified siRNA can be more effective with low concentration, which subsequently reduces the level of toxicity (high concentration and unstable siRNAs usually cause toxicity). The immune response is usually caused by native nucleosides such as A, C, G and U, which can be recognized by the immune system. The immune system can better recognize modified nucleosides, thereby reducing or eliminating immune response to siRNA therapeutics.

- **Long-lasting effect:** Modified RNAi therapeutics typically have extended half-life of therapeutic effect in the body of months, and are thus designed to fix the underlying cause of diseases with long durability, making RNAi therapeutics well-suited for various chronic indications.

- **Faster and higher success rate in development and relatively low manufacturing cost:** RNAi therapeutics have higher likelihood of approval and shorter time for

completing new product design together with relatively low manufacturing costs compared with conventional drugs, all contributing to a higher gross profit margin for RNAi companies. Based on the Clinical Development Rates and Contributing Factors 2011-2020 published jointly by Biotechnology Innovation Organization, PharmaInteligence and Quantitative Life Science, RNAi therapeutics show a higher likelihood of approval with 13.5% from Phase I clinical trials compared to monoclonal antibody and small molecule drug modalities, which show likelihood of approval of 12.1% and 7.5%, respectively, from Phase I.

RNAi therapeutics have had limited traction in achieving clinical success due to inadequacies in the technology to enable delivery of the siRNA molecules into the target tissues and cells for therapeutic action. Although the biological mechanism was discovered in 1998, according to Overcoming Barriers for siRNA Therapeutics: From Bench to Bedside published on MDPI, wide-scale adoption of RNAi technology for clinical practice has been hindered by a number of factors, including:

- **Intravascular Degradation and Renal Clearance**: The first biological barrier after injection of RNA is intravascular degradation by nucleases enzyme in the plasma. Naked or unmodified RNA is unstable in systemic circulation and more susceptible to A-type nucleases, which are ubiquitous in intracellular and extracellular space. In addition, fast renal clearance results in a very short half-life for siRNA, ranging from 5–10 min. Nucleases in plasma and tissues degrade unmodified siRNA in a few minutes to a hour, potentially limiting the use of siRNA-based therapeutics. siRNA modification alone may not be enough to achieve effective therapeutic activity. Physical encapsulation of siRNA and chemical modification of the RNA enhance therapeutic activity of the siRNA.

- **Activation of the Innate Immune System**: The function of innate immunity is to identify the pathogens, eradicate them, and contribute to adaptive immunity. Previously, it was thought that siRNA shorter than 30 nucleotides were small enough to evade the immune system and avoid nonspecific stimulation of interferon response. Subsequent experiments conducted on short synthetic siRNAs, which are published in Sequence-Dependent Stimulation of the Mammalian Innate Immune Response by Synthetic siRNA on Nature Biology, showed that siRNA can activate the immune response and trigger the production of cytokines in-vivo and in-vitro. This innate immune response can be triggered by the siRNA or by vehicles used with the siRNA, including cationic lipids used in LNP delivery technology. The aforementioned studies did not involve use of Sirnaomic's data or results.

- **Protein Binding**: To achieve cellular delivery of siRNA for effective concentration within the cell, a positively charged carrier molecule is an essential requirement. Blood complement proteins and cell membrane proteins are usually negatively charged in the systemic circulation. These blood complement proteins bind with the

positively charged siRNA carriers through electrostatic interaction. The opsonized carriers (i.e., siRNA carriers tagged by the blood complement proteins) then undergo reticuloendothelial system (RES) filtration, and their cell surface binding leads to inflammation. The opsonization process makes siRNA carriers more susceptible to RES filtration and results in fast renal clearance. Opsonized carriers loaded with siRNAs accumulate in the liver and spleen and may cause toxic effects. Ultimately, the opsonization process reduces the therapeutic concentration of siRNA in the body that is required for efficient RNAi therapeutic activity.

- **RES Entrapment**: A major problem is the uptake of nucleic acid drugs by the RES. siRNA loaded nanoparticles undergoing the opsonization process are readily removed by the macrophages in RES. Once the siRNA therapeutics reach the bloodstream, they must be protected from the phagocytic cells of the mononuclear phagocyte system (MPS). It is thought that a surface with a negative charge is more susceptible to clearance from blood as compared to positive or neutral charged carriers. Therefore, surface modification of the siRNA carrier is the primary strategy to bypass this barrier.

- **Membrane Impermeability**: Naked siRNA cannot cross the plasma membrane because of its negative charge. Despite its small size, negative charge and high hydrophilicity prevent naked siRNA from passing through the biological membrane. Hence, efficient delivery of siRNA needs modification to overcome this barrier. In this context, carriers that enable efficient siRNA delivery are required.

- **Endosomal Escape**: Following the internalization of the siRNA, a major barrier remains to be its inability to escape endosomes. Thus, a carrier or modification that allows for the disruption of the endosomal membrane is essential for efficient endosomal escape and gene silencing by siRNA.

- **Off-Target Effects**: siRNA accumulation in tumors is around 20 to 40% higher compared to accumulation in normal tissue. The enhanced permeation and retention (EPR) effect, which stems from leaky blood vessels in tumors, allows for the preferential uptake of the formulation in tumors compared to normal tissue but is not significant enough to rely on by itself. Thus, to overcome these off-target effects, the use of surface-ligand modifications for siRNA formulations have recently been utilized for more targeted delivery of cargo.

Delivery systems not only address the challenges involved in delivering naked RNAi triggers, including its chemically unstable features, extracellular and intracellular barriers, and innate immune stimulation, but may also offer "smart" targeted delivery. Over the past decade, significant efforts have been undertaken to develop RNAi delivery platforms that overcome these obstacles.

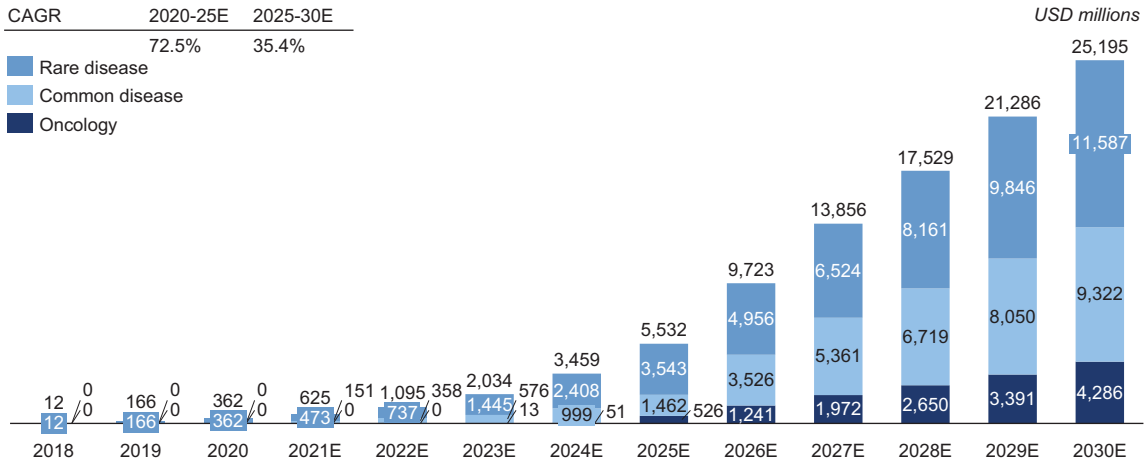
According to Therapeutic siRNA: state of the art, published in Signal Transduction and Target Therapies, RNAi therapeutics utilize distinct approaches to enable delivery of RNAi triggers to target tissues, such as lipid-based nanoparticles (LNPs), N-acetylgalactosamine (GalNAc) conjugates, polypeptide nano-particle (PNP) and other conjugates. Delivery platforms must be engineered to provide serum stability, offer high structural and functional tenability, mitigate interactions with non-target cells, enhance cell entry and endosome escape, resist renal clearance, and generate low toxicity and immunogenicity.

- **LNPs:** LNPs are chemically synthesized multicomponent lipid formulations (<100 nm in diameter) encapsulating siRNAs for delivery to the target tissue. En route to their destination, the siRNAs encapsulated in LNPs are protected against degradation by ubiquitous nucleases. LNPs are limited by complex manufacturing processes, and in some cases immunogenicity issues due to the high content usage of cationic lipids.

- **GalNAc conjugates:** GalNAc, or N-acetylgalactosamine, is a sugar molecule that can recognize and bind to a cell surface protein, the asialoglycoprotein receptor (ASGPR), which is abundantly expressed on liver cells (hepatocytes), resulting in rapid endocytosis. GalNAc conjugates are a mature technology and are highly specific to liver hepatocyte delivery.

- **PNP:** PNPs are composed of a branched histidine lysine peptide polymer (HKP), which controllably assemble into nanoparticles that envelop and protect 10k -100k siRNA to facilitate delivery into the targeted tissue and cell (e.g. activated blood vessel endothelial cells) through the NRP1 receptor. Histidine-mediated protonation may further facilitate siRNA payload release to the cellular site of action in the cytoplasm through increased endosome escape efficiency. PNPs have high safety, and potential to target a wide range of tissues and organs, due to the biodegradability of both polypeptide and RNA. Moreover, PNPs have huge potential to deliver siRNA, mRNA and other nucleic acids.

Global market size of RNAi therapeutics, 2018-2030E



Note: Rare diseases, common diseases and oncology in Industry Overview are defined to be mutually exclusive.

Source: the CIC Report

The total addressable market includes all of the available and potential product candidates for RNAi therapeutics. It is composed of three mutually exclusive categories, which are common diseases, rare diseases, and oncology. STP705 and STP707 are included in both oncology and common diseases categories. The revenue from both NMSC and liver cancer markets for STP705 contributes to the oncology market segment, and the revenue from HTS and keloid scarless healing markets for STP705 contributes to the common diseases market segment. Similarly, for STP707, the revenue from NMSC, liver cancer and NSCLC reflects on the oncology market segment, and the revenue from fibrosis reflects on common diseases market segment.

Global market size of RNAi therapeutics for all indications increased from US$12 million in 2018 to US$362 million in 2020 with CAGR of 449.2%, and is estimated to reach US$25 billion in 2030. The market size of RNAi therapeutics for common diseases and oncology will account for 54% of the total market size by 2030. The market size of RNAi therapeutics in China will increase from approximately US$4 million in 2022 to over US$300 million in 2025 with CAGR of over 300%, and is estimated to reach approximately US$3 billion in 2030. There are a number of favorable policies such as "13th Five-Year Plan" for the Development of the Biological Industry, which promotes the development of therapeutic vaccines, RNA interfering drugs and others, and "Guiding Opinions of the General Office of the State Council on Promoting the Healthy Development of the Pharmaceutical Industry", which promotes the development of targeted, highly selective and new therapeutic drugs.

The global RNAi therapeutics market is primarily driven by the following factors:

- **Increasing investments and partnerships accelerated the RNAi therapeutics development**: Accumulated investment in RNAi therapeutics by leading pharmaceutical companies increased from US$8.5 billion in 2017 to US$35 billion in 2020, a 300% increase in three years.

- **Technological breakthroughs widened scope of clinical application of RNAi:** Technological breakthroughs in delivery technology have increased the number of indications for RNAi therapeutics, including for oncology and common diseases with huge clinical needs. Improved RNAi delivery systems are potent, effective and non-toxic or minimally immunogenic carriers for formulating RNAi agents. According to Clinical Advances of siRNA-Based Nanotherapeutics for Cancer Treatment, published in MDPI, scientists have focused on developing and perfecting the gene delivery systems. In recent years, nanoparticles have been significantly embraced as a reliable gene carrier with good biocompatible and biodegradable properties. Manipulation of nanoparticles characteristics enables the gene vehicle to improve the half-life of siRNA in the circulatory system. The small dimension of

conjugated nanoparticles further allows localization and distribution into its molecular targets within the cell, which in turn increases the tumor residence time through enhanced permeability and retention effect.

- **Ever broadening scope of clinical targets sustain future growth of RNAi therapeutics**: Rational scientific identification of numerous targeted genes and genetic mutations can be leveraged to develop therapeutics with potency and specificity. The broad application of RNAi therapeutics to common diseases and oncology will sustain the further growth of the RNAi therapeutics market.

- **Validation by several successful clinical trials:** After the approval of Patisiran (the first RNAi therapeutic worldwide) in 2018, three additional siRNA therapeutics have been approved by FDA/EC, Givosiran and Lumasiran, approved by FDA and manufactured by Alnylam, and Inclisiran, approved by EC and manufactured by Novartis under license from Alnylam. Several successful clinical trials for RNAi therapeutics have validated safety and efficacy of RNAi therapeutics in both rare diseases and common diseases (e.g., high cholesterol).

In the near future, the RNAi therapeutics market is expected to demonstrate the following trends:

- **Breakthroughs in delivery and target selection:** Efficient and safe delivery systems are key, and we expect to see major breakthroughs in addressing the main delivery challenges in the near future, such as peptide or polymer particles and antibody-drug conjugates. Identification of targets with improved specificity and potency are key for target selection, with many projects aiming to achieve both, with oncology being a primary example.

- **Larger clinical application area:** Significant untapped market potential exists beyond liver-focused treatments. According to International Agency for Research on Cancer, in 2020, the five-year prevalent cases of liver cancer and all cancers is around 994 thousand and 50,550 thousand cases, respectively, which indicate that up to 50 times more patients may be reached if it is possible to treat other oncology types in a way that is competitive with standard care options. Novartis' acquisition of the first siRNA therapeutic for cardio-metabolic diseases paved the way towards treatments of common diseases and produced significant improvements.

- **Personalized treatment**: Genome-based personalized therapeutics, like RNAi therapeutics, for rare diseases and cancer may be a future trend, since gene sequencing is already a mature technology.

The number of ongoing RNAi clinical trials has increased from 14 in 2013 to more than 50 in July 2021. The RNAi clinical trial pipeline is distributed across different stages of

development. More oncology-related trials are in earlier stages of developments. Several approvals have been granted for common and rare diseases. At present, liver-related diseases are the most targeted amongst other types of diseases because the current delivery technology, LNP-based and GalNAc-based siRNA formulations, target liver hepatocytes and show efficient uptake predominantly in liver tissue, where practically all nanoparticulate and liposome delivery systems show the highest accumulation. These siRNA delivery systems have an inherent preference for the liver compared to other organs when administered systemically. New delivery platforms, such as the PNP-based delivery platform, goes beyond the liver to lung and other tumor tissues both preferentially target liver cells.

Key global players in RNAi therapeutics include Sirnaomics, Alnylam, Arrowhead, Dicerna, Silence Therapeutics, Quark, Sylentis and Brii Biosciences.

Competitive landscape of RNAi therapeutics market, as of September 2021

Major Players	Major drugs	Indications	Therapeutic area	Target/ organ	Clinical stage	Start date (location)	Trial number
Sirnaomics	STP 705	Non-Melanoma isSCC	Oncology	Skin	Phase II	5/2019 (US)	NCT04293679
		Non-Melanoma BCC	Oncology	Skin	Phase II	12/2020 (US)	NCT04669808
		Hypertrophic Scar Reduction	Fibrosis	Skin	Phase II	1/2017 (US)	NCT02956317
		Keloid Scarless Healing	Fibrosis	Skin	Phase II	4/2021 (US)	NCT04844840
		Liver Cancers (basket)	Oncology	Liver	Phase I	3/2021 (US)	NCT04676633
	STP 707[(1)]	Solid Tumor	Oncology	Liver	Phase I	11/2021 (US)	NCT05037149
Alnylam	ONPATTRO (Patisiran)	TTR (hereditary transthyrein amyloidosis, polyneuropathy)	Genetic Disease	Liver	Commercialized; 1st FDA approved RNAi drug	8/2018 (FDA) 8/2018 (EC)	NCT01960348
	GIVLAARI (Givosiran)	ALAS1 (acute hepatic porphyria)	Genetic Disease	Liver	Commercialized; 2nd FDA approved RNAi drug	11/2019 (FDA) 3/2020 (EC)	NCT03338816
	OXLUMO (lumasiran)	Primary hyperoxaluria type 1	Genetic Disease	Liver	Commercialized; 3rd FDA approved RNAi drug	12/2020 (FDA) 11/2020 (EC)	NCT04152200
	Inclisiran[(2)] (ALN-PCSsc)	Hypercholesterolemia, mixed dyslipidaemia	Metabolic Disease	Liver	NDA filed with FDA (approved in EU)	7/2021 (FDA) 12/2020 (EC)	NCT03397121
	Vutrisiran (ALN-TTRsc02)	Hereditary amyloidosis	Genetic Disease	Liver	NDA filed with FDA	4/2021 (Global excluding China)	NCT03759379
	Fitusiran[(3)] (ALN-AT3)	Hemophilia A and B	Genetic Disease	Liver	Phase III	2/2018 (Global)	NCT03417102

Major Players	Major drugs	Indications	Therapeutic area	Target/ organ	Clinical stage	Start date (location)	Trial number
	Lumasiran (ALN-GO1)	Severe Primary Hyperoxaluria Type 1 (PH1)	Genetic Disease	Liver	Phase III	11/2018 (Global excluding China)	NCT03681184
	Patisiran	ATTR Amyloidosis Label Expansion	Genetic Disease	Liver	Phase III	3/2019 (Global excluding China)	NCT03862807
	Cemdisiran/ Pozelimab Combo	Complement-mediated diseases	Metabolic Disease	Liver	Phase III	9/2021 (N.A.)	NCT05070858
	Cemdisiran (ALN-CC5)	Complement-mediated diseases	Genetic Disease	Liver	Phase II	1/2015 (Global excluding US and China)	NCT02352493
	ALN-HBV02 (VIR-2218)	Chronic HBV infection	Viral Disease	Liver	Phase II	8/2020 (Global)	NCT04507269
	ALN-AGT01	Hypertension	Viral Disease	Liver	Phase II	7/2021 (US)	NCT04936035
	ALN-HSD	NASH	Metabolic Disease	Liver	Phase I	10/2020 (Global excluding China)	NCT04565717
Arrowhead	ARO-APOC3	Familial Chylomicronemia	Genetic Disease	Liver	Phase III	11/2021 (US)	NCT05089084
	ARO-AAT	α1-Antitrypsin deficiency	Genetic Disease	Liver	Phase II	8/2019 (Global excluding China)	NCT03945292
	AMG 890	Cardiovascular Disease	Genetic Disease	Liver	Phase II	7/2020 (Global excluding China)	NCT04270760
	ARO-ANG3	Mixed Dyslipidemia	Genetic Disease	Liver	Phase II	6/2021 (Global excluding China)	NCT04832971
	JNJ-3989	Hepatitis B	Viral Disease	Liver	Phase II	9/2020 (Global)	NCT04535544
	ARO-ENaC	Cystic Fibrosis	Fibrosis	Lung	Phase I/II	8/2020 (Global excluding China and US)	NCT04375514
	ARO-HSD	NASH	Hepatic disease	Liver	Phase I	3/2020 (Global excluding China and US)	NCT04202354
	ARO-HIF2	Renal Cell Carcinoma	Oncology	Tumor	Phase I	8/2020 (US)	NCT04169711
	JNJ-75220795[4]	Fatty Liver	Metabolic Disease	Liver	Phase I	11/2021 (Japan)	NCT05039710

Major Players	Major drugs	Indications	Therapeutic area	Target/ organ	Clinical stage	Start date (location)	Trial number
Dicerna	Nedosiran[5] (DCR-PHXC)	Primary Hyperoxaluria	Genetic Disease	Liver	Phase III	7/2019 (Global excluding China)	NCT04042402
	DCR-HBVS[6] (RG6346)	Chronic hepatitis B virus	Viral Disease	Liver	Phase II	7/2020 (Global)	NCT04225715
	Belcesiran (DCR-A1AT)	Alpha 1-Antitrypsin Deficiency	Genetic disease	Liver	Phase II	2/2021 (Global excluding China and US)	NCT04764448
	LY3561774	Cardiometabolic	Genetic Disease	Liver	Phase I	11/2020 (US)	NCT04644809
	LY3819469	Cardiometabolic	Cardiometabolic	Liver	Phase I	6/2021 (Global excluding China)	NCT04914546
	DCR-AUD	Alcohol Use Disorder	Genetic disease	Liver	Phase I	9/2021 (US)	NCT05021640
Silence Therapeutics	SLN 360	Cardiovascular disease with high Lp(a)	Genetic Disease	Liver	Phase I	11/2020 (Global excluding China)	NCT04606602
	SLN 124	Myelodysplastic Syndrome	Oncology	Liver	Phase I	4/2021 (Global excluding China and US)	NCT04718844
Brii Bioscience	Brii 835	Hepatitis B	Viral Disease	Liver	Phase II	4/2021 (Global excluding US)	NCT04749368
Quark	Teprasiran[7]	Delayed Graft funtion	Genetic Disease	N.A.	Phase III	3/2016 (Global excluding China)	NCT02610296
Sylentis	Tivanisiran	Dry Eye Disease	Genetic Disease	Eye	Phase III	5/2017 (Global excluding China and US)	NCT03108664

Source: U.S. National Library of Medicine; the CIC report

Note：The table only includes the major players in RNAi therapeutics. Only Inclisiran, Fitusiran and Brii 835 are regulated by both FDA and NMPA, others are only regulated by FDA.

1. *STP 707 started phase I clinical trial in November*
2. *Alnylam out-licensed Inclisiran to Novartis*
3. *Alnylam out-licensed Fitusiran to Sanofi*
4. *Arrowhead out-licensed JNJ-75220795 to Janssen*
5. *Dicerna out-licensed Nedosiran to Alnylam*
6. *Dicerna out-licensed DCR-HBVS to Roche*
7. *Quark out-licensed Teprasiran to Novartis*

Indications and therapeutic areas as well as target/organ are listed for illustration of approved drugs, and ongoing trials. Ongoing clinical trials span the various stages clinical trial, whereas only three RNAi drugs approved by FDA as of November 2021. Most of the core products and pipelines primarily target liver, and the therapeutic areas are mainly focus on genetic diseases and hepatic diseases.

Source: the CIC Report, Clinical Trial, Annual Report

Note: Data as of September 2021

Approved RNAi therapeutics, 2020

Generic Name (Product Name)	**Leqvio (Inclisiran)**	**Oxlumo (Lumasiran)**	**Givlaari (Givosiran)**	**Onpattro (Patisirnan)**
First Approval Date	2020/12/11 (CE)	2020/12/03	2019/11/20	2018/08/10
Indication	low-density lipoprotein cholesterol (LDL-C)	primary hyperoxaluria type 1	acute hepatic porphyria (AHP)	polyneuropathy of hereditary transthyretin-mediated amyloidosis
Annual cost (thousand US$)	150	493	575	564
Global revenue (million US$)	~0.8	~0.3	~55.1	~306.1
Market share	~0.2%	~0.1%	~15.2%	~84.5%

Source: FDA; EC; Annual Report; the CIC Report

As of the Latest Practicable Date, there are approximately 10 siRNA drugs that either are in ongoing or completed Phase III clinical trials. There are numerous verticals within which RNAi therapeutics are developing besides cancer, including cardiovascular, kidney, urologic, genetic diseases, and blood disorders, as well as rare diseases such as amyloidosis, primary hyperoxaluria and hemophilia and others.

siRNA Drugs in Ongoing/Completed Phase III Clinical Trial, as of September 2021

Drug name	**Company**	**Indications**	**Status**	**Start date**	**Trial number**
Vutrisiran (ALN-TTRsc02)	Alnylam	• Hereditary amyloidosis	NDA filed with FDA	4/2021 (Global excluding China)	NCT03759379
Inclisiran (ALN-PCSsc)	Alnylam Novartis	• Hypercholesterolemia, mixed dyslipidaemia	NDA filed with FDA (already approved in EU)	7/2021 (FDA) 12/2020 (EC)	NCT03397121
Nedosiran (DCR-PHXC)	Dicerna Alnylam	• Primary Hyperoxaluria	Phase III	7/2019 (Global excluding China)	NCT04042402

Drug name	Company	Indications	Status	Start date	Trial number
Fitusiran (ALN-AT3)	Alnylam Sanofi Genzyme	• Hemophilia A and B	Phase III	2/2018 (Global)	NCT03417102
Teprasiran (QPI-1002)	Quark Novartis	• Delayed Graft Function	Phase III	3/2016 (Global excluding China)	NCT02610296
Tivanisiran (SYL 1001)	Sylentis	• Dry Eye Disease	Phase III	5/2017 (Global excluding US)	NCT03108664
Lumasiran (ALN-GO1)	Alnylam	• Severe Primary Hyperoxaluria Type 1 (PH1)	Phase III	11/2018 (Global excluding China)	NCT03681184
Patisiran	Alnylam	• ATTR Amyloidosis Label Expansion	Phase III	3/2019 (Global excluding China)	NCT03862807
Cemdisiran (ALN-CC5)	Alnylam	• Complement-mediated diseases	Phase III	9/2021 (N.A.)	NCT05070858
ARO-APOC3	Arrowhead	• Familial Chylomicronemia	Phase III	11/2021 (US)	NCT05089084

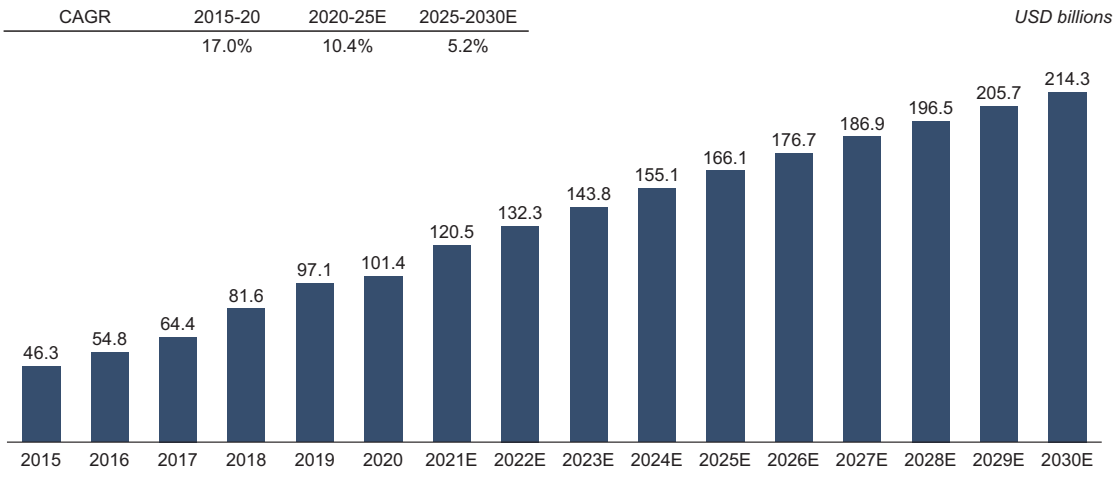
Source: U.S. National Library of Medicine; FDA; NCBI; the CIC report

Oncology pharmaceutical market in U.S. and China

In 2020, the market size of the U.S. oncology pharmaceutical market reached US$101.4 billion, representing a CAGR of 17.0% from 2015 to 2020. Driven by a larger number of oncology drugs launched on the market, the market size of oncology pharmaceuticals in the U.S. is expected to undergo a period of rapid growth, reaching US$214.3 billion in 2030. Currently, no RNAi drugs are approved for oncology. RNAi therapeutics are expected to grow rapidly after expanding indication into oncology in the following years. By 2030, RNAi drugs for oncology is projected to reach approximately US$2 billion and US$0.4 billion in the U.S. and China, respectively. Although RNAi therapeutics will experience rapid growth, they are still in relatively early-stage in oncology market until 2030, accounting for approximately 1% of the oncology drug market both in the U.S. and China.

In the U.S., pharmaceutical companies developing RNAi therapeutics, such as Alnylam, have developed in-house teams to educate doctors about the disease and RNAi therapeutics treatment information. In addition, these pharmaceutical companies also have grants and partnering programs with the healthcare community to support education programs and initiatives that conduct community education about therapeutic areas of interest. In China, pharmaceutical companies developing RNAi therapeutics will also use similar approaches to educate the healthcare community and patients about RNAi therapeutics.

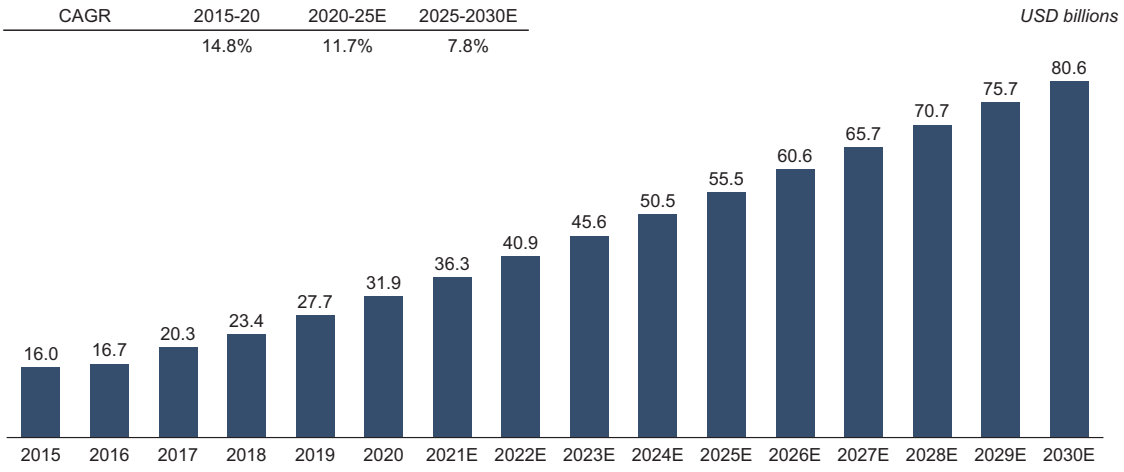
Market size of oncology pharmaceutical in the U.S., 2015-2030E



Source: the CIC report

In 2020, the market size of China's oncology pharmaceutical market reached US$31.9 billion, representing a CAGR of 14.8% from 2015 to 2020. Due to the relatively late launch of molecularly targeted drugs and biologics in China, a significant number of patients with cancer cannot be adequately treated through the use of traditional chemotherapeutic drugs, resulting in growing needs for new and better treatments. This need is nonetheless being addressed through improved affordability and supportive policies for new drug development and approvals, which is expected to lead to a faster growing oncology pharmaceutical market in China. For example, the "Guiding Opinions of the General Office of the State Council on Promoting the Healthy Development of the Pharmaceutical Industry" published in 2016, promotes the development of targeted, highly selective and new therapeutic drugs. Similarly, the "13th Five-Year Plan" for the Development of the Biological Industry, published in 2016, promotes the development of therapeutic vaccines, RNA interfering drugs, suitable sub-drugs, and biological therapeutic products. The market size of oncology pharmaceutical products is expected to experience a period of fast-paced growth in the years ahead, reaching US$80.6 billion in 2030.

Market size of oncology pharmaceuticals in China, 2015-2030E



Source: the CIC report

The continued growth of the oncology pharmaceutical market in China and the U.S. is primarily driven by the following factors:

- **Novel pharmaceuticals and combination therapies:** Continued and significant research and development investment generates the development of novel therapies, such as innovative RNAi therapeutics, cell therapies and gene therapies, for new indications with better efficacy and safety profiles. Moreover, the development of combination therapies is expected to expand access to unapproved indications.

- **Expanded usage and long-term maintenance usage:** Usage of drugs is expanding to different stages of cancer treatments, including neoadjuvant and adjuvant treatments. In addition, formulations with improved safety and convenience enable long-term maintenance usage by oncology patients.

- **Growing clinical demands driven by increasing incidence of cancer:** The trend of an aging population is expected to continue in the coming decades. Cancer and its associated sequelae disproportionately affect elderly adults. Consequently, population aging contributes to a rising cancer incidence in a population.

RNAi therapeutics for oncology

RNAi therapeutics for oncology is still at an early stage, with no RNAi therapeutics yet approved for the treatment of any cancer. The main characteristics of RNAi therapeutics for oncology are high efficacy, high specificity, low rate of side effects, induction of silencing in advanced stages of growth, and low cost compared to other methods of gene therapy. According to RNA Interference-Based Therapy and Its Delivery Systems published in NCBI, the advantages of RNAi therapeutics in cancer therapy are effective suppression of the growth of advanced-stage tumors, relatively low cost, and high specificity. When multiple distinct

siRNAs are delivered simultaneously, RNAi therapeutics can inhibit multiple genes of various pathways simultaneously, which could be conducive to reducing drug resistance. For example, Guan et al. found that inhibition of SH3GL1 using siRNA could reverse MDR by decreasing P-glycoprotein expression via the EGFR/ERK/AP-1 pathway. With the development of more effective delivery systems, RNAi could also be used to develop personalized drugs for specific patients as adjuvants to chemotherapy. According to Nano-based delivery of RNAi in cancer therapy published by Springer, RNAi therapeutic is an economics therapy. siRNA and new nano-delivery systems, are expected to achieve low adverse reactions because of their high specificity to molecular targets and delivery strategies based on the article Insight Into the Prospects for RNAi Therapy of Cancer. RNAi therapeutics for oncology have two major advantages. First, some RNAi therapeutics are capable of targeting multiple genes in various cellular pathways involved in tumor progression. Simultaneous inhibition of multiple genes is an effective approach to treat cancer as well as leading to a reduction in the possibility of multiple drug resistance caused by continued use of chemical drugs. Second, RNAi therapeutics are able to specifically inhibit any of the large sets of cancer-associated genes without regard to the druggability of their protein products.

siRNAs face physiological and biological barriers that prevent their delivery to the active site when administered systemically as an oncology therapy. Hence, delivery systems can improve siRNA in terms of its stability and cancer cell-specificity, with optimization of delivery systems for cancer being critical. Delivery formulations as well as chemical modification of siRNA are required to overcome these challenges and facilitate siRNAs in reaching their target cells.

Current status of Oncology siRNA based drug worldwide, as of September 2021

Company	Drug	Target	Delivery platform	Indications	Clinical trial stage	Start date (location)	Trial Number
Sirnaomics	STP705	TGF-ß1, COX-2	PNP	NMSC(isSCC)	Phase II	5/2021(US)	NCT04844983
				NMSC(BCC)	Phase II	12/2020(US)	NCT04669808
				Liver Cancers	Phase I	3/2021(US)	NCT04676633
	STP707[(1)]	TGF-ß1, COX-2	PNP	Solid tumor	Phase I	11/2021(US)	NCT05037149
Silenseed	siG12D LODER	KRAS, G12D	LODER polymer matrix	Pancreatic Neoplasms	Phase IIb	3/2018(Global excluding China)	NCT01676259
Arrowhead	ARO-HIF2	HIF-2α	TRiM platform	Renal Cell Carcinoma	Phase I	8/2020(US)	NCT04169711
Nanocarrier	NC-6100 (PRDM14 siRNA)	PRDM14	PEG-poly cation	Breast cancer	Phase I	N.A.	N.A.
Nitto	NBF-006	Glutathione S-Transferase P	LNP	NSCLC Cancer, Pancreatic Cancer, Colorectal Cancer	Phase I	3/2019(US)	NCT03819387

Source: U.S. National Library of Medicine; FDA; the CIC report

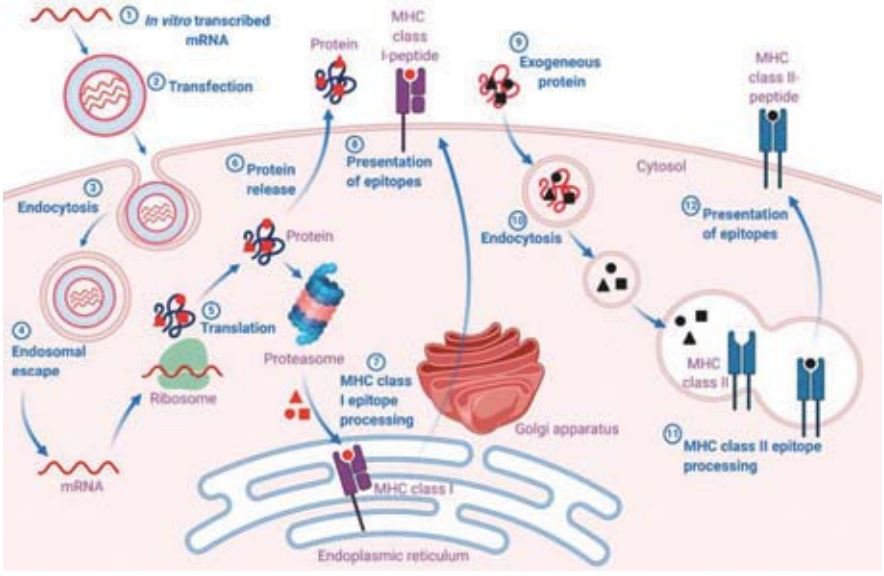
Note: Except for NC-6100 regulated by Ministry of Health in Japan, others are all regulated by FDA
1. STP 707 started phase I clinical trial in November

mRNA vaccine market

Messenger RNA is a large family of RNA molecules that are complimentary to DNA molecules and convey genetic information from the DNA to be translated by ribosomes into proteins. Similar to DNA, mRNA is a type of nucleic acid that contains a specific sequence of nucleotides. After transcription of the mRNA from the corresponding gene in the DNA, the mRNA nucleotides are translated by ribosomes to assemble a polymer of amino acids, a protein. The mRNA plays a key role in the 'central dogma' of molecular biology, which deals with the transfer of sequence information from DNA to RNA to protein. Normal information transfer in most cells is that from DNA to RNA (transcription), DNA to be copied to DNA (replication), and mRNA causing the synthesis of protein (translation or protein synthesis).

Although the concept of mRNA vaccines has been scientifically prevalent since the early 21st century, it has not been massively applied and inoculated until the Moderna and BioNTech/Pfizer COVID-19 vaccine roll out. Previous vaccine platforms utilized similar mechanisms of vaccination by exposing a subject to a pathogen, or a specific aspect of a pathogen, such as a sugar or capsid protein. mRNA vaccines provide a novel and alternative approach to providing pathogen immunity by providing the genetic code of the pathogen's relevant antigen in mRNA form. This messenger RNA is then translated by the host cell to form the corresponding protein from the pathogen at issue. The vaccine thereby provides the cells with a blueprint to construct the protein. This process allows the host to mount an immune response against the constructed foreign protein.

Mechanism of action of mRNA vaccines



Source: the CIC Report; Wadhwa, et al. Pharmaceutics 2020, 12(2), 102.

The development and manufacture of mRNA for use as therapeutics and vaccines are comparatively simple and rapid. The large-scale GMP production of mRNA vaccine has proven to be feasible by several early clinical evaluations, and mRNA vaccines have a favorable safety profile. mRNA vaccines have advantages when vaccines based on other types of nucleic acids, which already demonstrate significant advantages over traditional vaccines in terms of safety, efficacy, induction of both B- and T-cell responses and specificity.

There are several advantages of mRNA vaccines over the other platforms.

- **Rapid process development.** The core principle of mRNA vaccines is to deliver a transcript that encodes a target antigen or immunogen. The RNA synthesis can immediately be carried out using existing technology as soon as the sequence encoding the immunogen is available and the process can be easily scalable and cell-free, requiring minimal platform change during mRNA formulation and manufacturing.

- **Simpler manufacturing.** The unique production process does not require cell culture, antigen extraction or purification processes, shortening the production time. It is relatively easy to achieve mass production, which improves the production capacity of vaccines.

- **Simplified quality control during the production process.** The mRNA vaccine is synthesized through the process of enzymatic in vitro transcription, which does not depend on the expansion of cells, simplifying the monitoring and quality control of all production processes.

- **High potency of immune response.** The mRNA vaccine may induce humoral immunity and cellular immunity at the same time, protecting the body through multiple mechanisms.

- **Favorable safety profiles.** mRNA vaccines show higer safety profiles compared with DNA-based vaccines. mRNA vaccines express target proteins (antigens) via translation from the mRNA rapidly after transfection of the mRNA into the target cell. mRNA vaccines possess much higher biosafety than DNA-based vaccines as the translation of the antigens takes place in the cytoplasm and the mRNA does not enter the nucleus, thus materially decreasing the risk of mRNA integrating into the genome compared to a DNA-based vaccine. mRNA is also a safer vector than DNA since mRNA primarily carries a short sequence to be translated, is a quickly degraded and transient molecule in the host cell, and does not interact with the host genome.

The application of mRNA vaccines requires solutions to the problem of poor stability, easy degradation and difficulty of cellular delivery of mRNA. Lipid nanoparticles (LNP), which are the most commonly utilized system for in vivo RNA delivery, shelter mRNA from

degradation, and mediate endocytosis and endosomal escape. Positively charged lipid nanoparticles help bring mRNA to the negatively charged cell membranes, and facilitate subsequent cytoplasmic endocytosis. Ionizable amino lipids are the major LNP component influencing the efficacy and tolerability of LNP-mRNA therapies. However, this lipid is known to have a long half-life in the organism, leading to mild-to-moderate adverse effects in clinical trials, thus being suboptimal for repeated dosing applications. Therefore, some novel mRNA delivery platforms, like the polypeptide-lipid nanoparticles (PLNP) platform, were developed to potentially improve the delivery efficacy and safety.

In the case of mRNA vaccines for COVID-19, the mRNA provides the genetic blueprint for the spike protein of SARS-CoV-2, the virus that causes the COVID-19 disease. Specifically, the vaccine is a lipid nanoparticle-encapsulated mRNA vaccine that encodes a perfusion stabilized full-length spike protein. Lipid nanoparticles – which are the most commonly utilized vectors for in vivo RNA delivery – protect mRNA from degradation, and mediate endocytosis and endosomal escape. Positively charged lipid nanoparticles help bring mRNA to the negatively charged cell membranes, facilitating subsequent cytoplasmic endocytosis. For the mRNA to be transcribed, it must escape both the lipid nanoparticle as well as the endosome. Once the spike protein is transcribed, immune cells display the spike protein on their surface while the mRNA gets degraded in the cell by normal cellular processes. The immune system recognizes the spike protein as foreign and causes the development of antibodies against the spike protein, which will be capable of also recognizing the SARS-CoV-2 virus. This mechanism provides the immune system with protection against subsequent infection by the SARS-CoV-2 virus while bypassing the risks associated with injecting the actual viral pathogen into the body, whether live or attenuated.

In December 2020, each of Moderna and Pfizer-BioNTech received approval for emergency use of their COVID-19 vaccines, Spikevax and Comirnaty, respectively. Pfizer-BioNTech received full approval for Comirnaty on August 23, 2021. Sales of Spikevax were US$11.3 billion for the nine months ended September 30, 2021, while Comirnaty generated US$24.3 billion global revenues during the same period. The size of the global addressable COVID-19 mRNA vaccine market is projected to reach approximately US$100 billion in 2021.

Global mRNA COVID-19 vaccine sales, 2021Q1-Q3

Company name	Product name	Emergency use authorization date / Full approval	Target	Global revenue 2021 Q1-Q3
Pfizer-BioNTech	Comirnaty	2020/12/02/ 2021/08/23	SARS-CoV-2 Spike protein	US$24.3 billion
Moderna	Spikevax	2020/12/18	SARS-CoV-2 Spike protein	US$11.3 billion

Source: Quarterly Reports of Pfizer and Moderna, the CIC Report

There are seven COVID-19 vaccines approved in China, including conditional and emergency approvals, five of which comprise inactivated virus, one is made by recombinant viral vector, and one is made by recombinant new virus. Most vaccines in the development in China are recombinant vaccines; only three mRNA vaccines entered clinical stage.

Existing products in China market, as of September 2021

Product name	Routes	Manufacturer	Approved time by NMPA	Price ranges
Covilo 眾愛可維	Inactivated	Beijing Institute of Biological Product 北京生物製品研究所	12/2020 (Conditional Approval)	~RMB200
CoronVac 克爾來福	Inactivated	Sinovac Biotech 科興控股生物技術	2/2021 (Conditional Approval)	~RMB200
Convidecia 克威莎	Recombinant viral vector	CanSino 康希諾生物	2/2021 (Conditional Approval)	~RMB200
Covilo 眾康可維	Inactivated	Wuhan Institute of Biological Product 武漢生物製品研究所	2/2021 (Conditional Approval)	~RMB200
CHO cells 智克威得	Recombinant New Coronavirus virus vaccine	Anhui Zhifei Longcom Biopharmaceutical 安徽智飛龍科馬生物製藥	3/2021 (Approval for urgent use)	~RMB200
Kconvac 可維克	Inactivated	BioKangtai 康泰生物	5/2021 (Approval for urgent use)	~RMB200
Keweifu 科維福	Inactivated	Institute of Medical Biology Chinese Academy of Medical Sciences 中國醫學科學院醫學生物學研究所	6/2021 (Approval for urgent use)	~RMB200

Source: WHO; Administration of Public Resources Trading Platforms; Official Website; the CIC report

Pipeline of mRNA COVID-19 vaccines in China, as of September 2021

Company	Product name	Phase	Type of developer	Start date[(1)]
Suzhou Abogen Bioscience/Walvax/ Academy of Military Science	SARS-CoV-2 Mrna Vaccine	Phase III	Domestic	7/2021

Company	Product name	Phase	Type of developer	Start date[1]
BioNTech SE	Comirnaty (BNT162b)	Phase II	International	11/2021
Liverna	LVRNA009	Phase I	Domestic	3/2021
Stemirna	COVID-19-mRNA vaccine	Phase I	Domestic	3/2021
RNAimmune (Sirnaomics)	RIM 730 (SARS-CoV-2 mRNA vaccine)	IND enabling	N.A.	N.A.

Source: ChiCTR; the CIC Report

Note: 1. For approved vaccines, the starting date is date of approval. For vaccine that have not been approved, the starting date is the "Study execute time" of the corresponding clinical trial posted on website of Chinese Clinical Trial Registry.

mRNA vaccines are a promising platform for cancer immunotherapy. Upon vaccination, mRNA vaccines efficiently cause expression of tumor antigens in antigen-presenting cells (APCs), facilitating APC activation and thus stimulation of innate/adaptive immunity against the tumor antigens. mRNA vaccines are capable of inducing both antibody/B cell mediated humoral responses and CD4+ T/ CD8+ cytotoxic T cell responses, which are beneficial for efficient clearance of malignant cells. mRNA cancer vaccines have the potential to surpass other conventional vaccine platforms due to high potency, safe administration, rapid development potentials, and cost-effective manufacturing. Cancer immunotherapies aim to activate the host anti-tumor immunity, modify the suppressive tumor microenvironment and ultimately result in tumor reduction and increased overall patients' survival rate. Cancer vaccines are an attractive alternative immunotherapeutic option with both prophylactic and therapeutic potentials.

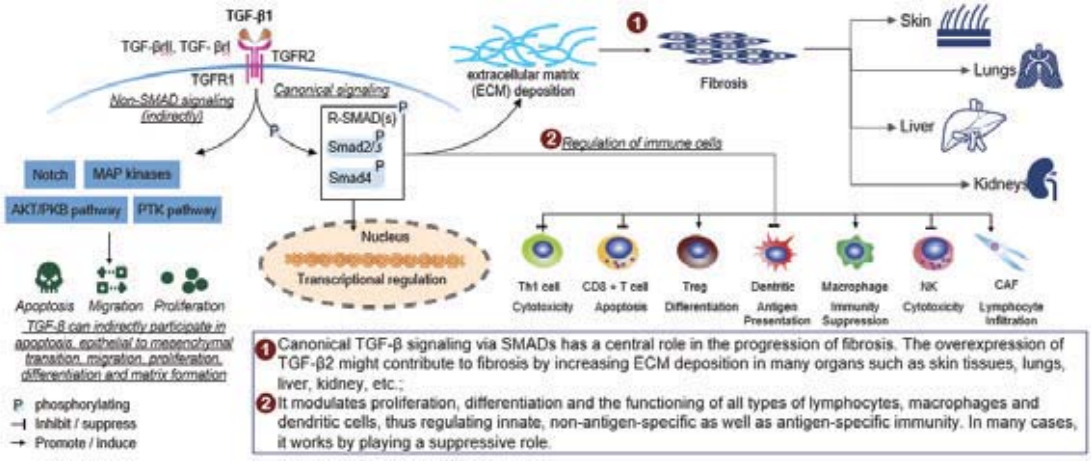
mRNA therapeutics are not only applicable to infectious disease and oncology vaccines, but also protein replacement therapy and gene editing. With the dozens of mRNA-based vaccine candidates currently in preclinical and clinical phases of development, it is evident that the mRNA-based technology is a promising tool for the development of novel therapeutic and prophylactic vaccines against infectious diseases.

TGF-ß1 and COX-2

The transforming growth factor-ß1 (TGF-ß1) family is a family of potent multifunctional cytokines that modulate a wide variety of cellular activities, including cell proliferation, recognition, differentiation, apoptosis, and specification of developmental fate, during embryogenesis as well as in mature tissues. In normal conditions, TGF-ß signaling maintains tissue homeostasis via the regulation of cell proliferation. TGF-ß switches its functioning to accelerate the progress and the development of diseases such as cancer and fibrosis in abnormal conditions. TGF-ß has been an innovation hot spot for oncology, with most trials focused on melanoma, lung, urothelial and colorectal cancer. In addition to oncology, active

trials in developing TGF-ß therapeutics have been observed for musculoskeletal, blood and respiratory diseases.

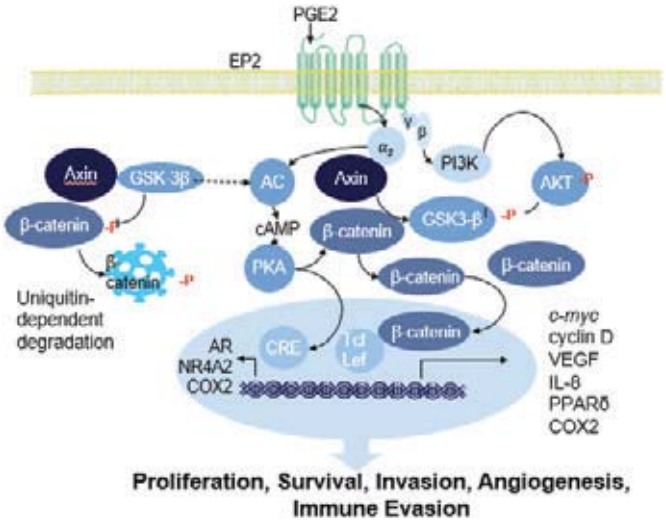
TGF-ß mechanisms of action



Source: Onco Targets and Therapy 2019:12 Bai et al., Yun, S., Kim, S. and Kim, E. (2019), the CIC Report

Cyclooxygenase (COX) is the rate-limiting enzyme in prostanoid synthesis. There are three isoforms of COX: COX-1, COX-2, and COX-3. COX-2 is a membrane-bound, short-lived, and rate-limiting enzyme that has long been known as a target for the relief of pain and treatment of inflammation. Over-expression of COX-2 has been observed in various chronic inflammatory diseases and malignant diseases, such as colon cancer and pancreatic cancer. PGE2, the principle metabolic product of COX-2 enzymatic activity, has been shown to up-regulate tissue inhibitors of metalloproteinases-2 in rats and lead to matrix accumulation. Expressions of COX-2 are parallel with PGE2, and the lack of PGE2 is speculated to contribute to disease pathogenesis like that of pulmonary fibrosis. COX-2 has been an innovation hot spot for musculoskeletal diseases, immune disorders, skin and connective tissue diseases, tumors, along with other diseases.

COX-2 mechanisms of action



Source: Nasser Hashemi Goradel et al. (2018), the CIC Report

Inhibition of TGF-ß1 and COX-2 can synergistically induce fibroblast apoptosis, leading to significant anti-fibrosis activity. Downregulation of TGF-ß1 and COX-2 expression also demonstrates potent anti-tumor activities, suppressing inflammation in the tumor microenvironment to inhibit pro-tumorigenic effects and invasiveness, removing resistance to apoptosis in cancer cells by downregulating anti-apoptotic factors and upregulating pro-apoptotic factors, and suppressing metastasis. Downregulation of TGF-ß1 and COX-2 modulate the TGF-ß signaling pathway to inhibit extracellular matrix synthesis, which is the heart of fibrogenesis. Inhibition of TGF-ß1 and COX-2 in the tumor microenvironment promote T-cell infiltration into the tumor.

Other Drug Targets

VEGFR2: The Vascular Endothelial-derived Growth Factor (VEGF) family is the primary regulator of angiogenesis, the formation of new blood vessels, in both normal physiology as well as pathological angiogenesis, such as cancer. VEGF acts on its endothelial cell target through binding with receptors. After binding to VEGFR2, VEGF triggers a series of signal transducing pathways stimulating endothelial cell proliferation, increased vascular permeability, endothelial cell migration and new blood vessel formation. VEGF overexpression is found in most cancers, and causes aberrant neo-angiogenesis within both the tumor and surrounding tissues to meet the nutrition demand for uncontrolled proliferation of tumors. Studies of VEGF functionality have led to therapeutic strategies specifically targeting the VEGF/VEGFR signaling pathway, including the monoclonal antibodies Avastin (Bevacizumab) and Cyramza (ramucirumab) as well as small molecule drugs such as Sutent (sunitinib), Nexavar (sorafenib), and Fotivda (tivozanib), which have been widely applied in many different cancer therapies. Preclinical studies have consistently shown additive or synergistic benefits from combinations of VEGF inhibitors with cytotoxic agents.

Factor XI: Factor XI is a plasma glycoprotein that is primarily synthesized in the liver and is part of the coagulation cascade, playing a role in clot stabilization and expansion. High levels of Factor XI increase the risk of thrombosis, an abnormal clot within blood vessels that can lead to heart attacks and strokes. Individuals deficient in Factor XI have reduced risk of thrombosis-related events, but exhibit little increase in bleeding. Factor XI is an attractive target for the development of therapeutics to prevent thrombosis with limited risk for bleeding side effects. Current product candidates in clinical development that target Factor XI include an antisense-based candidate from Ionis Pharmaceuticals and Bayer and a small molecule from Exithera Pharmaceuticals.

PCSK9: Proprotein convertase subtilisin/kexin type 9, or PCSK9, is expressed in the liver and is involved in the regulation of LDL-C in the blood. PCSK9 binds to the LDL receptor on the surface of hepatocytes, preventing LDLR from binding LDL-C to remove LDL-C from circulation for breakdown in hepatocytes. Two FDA-approved monoclonal antibodies, Repatha (evolocumab) and Praluent (alirocumab), and Leqvio (inclisiran), an siRNA therapeutic, approved in Europe, target PCSK9. Additional products in development that target PCSK9 include small molecule PCSK9 inhibitors from Dogma Therapeutics/Astra Zeneca and Serometrix LLC/Esperion Therapeutics, Inc., as well as PCSK9 gene therapies from Precision BioSciences and Verve Therapeutics.

Non-Melanoma Skin Cancer, Liver Cancer and Non-Small Cell Lung Cancer Pharmaceutical Markets

Non-Melanoma Skin Cancers (NMSCs)

Non-melanoma skin cancers (NMSCs) are the most common forms of human neoplasia. NMSCs constitute a large group of skin cancers that are not melanoma, including squamous cell carcinoma (SCC), basal cell carcinoma (BCC), Extramammary Paget's Disease (EMPD), Merkel cell carcinoma (MCC), and skin adnexal carcinomas. Among these, BCC and SCC account for the majority of NMSCs with more than five million newly diagnosed cases estimated to occur in the U.S. every year. Most NMSCs are associated with exposure to ultraviolet radiation from the sun; other common risk factors include light-colored skin, older age, male gender, and a history of previous skin cancer.

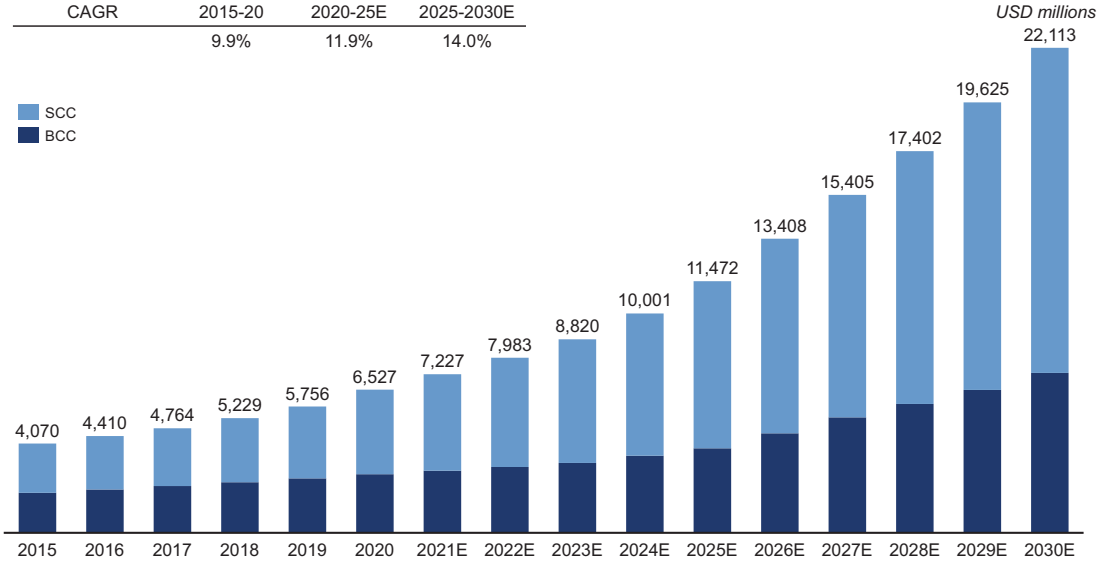
BCC and SCC usually do not spread to other parts of the body, therefore the vast majority of NMSCs are pre-metastatic. Metastatic NMSCs are relatively rare. Once metastasis occurs, the prognosis of NMSCs becomes extremely poor. The estimated metastasis rate of BCC ranges from 0.0029% to 0.55%, and common metastatic sites are regional lymph nodes, lungs, bones, skin, and liver. The biology of SCC can be more aggressive with a higher chance of local extension and/or metastasis. The risk for metastasis in cSCC (cutaneous SCC) is reported to be approximately 2% – 5%. The low risk NMSC is defined by NCCN guidelines as primary tumors located in trunk and extremities with size smaller than 2cm with well-defined borders. Squamous cell carcinoma in situ (isSCC), also called Bowen disease, is the earliest form of

squamous cell skin cancer (SCC). Along with basal cell carcinoma, SCC is one of two major subtypes of NMSC. isSCC has a 3%-5% risk to develop into invasive SCC. Therefore, although isSCC and low risk NMSC are different by definition, the majority of isSCC can be categorized into low-risk NMSC.

The number of new cases of BCC and SCC increased by 33% from 2015 to 2020 in the U.S., with 2.4 million and 3.2 million new patients respectively in 2020. In China, the number of new cases is relatively small, with 76 thousand patients diagnosed of BCC and 28 thousand patients diagnosed of SCC. These increases are associated with several factors, including raised awareness of NMSC, improved registration, aging population, and increased exposure to UV radiation. In the past many SCCs in situ may have been misdiagnosed as actinic keratosis and now "diagnostic drift" to isSCCs may be contributing to the increased incidence of SCC. Consequently, SCC is projected to increase at a faster rate in the future.

The market size of SCC and BCC treatment in the U.S. based on retail price from the patient side is US$6.5 billion in 2020 (the isSCC segment is US$1.5 billion, or over 20%) and is expected to reach US$11.5 billion and US$22.1 billion by 2025 and 2030, respectively, representing a CAGR of 11.94% from 2020 to 2025 and a CAGR of 14.03% from 2025 to 2030. The market size of SCC and BCC treatment in China based on retail price from the patient side is US$38 million in 2020 (the isSCC segment is US$4.3 million, or approximately 11%) and is expected to reach US$64 million and US$149 million by 2025 and 2030, respectively, representing a CAGR of 10.87% from 2020 to 2025 and a CAGR of 18.55% from 2025 to 2030.

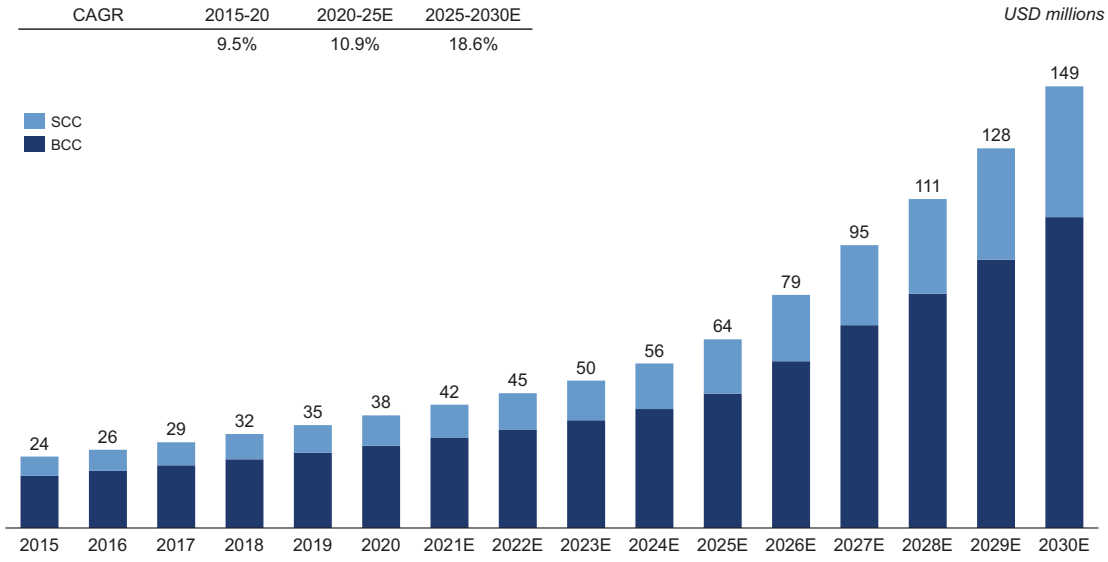
Market size of NMSC treatment in the U.S., 2015-2030E



Notes: The market size of NMSC only includes the market size of SCC and BCC treatment

Source: the CIC report

Market size of NMSC treatment in China, 2015-2030E



Source: the CIC report

US Market

For the U.S. market, the addressable market size of isSCC = Number of target patients * treatment rate of isSCC * average annual spending of available treatment options. According to *Incidence Estimate of Nonmelanoma Skin Cancer (Keratinocyte Carcinomas) in the US Population, 2012*, the number of new cases of isSCC in the U.S. is 1.3 million in 2020 and is projected to increase to 3.4 million in 2030. Based on *Incidence and Trends of Basal Cell Carcinoma and Cutaneous Squamous Cell Carcinoma: A Population-Based Study in Olmsted County, Minnesota, 2000 to 2010* published in *Cancer Research and Treatment*, there are four categories of patients with proportions listed in the table below.

isSCC patients distribution	**Proportion**
Patients applicable for surgery with tumor in head or neck	56%
Patients applicable for surgery with tumor in trunk or extremity	41%
Patients not applicable for surgery with tumor in head	1%
Patients not applicable for surgery with tumor in trunk or extremity	1%

The treatment rate of isSCC is assumed to be around 97%, according to *Prevalence and Costs of Skin Cancer Treatment in the U.S., 2002-2006 and 2007-2011*. The average annual spending of available treatment options ranged between US$1,100 and US$2,500 in 2020, as referenced by *Prevalence and Costs of Skin Cancer Treatment in the U.S., 2002-2006 and 2007-2011*. For the core product, STP705, the estimated demand solely with respect to isSCC in the U.S. is expected to be around US$43 million in the anticipated launch year of 2023.

The addressable market size of BCC = Number of target patients * treatment rate of BCC* average annual spending of available treatment options

In the U.S., according to *Incidence Estimate of Nonmelanoma Skin Cancer (Keratinocyte Carcinomas) in the US Population, 2012*, the number of new cases of BCC is 2.4 million in 2020 and is projected to increase to 4.2 million in 2030. Based on *Incidence and Trends of Basal Cell Carcinoma and Cutaneous Squamous Cell Carcinoma: A Population-Based Study in Olmsted County, Minnesota, 2000 to 2010* published in *Cancer Research and Treatment*, there are four categories of patients with proportions listed in the table below.

BCC patients' distribution	**Proportion**
Patients applicable for surgery with tumor in head or neck	61%
Patients applicable for surgery with tumor in trunk or extremity	33%
Patients not applicable for surgery with tumor in head	1%
Patients not applicable for surgery with tumor in trunk or extremity	1%

The treatment rate of BCC is assumed to be around 97%, according to *Prevalence and Costs of Skin Cancer Treatment in the U.S., 2002-2006 and 2007-2011*. The average annual spending of available treatment options ranged between US$1,100 and US$2,500 in 2020, as referenced by *Prevalence and Costs of Skin Cancer Treatment in the U.S., 2002-2006 and 2007-2011*.

China Market

For the China market, the addressable market size of isSCC = Number of target patients * treatment rate of isSCC * average annual spending of available treatment options

In China, according to *Chinese Society of Clinical Oncology*, the number of new cases of isSCC is 11 thousand in 2020 and is projected to increase to 26 thousand in 2030. Based on *Nationwide Trends in the Incidence of Melanoma and Non-melanoma Skin Cancers from 1999 to 2014 in South Korea*, there are four categories of patients with proportion listed in the table below.

isSCC patients distribution	**Proportion**
Patients applicable for surgery with tumor in head or neck	68%
Patients applicable for surgery with tumor in trunk or extremity	28%
Patients not applicable for surgery with tumor in head	1%
Patients not applicable for surgery with tumor in trunk or extremity	1%

The treatment rate of isSCC is assumed to be around 95%, according to *Prevalence and Costs of Skin Cancer Treatment in the U.S., 2002-2006 and 2007-2011* and physician interviews. The average annual spending of available treatment options ranged between US$350 and US$700 in 2020, according to physician interviews. For the core product, STP705, the estimated demand is expected to be around US$68 million in China with respect to multiple indications including isSCC, BCC, HTS and keloids in the anticipated launch year of 2024.

Addressable market size of BCC = Number of target patients * treatment rate of BCC* average annual spending of available treatment options

In China, according to *Special features of non-melanoma skin cancer in Hong Kong Chinese patients: 10-year retrospective study*, the number of new cases of BCC is 76 thousand in 2020 and is projected to increase to 178 thousand in 2030. Based on physician interviews, there are four categories of patients with proportion listed in the table below.

BCC patients distribution	**Proportion**
Patients applicable for surgery with tumor in head or neck	88%
Patients applicable for surgery with tumor in trunk or extremity	8%
Patients not applicable for surgery with tumor in head	2%
Patients not applicable for surgery with tumor in trunk or extremity	1%

The treatment rate of BCC is assumed to be around 95%, according to *Prevalence and Costs of Skin Cancer Treatment in the U.S., 2002-2006 and 2007-2011* and physician interviews. The average annual spending of available treatment options ranged between US$350 and US$700 in 2020, according to physician interviews.

NMSC treatment market is driven by the following factors:

- **Increasing incidence:** Due to changed lifestyle and increased outdoor activities, people have longer exposure times to UV radiation. The incidence of precancerous skin conditions such as actinic keratoses, moles and freckles, is likely to increase, owing to an aging population. Genetic susceptibility to diseases, for example, nevoid BCC syndrome, will also lead to increased incidence.

- **Emerging treatment and diagnosis:** Country-wide skin cancer screening was introduced and became more prevalent for residents older than 35 years of age with health insurance since 2008 in the U.S., leading to an increase in diagnosis rate. In the meantime, more therapeutic options available for NMSC provide more choices for patients, which can increase treatment rate consequently.

- **Clinical needs:** Cosmetic appearance remains one of the key needs for NMSC treatment and has a large influence on patient preferences, especially for those with lesions on the head or neck, yet current treatments are unable to satisfy this special need.

While a standard management strategy for treatment of metastatic NMSC has not been established, advances in our molecular biological understanding of NMSC and improvement of drug discovery techniques over the past several decades have facilitated the establishment of novel treatment strategies. While there were several targeted therapies for advanced NMSC approved by FDA in recent years, including molecular targeting agents and immune checkpoint inhibitors, these are restricted to metastatic disease.

Conventional and Standard Treatment Methods for BCC and isSCC, November 2021

Indication	Treatment methods
BCC & isSCC	Standard Surgical excision Mohs micrographic surgery
	5'-fluorouracil Imiquimod
	Cryosurgery Laser therapy Electrodesiccation Radiation therapy

Sources: The CIC Report; Expert consensus on Basal Cell Carcinoma, China, 2021; Bittner et al. Mohs micrographic surgery: a review of indications, technique, outcomes, and considerations. An Bras Dermatol. 2021 May-Jun;96(3):263-277; Lin, M. Innovations in Geriatrics: Nonmelanoma Skin Cancer Prevention, Diagnosis, and Treatment. Today's Geriatric Medicine. 2017; 10:30.

Currently, there are surgical and non-surgical treatment pathways for pre-metastatic BCC and SCC. Surgical treatment pathways include Mohs micrographic surgery and surgical excision. Mohs micrographic surgery is the standard of care, with the highest reported cure rate and the ability to intraoperatively analyze almost all the excision margin. An important alternative to Mohs micrographic surgery is surgical excision. The cosmetic appearance of surgical treatment, however, usually results in significant scarring due to invasive operation. Non-surgical treatment pathways include curettage and electrodesiccation, topical creams, radiation, photodynamic therapy and cryotherapy, although these non-surgical pathways are considered to be less effective compared to surgical pathways. 5'-fluorouracil and imiquimod are the only two drugs approved by US FDA for pre-metastatic BCC patients, both of which are used off-label for pre-metastatic SCC patients. Both are administered topically and can cause skin reactions in some patients.

Efficacy and Side Effects for Original Drug Products Approved for Pre-Metastatic BCC, as of September 2021

Company name	Drug name	Generic name	Approved markets	Indication	Efficacy	Side effects	Approval date	Price[1]
Teva Parenteral Medicines	Adrucil	5'-fluorouracil	US	BCC	With isolated, easily accessible basal cell carcinomas, the success rate with fluorouracil cream and solution is approximately 93%	Burning, crusting, allergic contact dermatitis	2/2000 (FDA)	~US$15
iNova	Aldara	Imiquimod	US	BCC	Superficial BCC imiquimod vs vehicle clearance rate is 75% vs 2%	Headache, back pain, burning	7/2004 (FDA)	~US$8

Source: FDA; U.S. FDA Drugs Database; U.S. National Library of Medicine; the CIC Report
Note: 1. retail price per unit

Liver Cancer

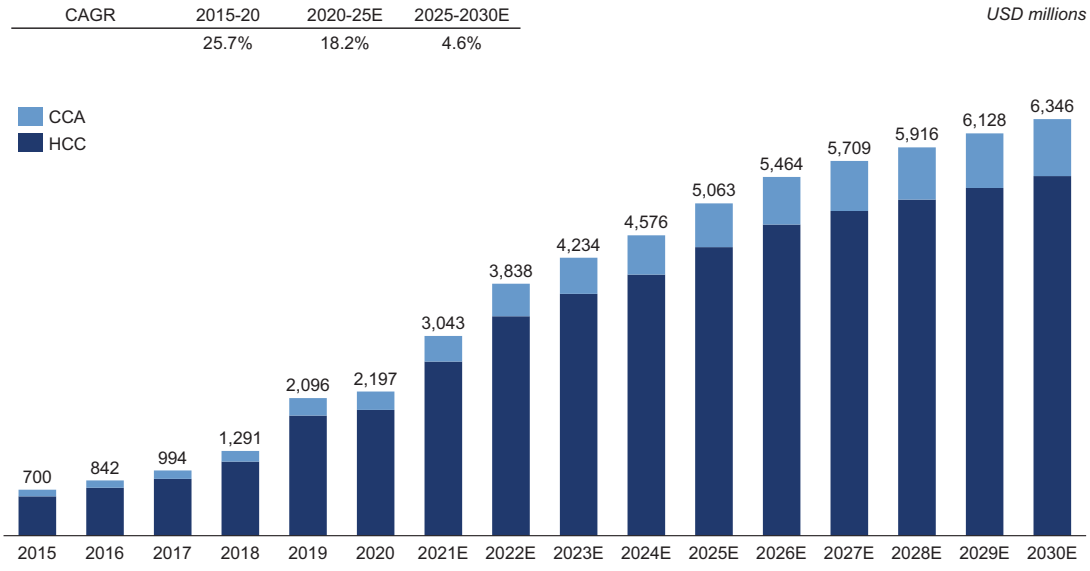
The leading cause of primary liver cancer is cirrhosis due to hepatitis B, hepatitis C, or excessive alcohol consumption. The signs and symptoms of liver cancer depend on the type of cancer present. Common symptoms include abdominal pain, jaundice and weight loss. The most common types are hepatocellular carcinoma (HCC), which makes up 80% of cases, as well as intrahepatic cholangiocarcinoma (CCA).

The number of new cases of liver cancer in China was 509.6 thousand in 2020, and is expected to increase to 570.3 thousand in 2025 and 630.3 thousand in 2030, representing a CAGR of 2.3% from 2020 to 2025 and a CAGR of 2.1% from 2025 to 2030, respectively. The number of new cases of liver cancer in the U.S. was 41.7 thousand in 2020, and is expected to increase to 45.2 thousand in 2025 and 48.5 thousand in 2030, representing a CAGR of 1.6% from 2020 to 2025 and a CAGR of 1.4% from 2025 to 2030, respectively.

The size of the HCC pharmaceutical market in the U.S. grew from US$1.9 billion in 2020 to US$4.4 billion and further to US$5.5 billion in 2030, with a CAGR of 18.1% from 2020 to 2025 and a CAGR of 4.5% from 2025 to 2030. The CCA pharmaceutical market is expected to reach over US$0.9 billion by 2030, accounting for approximately 13.7% of the overall liver cancer pharmaceutical market. Meanwhile, the size of the HCC pharmaceutical market in China is projected to grow from US$1.2 billion in 2020 to US$5.2 billion in 2025 and further to US$7.0 billion in 2030, with a CAGR of 33.9% from 2020 to 2025 and a CAGR of 6.2% from 2025 to 2030. The CCA pharmaceutical market in China is projected to grow from

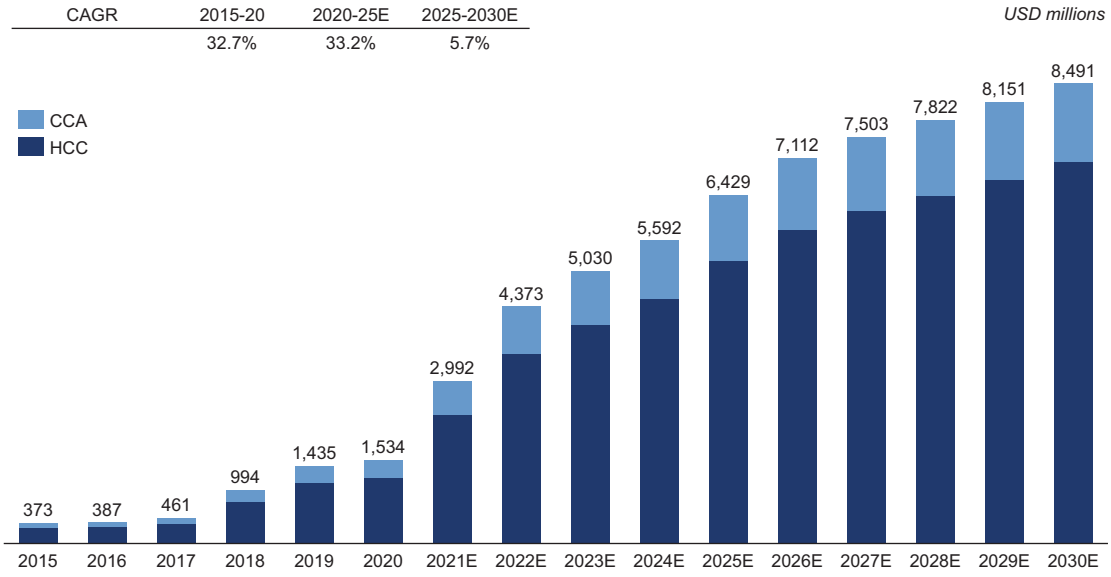
US$0.3 billion in 2020 to US$1.2 billion in 2025 and further to US$1.5 billion in 2030, with a CAGR of 30.5% from 2020 to 2025 and a CAGR of 3.6% from 2025 to 2030.

Market size of HCC and CCA pharmaceuticals in the U.S., 2015-2030E



Source: the CIC report

Market size of HCC and CCA pharmaceuticals in China, 2015-2030E



Source: the CIC report

The liver cancer pharmaceutical market is driven by the following factors:

- **Increasing incidence:** 85% of liver cancer cases in China are attributable to HBV infections, which remains an incurable disease. Other risk factors such as diabetes, NASH, and excessive alcohol consumption continue to increase in their prevalence.

- **Emerging diagnosis and treatment:** Improvements in liver cancer early screening and diagnosis, greater accessibility to therapeutics, and more liver cancer drugs covered by national health insurance scheme contribute to higher diagnosis and treatment rates.

- **Clinical needs:** Prognosis for liver cancer patients is generally bleak. Advanced HCC frontline therapeutic options all have limited efficacies, resulting in need for patients refractory to first and second line treatment. Similarly, targeted drugs for CCA are very limited resulting in need for systemic therapies for advanced CCA.

Conventional and Standard Treatment Methods for Liver Cancer (November 2021)

Indication	Treatments methods
Liver cancer	Surgery excision Liver transplant Ablation therapy Embolization therapy Targeted therapy Immunotherapy Radiation therapy

Sources: The CIC Report; Guidelines for Diagnosis and Treatment of Primary Liver, 2020, CSCO; Guidelines for Diagnosis and Treatment of Liver Cancer/Hepatobiliary Cancers, 2021, NCCN

There are two different treatment paths for HCC and CCA, both of which include early stage and advanced stage:

Early stage HCC is typically treated by surgery, such as radiofrequency ablation (RFA) or microwave ablation (MWA), while advanced HCC usually employs chemoembolization and radioembolization, targeted therapy and immunotherapy. The cornerstone treatment for early stage CCA includes surgery and radiation therapy, and advanced CCA is generally treated with chemotherapy, targeted therapy and immunotherapy.

Efficacy and Side Effects for Drug Products Approved for HCC and CCA, as of September 2021

Company name	Drug name	Generic name	Approved markets	Indication	Efficacy (experimental cohort, placebo or other cohorts)	Side effects (control: % of all grades, % of grades 3-4; placebo: % of all grades, % of grades 3-4)	Price	Approval date	Trial number
Roche	Tecentriq	Atezolizumab	US, China	HCC	Median OS (NE, 13.2; hazard ratio, 0.58) Median PFS (Tecentriq in combination with Bevacizumab: 6.8, 4.3; hazard ratio,0.59)	Hypertension (Tecentriq in combination with Bevacizumab:30%, 15%; Sorafenib: 24%, 12%) Fatigue/asthenia (Tecentriq in combination with Bevacizumab:26%, 2%; Sorafenib: 32%, 6%) Proteinuria (Tecentriq in combination with Bevacizumab:20%, 3%; Sorafenib: 7%, 0.6%)	~US$500/unit (US) ~RMB5800/5 mg (China)	5/2020 (US) 10/2020 (China)	NCT03434379
Roche	Avastin	Bevacizumab	US, China	HCC	Median OS (Avastin in combination with Atezolizumab: NE, Sorafenib: 13.2; hazard ratio, 0.58) Median PFS (Avastin in combination with Atezolizumab: 6.8, Sorafenib: 4.3; hazard ratio,0.59)	Hypertension (Avastin in combination with Atezolizumab:30%, 15%; Sorafenib: 24%, 12%) Fatigue/asthenia (Avastin in combination with Atezolizumab:26%, 2%; Sorafenib: 32%, 6%) Proteinuria (Avastin in combination with Atezolizumab:20%, 3%; Sorafenib: 7%, 0.6%)	~US$840/4ml (US) ~RMB2500/100 mg (China)	5/2020 (US) 10/2020 (China)	NCT03434379
Exelixis	Cabometyx	Cabozantinib-S-Malate	US	HCC	Median OS (10.2, 8.0; hazard ratio, 0.76)	Diarrhea (54%, 10%;19%, 2%) Fatigue (45%, 10%; 30%, 4%) Decreased appetite (48%, 6%; 18%, <1%)	~US$23000/ 30 tablets	1/2019 (US)	NCT01908426
Merck	KEYTRUDA	Pembrolizumab	US	HCC	Single arm, ORR 17%	Fatigue, Rash, vitiligo, arthralgia, ascites (8% Grades 3-4), immune-mediated hepatitis (2.9%)	~US$13000/ 100 mg	11/2018 (US)	NCT02702414
Eisai And Merck	Lenvima	Lenvatinib Mesylate	US, China	HCC	Median OS (Lenvima: 13.6, Sorafenib: 12.3; hazard ratio: 0.92)	SAE Total (Lenvima: 43.07%, Sorafenib: 30.32%) Hypertension (45%, 24%) Cardiac dysfunction (NA, 3%) Arterial thromboembolic (2%, NA)	~US$21000/ 30 tablets (US) ~RMB20000/ 30 tablets (China)	8/2018 (US) 9/2018 (China)	NCT01761266

Company name	Drug name	Generic name	Approved markets	Indication	Efficacy (experimental cohort, placebo or other cohorts)	Side effects (control: % of all grades, % of grades 3-4; placebo: % of all grades, % of grades 3-4)	Price	Approval date	Trial number
Bristol-Myers Squibb	Opdivo[1]	Nivolumab	US	HCC	Cohort 4 (in Combination with Ipilimumab), ORR 33%	Cohort 4 (in Combination with Ipilimumab): Rash (53%,8%); Pruritus (53%,4%); Musculoskeletal pain (41%,2%)	~US$300/ 1 ml	9/2017 (US)	NCT01658878
Incyte	Pemazyre	Pemigatinib	US	Cholangiocarcinoma	Single arm, ORR 36%	Hyperpfhosphatemia (60%, 0%) Alopecia (49%,0) Diarrhea (47%,2.7)	~US$18000/ 4.5 mg	4/2020 (US)	NCT02924376
Eli Lilly	Cyramza	Ramucirumab	US	HCC	Median OS (8.5, 7.3; hazard ratio 0.71) PFS (2.8, 1.6; hazard ratio 0.45)	Fatigue (36%, 5%; 20%,3%) Peripheral edema (25%,2%; 14%,0%), Decreased appetite (23%, 2%; 20%,1%)	~US$1300/ 10 ml	5/2019 (US)	NCT02435433
Bayer HealthCare	Stivarga	Regorafenib	US, China	HCC	Median OS (10.6, 7.8; hazard ratio 0.63) PFS (3.4,1.5, hazard ratio 0.43)	Skin and subcutaneous tissue disorders (51%,12%; 7%, <1%) Pain (55%,9%; 44%,8%) Asthienia/Fatigue (20%,0%; 7%,0%)	~US$20000/ 40 mg (US) ~RMB10000/40 mg (China)	4/2017 (US) 12/2017 (China)	NCT01774344
Bayer and Onyx Pharmaceuticals	Nexavar	Sorafenib Tosylate	US, China	HCC	Median OS (10.7,7.9; hazard ratio 0.69)	Gastrointestinal (98%, 45%; 96%,32%), Fatigue (46%,10%; 45%, 13%), Diarrhea（55%, <11%; 25%, 2%）	~US$22000/ 200 mg (US) ~RMB12000/ 200 mg (China)	11/2007 (US) 12/2017 (China)	NCT00105443
BridgeBio Pharma	Truseltiq	Infigratinib Phosphate	US	Cholangiocarcinoma	Single arm, ORR 23%	Nail toxicity (57%, 2%), Stomatitis（56%,15%), Dry Eye(44%,0)	~US$23000/ 42 capsules	5/2021 (US)	NCT02150967

Source: U.S. National Library of Medicine; the CIC report

NOTE: 1. On September 22, 2017, the FDA granted accelerated approval to nivolumab (OPDIVO, Bristol-Myers Squibb Co.) for the treatment of hepatocellular carcinoma (HCC) in patients who have been previously treated with sorafenib. However, the accelerated approval for OPDIVO has been removed in 2021.

The liver cancer market pipeline is highly innovative and diverse. The market offers tremendous opportunities to develop breakthrough first-in-class therapies due to needs. In recent years, innovative treatment approaches such as oncolytic viruses and RNA interference (RNAi) technology have gained significant traction in the market, although none have resulted in commercialized treatments.

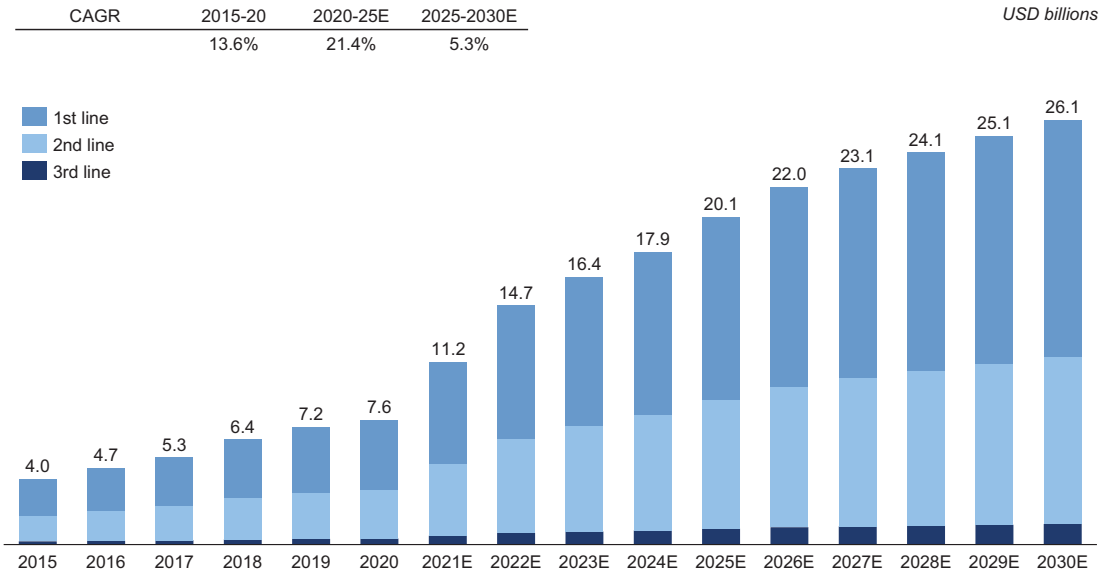
Non-small Cell Lung Cancer (NSCLC)

NSCLC is the most common type of lung cancer, accounting for the majority of total lung cancer cases. NSCLC is defined as any type of epithelial lung cancer other than SCLC, including adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and NSCLC-NOS (not otherwise specified) / NSCLC undifferentiated. There were 176 thousand cases in the U.S.

and 757 thousand cases in China in 2020. Moreover, around 110 thousand people die from NSCLC in the U.S. annually as of 2020, while in China, the number has increased to 360 thousand in the latest figures.

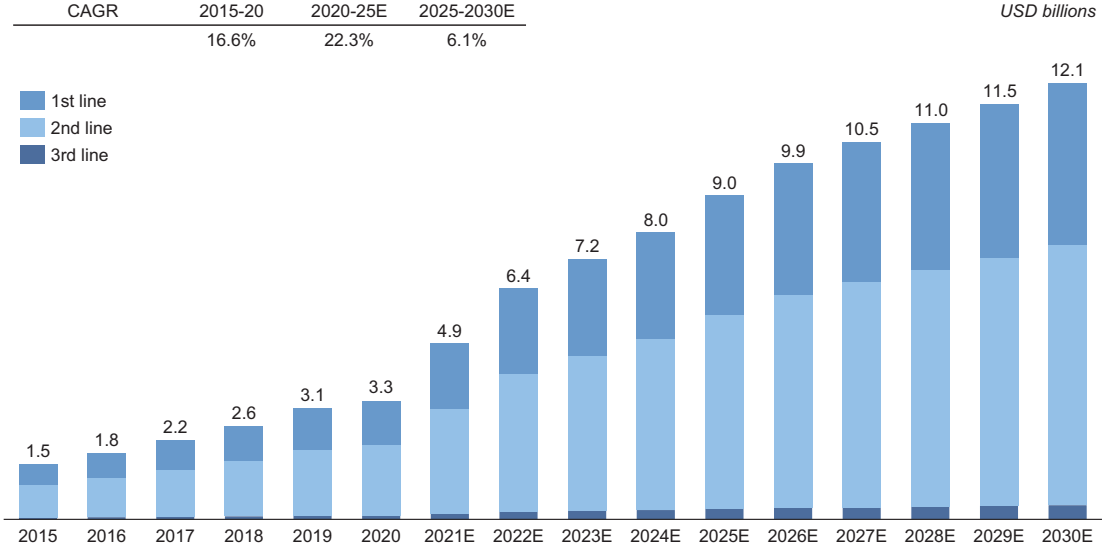
The market size of NSCLC pharmaceutical in the U.S. is expected to grow slower in the years ahead, rising from US$7.6 billion in 2020 to US$26.1 billion in 2030, with a CAGR of 13.1%. Meanwhile, the market size of NSCLC drugs in China are projected to rise from US$3.3 billion in 2020 to US$12.1 billion in 2030 with a CAGR of 13.9%.

Market size of NSCLC pharmaceuticals in the U.S., 2015-2030E



Source: the CIC report

Market size of NSCLC pharmaceuticals in China, 2015-2030E



Source: the CIC report

The NSCLC pharmaceutical market is driven by the following factors:

- **Increasing incidence:** An increasing incidence of NSCLC in the U.S. and China will drive growth.

- **Emerging treatments:** An increasing incorporation of premium-priced immune checkpoint inhibitor immunotherapies into the NSCLC treatment algorithm, particularly in the first-line setting, will be one major driver. Targeted therapies and RNAi therapeutics are also expected to contribute to the growth of the NSCLC market.

- **Clinical needs:** There is a significant lack of targeted therapy options in the second line once a patient develops resistance to immune-checkpoint inhibitors. In addition to effective therapy options post-ICIs, a personalized therapeutic approach requires further refinement for patients harboring actionable mutations. The five-year survival rate of NSCLC patients is still very low, meaning there is an urgent need to improve curative options and patient outcomes. Additionally, the probability of a cure in an advanced setting is rare.

Existing treatment pathways for different stages of NSCLC are relatively clear. Stage I and II patients usually adopt surgery with chemotherapy first before radiation therapy. Stage III patients usually adopt a combination of immunotherapy, radiation therapy and chemotherapy. Stage IV and metastatic patients usually adopt systemic therapy using chemotherapy, targeted therapy or immunotherapy.

There are two drugs targeting TGF-ß1 for anticancer therapy in NSCLC now entering into the late stage of clinical trials, which show a feasibility for TGF-ß1 target therapy in NSCLC. In vitro and ex vivo evidence support the value of siRNA in NSCLC.

Pipeline of RNA-based drugs in NSCLC, worldwide, as of September 2021

Company	Drug name	Phase	Modality	Indication	Target	Start date
Dynavax	DV-281	Ib	Oligonucleotide	Advanced NSCLC	TLR9	2017/09
Nitto Biopharma Inc	NBF-006	I	siRNA	NSCLC PC Colorectal Cancer	GSTP1	2019/03

Source: the CIC report, Clinical Trial

Fibrosis pharmaceutical market

Repair of damaged tissues is a fundamental biological process that allows the ordered replacement of dead or injured cells during an inflammatory response, a mechanism that is

crucial for survival. The repair process involves two distinct stages: regenerative, where injured cells are replaced by cells of the same type and fibroplasia or fibrosis, where connective tissue replaces normal parenchymal tissue. The healing process can become pathogenic if it continues unchecked, leading to considerable tissue remodeling and the formation of permanent scar tissue. In some cases, it might ultimately cause organ failure and death. Fibrotic scarring is often described as a wound-healing response gone awry.

Fibrosis diseases include major-organ fibrosis, fibroproliferative disorders, and scarring associated with trauma. Major-organ fibrosis includes interstitial lung disease (ILD), liver cirrhosis, kidney disease, untreated hypertensive diseases, heart disease, diseases of the eye. Fibroproliferative disorders include systemic and local scleroderma, keloids and HTS and atherosclerosis and restenosis. Scarring associated with trauma includes surgical complications, chemotherapeutic drug-induced fibrosis, radiation-induced fibrosis, accidental injury and burns.

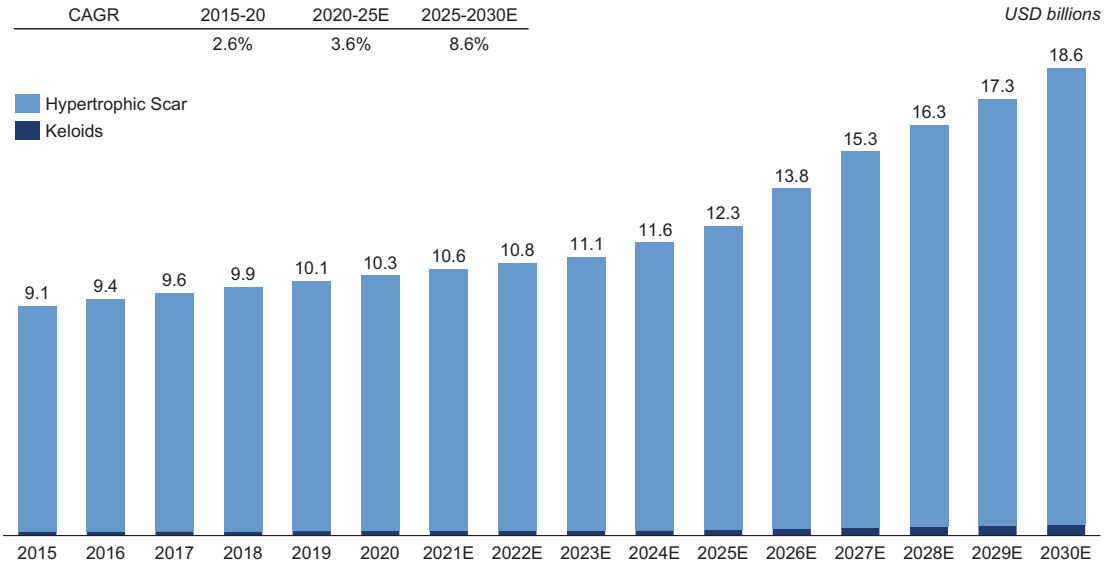
Studies and clinical data have shown that RNAi therapeutics as novel treatments for fibrosis disease are effective, have sustained siRNA release and good biocompatibility. For the treatment and prevention of certain fibrotic diseases, several studies and clinical data have shown that the application of siRNA-based therapies are effective, as the challenge of the safety, stability, and effective delivery of siRNA, including to the liver, was overcome. In addition, RNAi therapeutics are promising drug modalities and are especially ideal for respiratory diseases due to its potential for convenient topical airway administration and minimal systemic toxicity.

Hypertrophic scars (HTS) and Keloids

HTS refers to scars that become swollen, puffy and reddened, causing the scar to stand out from the surrounding skin, and are usually caused by burn injuries, traumatic injuries and surgical procedures. Keloids refers to raised lumps of collagen that form when scar tissue grows irregularly or otherwise more quickly than a wound heals. Keloids are usually caused by acne, burn injuries, traumatic injuries, and surgical procedures.

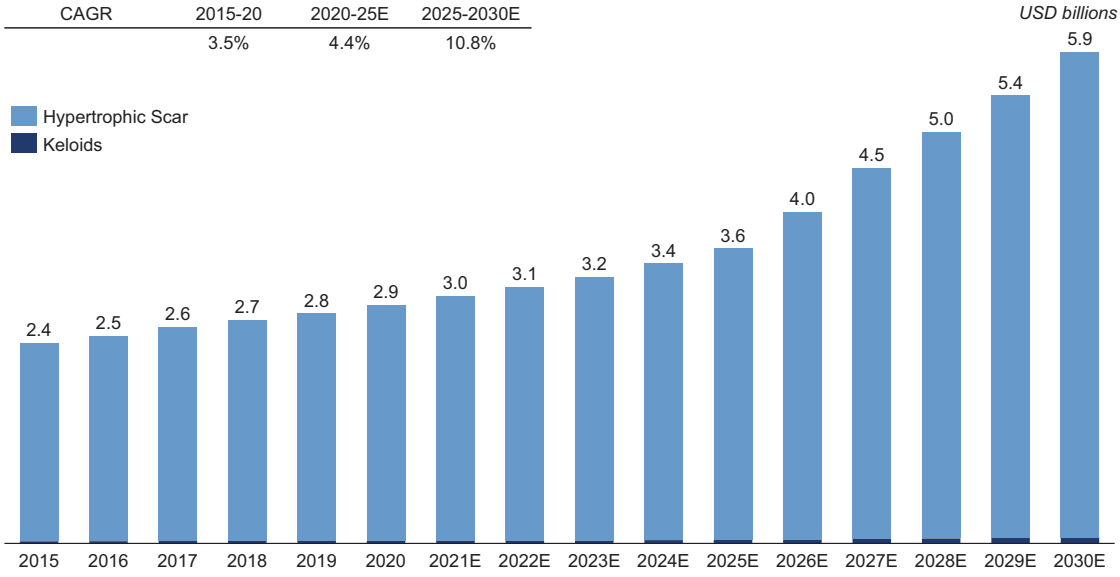
HTS and keloids are common dermatological conditions affecting more than 16 million patients in the U.S. and China annually, which can result in permanent functional loss and the stigma of disfigurement. The combined market size for HTS and keloids treatments in the U.S. is projected to grow faster in the years ahead, rising from US$10.3 billion in 2020 to US$12.3 billion in 2025 and further to US$18.6 billion in 2030, with a CAGR of 3.6% from 2020 to 2025 and a CAGR of 8.6% from 2025 to 2030. The market size for HTS and keloid treatments in China is also expected to grow faster, rising from US$2.9 billion in 2020 to US$3.6 billion in 2025 and further to US$5.9 billion in 2030, with a CAGR of 4.4% from 2020 to 2025 and a CAGR of 10.8% from 2025 to 2030.

Market sizes of HTS & Keloids treatments in the U.S., 2015-2030E



Source: the CIC report

Market sizes of HTS & Keloids treatments in China, 2015-2030E



Source: the CIC report

U.S. Market

In the U.S., the addressable market size of HTS and keloids = Number of target patients * treatment rate of HTS and keloids * average annual spending of available treatment options

In the U.S., according to *Formation of Hypertrophic Scars: Evolution and Susceptibility,* and *Estimate of Keloid Formation Incidence Based on Race in the U.S.,* the number of new

cases of HTS and keloids is 8.4 million in 2020 and is projected to increase to 10.1 million in 2030. Based on *A Prospective Study of Time to Healing and Hypertrophic Scarring in Paediatric Burns: Every Day Counts*, and *Formation of Hypertrophic Scars: Evolution and Susceptibility*, there are five categories of HTS patients and one type of keloids patients with proportions listed in the table below.

HTS and Keloids patients distribution	**Proportion**	**Treatment rate**
HTS — Burns	1%	50%
HTS — Cosmetic Procedures	7%	80%
HTS — Reconstructive Procedures	22%	80%
HTS — Skin Tumor Removal Procedures	0.4%	50%
HTS — Other surgery procedures	68%	50%
Keloids	2%	50%

Treatment rates are shown in the previous table, according to *Insights into Patient and Clinician Concerns About Scar Appearance: Semiquantitative Structured Surveys*. The average annual spending of available treatment options ranged between US$1,100 and US$2,500 in 2020, as referenced by *Medicare Unit Cost Increases Reported as of April 2020*.

China Market

In China, the addressable market size of HTS and keloids = Number of target patients * treatment rate of HTS and keloids * average annual spending of available treatment options

In China, according to *Formation of Hypertrophic Scars: Evolution and Susceptibility,* and *Keloid Incidence in Asian People and its Comorbidity with other Fibrosis-related Diseases: a Nationwide Population-based Study,* the number of new cases of HTS and keloids is 7.4 million in 2020 and is projected to increase to 10.6 million in 2030. Based on *Epidemiological Analysis of 9,779 Burn Patients in China: An Eight-year Retrospective Study at a Major Burn Center in Southwest China* and physician interviews, there are four categories of HTS patients and one type of keloids patients with proportions listed in the table below.

HTS and Keloids patients distribution	**Proportion**	**Treatment rate**
HTS — Burns	34%	100%
HTS — Cosmetic Procedures	2%	80%
HTS — Skin Tumor Removal Procedures	0.01%	80%
HTS — Other surgery procedures	63%	50%
Keloids	1%	50%

Treatment rates are shown in the previous table, according to *Insights into Patient and Clinician Concerns About Scar Appearance: Semiquantitative Structured Surveys*. Annual spending of treatment: The average annual spending of available treatment options ranged between US$350 and US$700 in 2020, according to physician interviews.

The HTS & keloids treatment market is driven by:

- **Increasing incidence:** Since the incidence of forming HTS is relatively high after a surgical procedure, a rising number of various surgical procedures will lead to the increasing incidence of HTS and keloids.

- **The availability of more therapeutic options:** Various therapeutic modalities have been described for keloid treatment. Nevertheless, no single effective therapeutic regimen has been hailed as the gold standard, mainly owing to the high recurrence rates of keloids and a dearth of extensive research evaluating available treatments. Recently, researchers have devised several promising anti-keloid therapies including anti-hypertensive pharmaceuticals, calcineurin inhibitors, electrical stimulation, mesenchymal stem cell therapy, microneedle physical contact and ribonucleic acid-based therapies. The emerging treatments will potentially drive the treatment market.

- **Clinical needs:** An increasing level of awareness regarding appearance in both women and men has also led to a higher demand for HTS reduction and keloid scarless treatments. Increasing awareness of post-op wound management, with patients becoming more concerned not only with the speed of recovery, but also cosmetic outcomes, is also leading to higher demand. In addition, as people accumulate financial resources, they spend proportionately more to achieve successful cosmetic outcomes.

There is no standard of treatment for HTS and keloids; the available treatment options are intralesional injection, cryotherapy, bleomycin, laser therapy and surgical excision.

Conventional and Standard Treatment Methods for HTS and Keloids (November 2021)

Indication	Treatments
HTS & Keloid	Intralesional injection Cryotherapy Bleomycin Laser therapy Surgical excision

Sources: The CIC Report; Lee et al. Minimal-Invasive Technologies for Treatment of HTS and Keloids: Corticosteroids. Textbook on Scar Management. 2020: 243-250; Gupta et al.. Standard guidelines of care: Keloids and hypertrophic scars. Indian J Dermatol Venereol Leprol. 2011;77(1):94-100.

RNAi therapeutics have attracted much attention for HTS and keloids treatment, with Sirnaomics leading the market.

Pipeline of RNA-based drugs in Hypertrophic scar & Keloids, worldwide, as of September 2021

Company	Pipeline products	Indication	Current phase	Start date	Competent authorities	Trial number
Sirnaomics	STP705	Hypertrophic scars, Keloids	Phase II	1/2017	FDA	NCT02956317
miRagen Therapeutics	Remlarsen	Keloids	Phase II	6/2018	FDA	NCT03601052
Lemonex	LEM-S401	Hypertrophic scars, Keloids	Phase I	2/2022(Estimated)	FDA	NCT04707131

Source: U.S. National Library of Medicine; FDA; the CIC Report

Primary Sclerosing Cholangitis (PSC)

Primary sclerosing cholangitis (PSC) is a long-term progressive fibrotic disease of the liver that advances very slowly. It is characterized by inflammation and scarring of the bile ducts that normally allow bile to drain from the gallbladder and with time leading to cirrhosis, repeated infections and eventually leading to liver failure. Patients with PSC bear a significant risk of cholangiocarcinoma and colorectal cancer. The prevalence of PSC in the U.S. was 45 thousand in 2020 and in China 194 thousand in 2020.

At present there are no effective medical treatment options for PSC. Ursodeoxycholic acid is used off-label to treat PSC as the current mainstay of medical treatment even though there is no evidence that it alters long-term outcomes. Over the past two decades many clinical trials of medical therapies for PSC have been conducted; however, none have demonstrated real improvements in hard clinical endpoints.

To date, no medical therapy for PSC has proven to have significant impact on clinical outcomes and most patients ultimately need liver transplantation. Because of the complications and co-morbidities, although rare, PSC represents a significant burden for patients as well as for specialized health services. Critical needs include lack of effective medical therapy and tools for early detection. Advances in understanding of PSC pathogenesis and biliary physiology over recent years has, however, led to a surge of clinical trials targeting various mechanistic compartments, including small molecule chemotherapy, and other novel therapeutics like antibodies and cell therapies, and currently raising hopes for imminent changes in patient management. The increasing number of clinical trials and rising research and development investment on the development of new drugs are projected to propel the PSC treatment market. Annual screening for PSC by hepatobiliary imaging and full ileocolonoscopy have been recommended by international guidelines. The emerging treatment and diagnosis pathways will boost PSC treatment market.

Further therapeutic areas

The scope for expansion of therapeutic treatment options using RNAi-based or mRNA-based therapeutics and vaccines is ever-widening. Further therapeutic areas suited for RNAi or mRNA therapies and vaccines include:

Cardiometabolic diseases

Cardiometabolic diseases (CMDs) are the leading cause of death globally. CMDs describe a spectrum of conditions beginning with insulin resistance, progressing to metabolic syndrome, pre-diabetes, and finally to more severe conditions including cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM). These conditions are grouped under the umbrella term "cardiometabolic disease" as they are related or share risk factors, such as increased body mass index (BMI) and obesity, dyslipidemia, and high blood pressure.

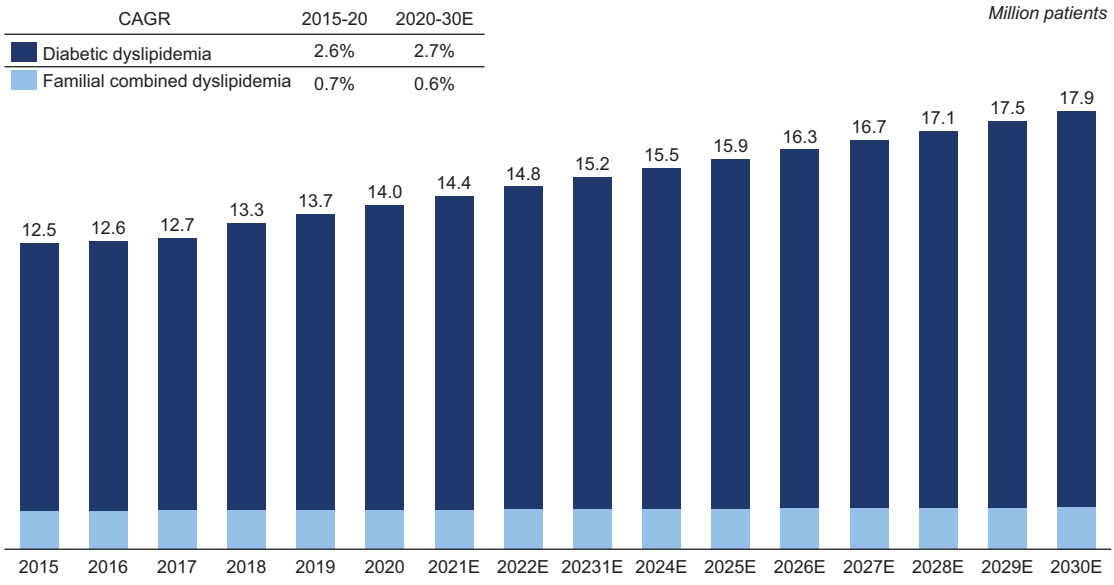
Dyslipidemia is defined as the presence of abnormal blood concentrations of one or more of the following: total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol and triglycerides. The classification of dyslipidemia defines the lipid phenotype as hypercholesterolemia, hypertriglyceridemia, or mixed hyperlipidemia (MHL). Dyslipidemias can be genetically determined (primary or familial dyslipidemias) or secondary to other conditions, such as diabetes mellitus, obesity or an unhealthy lifestyle. Dyslipidemia is a leading contributor to CVD and mortality globally. Dyslipidemias, particularly elevated plasma LDL-cholesterol levels, are major risk factors for cardiovascular disease, but some forms, such as hypertriglyceridemia, are associated with severe diseases in other organ systems, including non-alcoholic fatty liver disease and acute pancreatitis.

- **Diabetic dyslipidemia.** Dyslipidemia is a very common metabolic abnormality associated with diabetes. Diabetic dyslipidemia is a cluster of lipoprotein abnormalities characterized by increased triglyceride level, decreased high-density lipoprotein-cholesterol levels and increase in small dense LDL particles. Insulin resistance is believed to be the main trigger for diabetic dyslipidemia. In 2020, patients diagnosed with diabetic dyslipidemia represented a large patient population, 12.4 million in the U.S. and 89.6 million in China. Lifestyle and pharmacological interventions are the most important treatment strategies for diabetic dyslipidemia. Diabetic patients are prescribed generic statins as first-line therapy to manage their dyslipidemia. Utilization of second-line therapies has largely been limited to statin-intolerant patients due to the limited high-cost second-line therapies, despite positive real-world data.

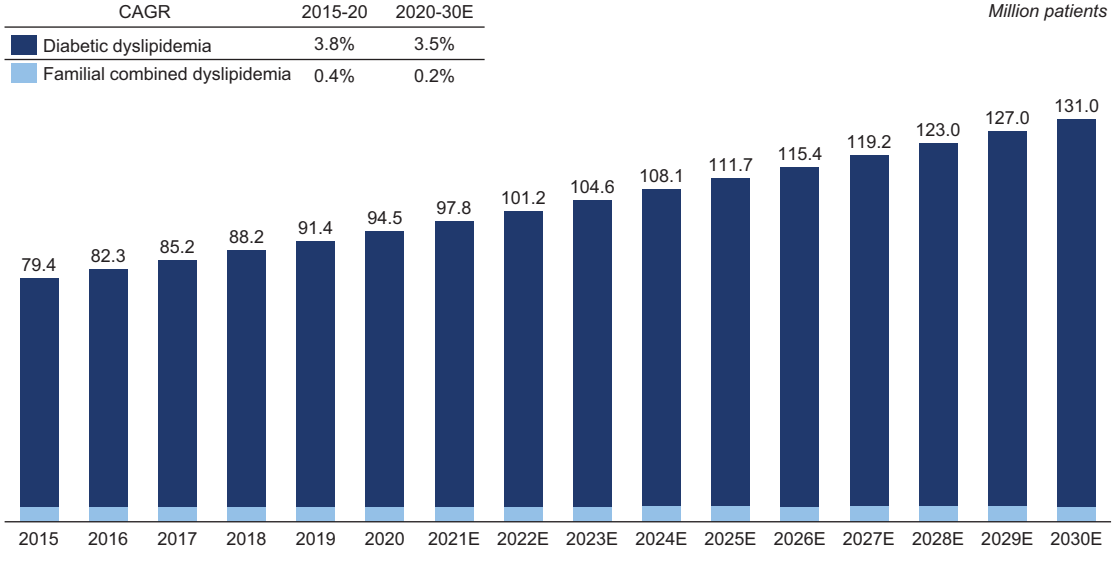
- **Familial combined dyslipidemia.** Familial combined hyperlipidemia (FCH) is a common metabolic disorder characterized by increase in cholesterolemia and/or triglyceridemia in at least two members of the same family, intra-individual or intrafamilial variability of the lipid phenotype and increased risk of premature

coronary heart disease. In 2020, patients diagnosed with FCH comprised around 6.6 million in the U.S. and China. There is a huge demand on additional non-statin therapies, such as PCSK9 inhibitors, for patients diagnosed with FCH. Recently approved U.S. FDA treatments, such as omega-3 fatty acid-based drugs, and currently underway clinical trials will continue to drive the second-line treatments.

Prevalence of diabetic dyslipidemia and familial combined dyslipidemia in the U.S., 2015—2030E



Prevalence of diabetic dyslipidemia and familial combined dyslipidemia in China, 2015—2030E

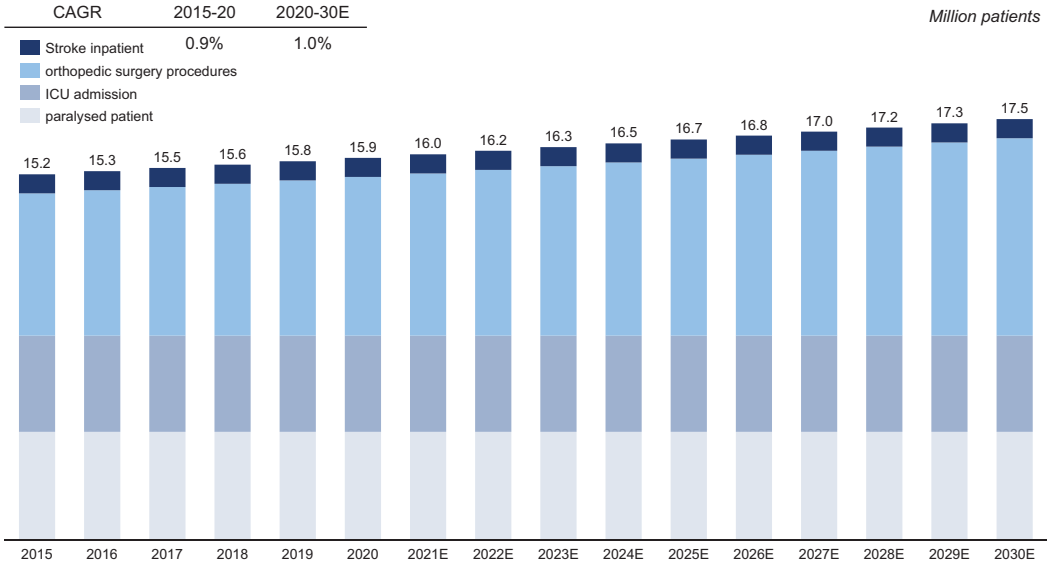


Source: the CIC report

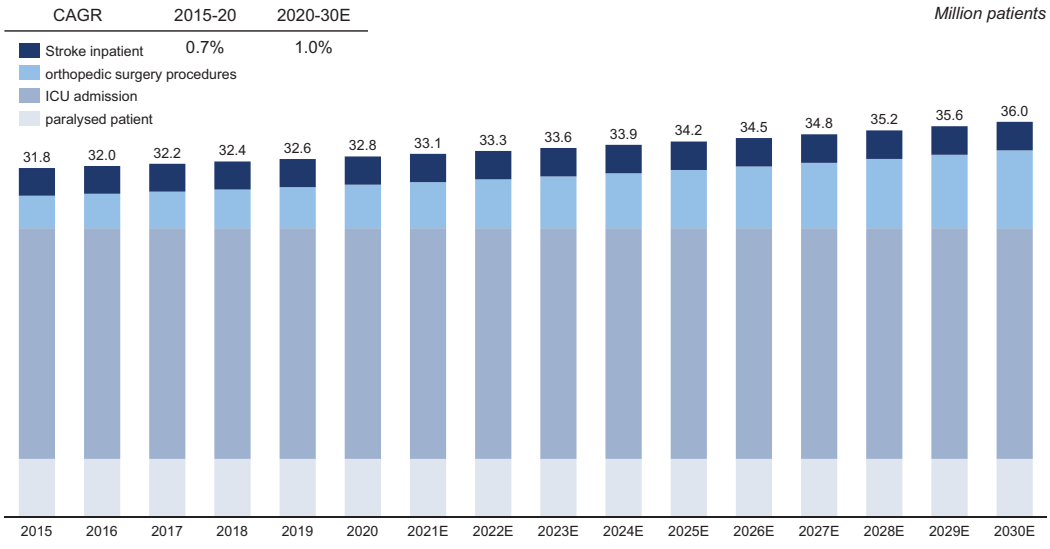
Anticoagulant therapy

There are a variety of patients in need of anticoagulant therapies, including patients with deep venous thrombosis (DVT) and pulmonary embolism (PE). Anticoagulant therapies can prevent DVT and PE in patients who have been previously treated and who have undergone surgery and also reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (AF). The target patient population for anticoagulant therapy is a very large group including stroke patients, orthopedic surgery patients, ICU admissions and paralyzed patients, and is forecasted to reach approximately 53.5 million patients in China and the U.S. in 2030.

Anticoagulant therapy target patient population in the U.S., 2015-2030E



Anticoagulant therapy target patient population in China, 2015-2030E



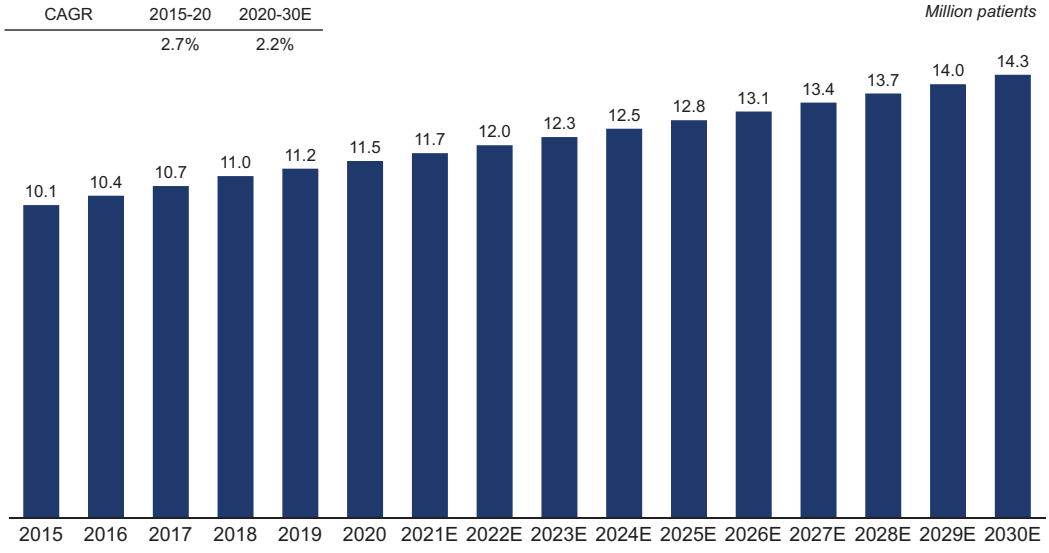
Source: the CIC report

Complement-mediated disease

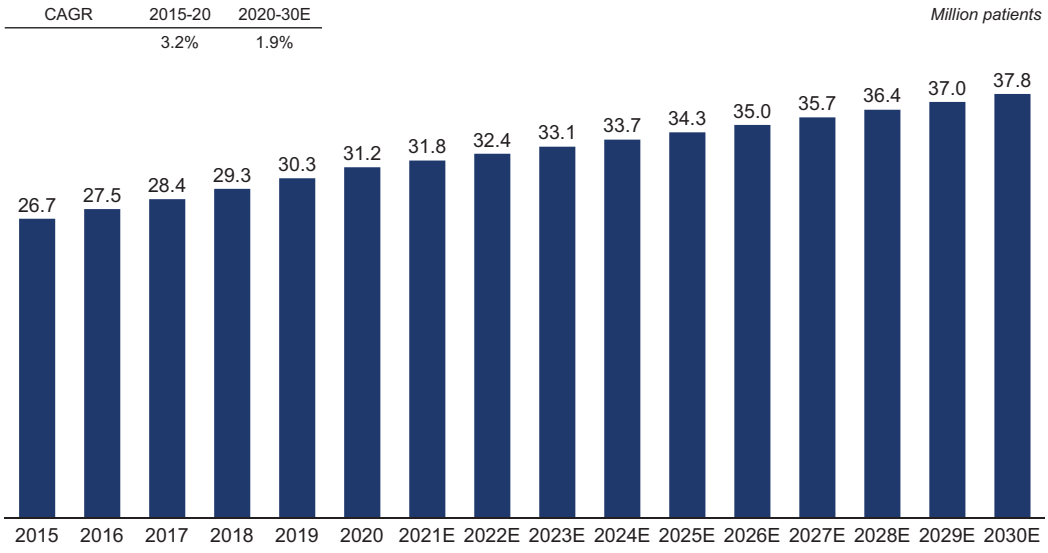
The complement system is so called because it complements (or enhances) the body's ability to fight disease. It is like an amplifier for the immune system, helping to remove any foreign microorganisms or damaged cells. Activation of the complement system is, however, also involved in the pathogenesis of a wide range of diseases such as cancer, rheumatic diseases, Alzheimer's disease, autoimmune diseases, age-related macular degeneration (AMD) and schizophrenia. Many complement-mediated diseases have a devastating impact on people's lives and can even be fatal; however, there are limited treatment options for this complex set of diseases.

- **Age-related macular degeneration (AMD).** AMD is a type of complement-mediated disease caused by degeneration of retinal pigment epithelial cells and decreased macular function, and is the primary cause of vision loss in the elderly. In addition to a strong correlation with age, it may also result from multiple factors of genes and environment. There are two types of AMD: Dry AMD, which usually progresses very slowly over several years, while wet AMD is a less common type of AMD that usually causes faster vision loss. There are treatment options available for wet AMD, such as regular anti-VEGF medicines administrated by eye injections and a light treatment called photodynamic therapy (PDT), but no treatment for the late-stage Dry AMD. Taking into consideration the rapidly aging population throughout the world, the morbidity resulting from AMD becomes increasingly significant and dry AMD remains a large clinical need. There are now approximately 11.5 million and 31.2 million individuals with AMD in United States and China, and are projected to be 14.3 million and 37.8 million by 2030 in United States and China.

Prevalence of AMD in the U.S., 2015-2030E



Prevalence of AMD in China, 2015-2030E



Source: the CIC report

Viral diseases

Viral diseases are one of the major threats to human health. Common human viral infections include influenza, AIDS, respiratory virus infection, hepatitis, herpes, chickenpox, and cervical cancer. These diseases caused by viral infection have different degrees of epidemic trend in the world. Although some diseases caused by viral infection are mild and can be self-limited to cure in a short period of time, serious infections can lead to lifelong diseases and may even affect other systems of the body, causing opportunistic infection and tumors. Unfortunately, some common viral diseases still lack effective vaccines or antiviral drugs.

- **COVID-19.** COVID-19 is a highly contagious respiratory disease caused by the SARS-CoV-2 virus. There are hundreds of coronaviruses, but only seven are known to affect people. Four human coronaviruses only cause mild cold- or flu-like symptoms. Three other coronaviruses pose more serious risks. Coronaviruses that infect animals can evolve to infect and cause illness in humans and thus become a new human coronavirus. Three recent examples of this are SARS-CoV-2, SARS-CoV, and MERS-CoV. Respiratory tract droplets and close contact transmission are the main route of transmission of novel coronaviruses, although contact with virus contaminated items may also cause infection. There are treatment options available for COVID-19, such as the antiviral drug Remdesivir, anticoagulation drugs, dexamethasone, which are able to speed up recovery time. However, safe and effective vaccines are critical to ending the COVID-19 pandemic. The number of persons in the PRC vaccinated against COVID-19 is estimated to increase from 1,150 million in 2021 to 1,300 million in 2025, and will remain stable

at approximately 1.4 billion per year from 2026 to 2030, creating a market that is worth hundreds of billions every year from 2021 to 2030. With a massive population requiring vaccination, demand for COVID-19 vaccines is expected to far outstrip supply in the future. In addition, due to the limited supply capacity of and uneven access to COVID-19 vaccines on the global market, there is an increasing global shortage, presenting a significant opportunity to PRC vaccine manufacturers.

- **Hepatitis B virus (HBV).** Hepatitis B is a viral infection that attacks the liver and can cause both acute and chronic disease. The virus is commonly transmitted from mother to child during birth and delivery, as well as through contact with blood or other body fluids. HBV is a rapid evolving DNA virus and has four regular subtypes, which are distinguishable by the antigenicity of HBsAg. Chronic hepatitis B infection can be treated with medicines, including oral antiviral agents, such as tenofovir and entecavir. Treatment can suppress hepatitis B virus, slow the progression of cirrhosis, reduce incidence of liver cancer and improve long term survival. Yet, Hepatitis B cannot be completely cured and most patients with HBV require long-term medication and treatment. There are currently around 31.1 million individuals with HBV in China, and 0.8 million individuals with HBV in the U.S. Huge numbers of patients with HBV and their clinical need make this disease a serious public health issue. Furthermore, the current treatment is extremely expensive, which further boosts the HBV treatment market.

- **Human papillomavirus (HPV).** Human papillomaviruses (HPV) are common DNA viruses. HPVs are a large and diverse group of viruses with 100+ characterized types. HPVs can be grouped to high-risk and low-risk HPV types. Types 16 and HPV 18 are commonly associated with development of cancer, together accounting for a majority of invasive cervical cancers. There are medical and surgical treatment options available for HPV infection, such as imiquimod, which enhances the immune system's ability to fight HPV, and cryotherapy with liquid nitrogen, but these options do not provide a complete cure for the virus, so they may reappear in the same place or other places. Even though the HPV vaccine is safe and effective in preventing cervical cancer, genital warts, and other cancers that affect both women and men, vaccination rates in both the U.S. and China remain surprisingly low among adolescents and young adults. HPV infection has needs and remains a key area of focus for pharmaceutical development. In 2020, the number of HPV infected individuals in the U.S. and China were 39.6 million and 257.8 million, respectively.

- **Influenza,** also called flu or grippe, is an acute viral infection of the upper or lower respiratory tract that is marked by fever, chills, and a generalized feeling of weakness and pain in the muscles, together with varying degrees of soreness in the head and abdomen. There are four types of influenza viruses: A, B, C and D. The most common types of human influenza A and B viruses cause seasonal epidemics of disease almost every winter. Influenza A viruses are the only influenza viruses

known to cause flu pandemics, i.e., global epidemics of flu disease. A pandemic can occur when a new and very different influenza A virus emerges that both infects people and has the ability to spread efficiently between people. Influenza B viruses generally change more slowly in terms of their genetic and antigenic properties than influenza A viruses. Antiviral drug are utilized in influenza treatment. These drugs can include oseltamivir (Tamiflu), zanamivir (Relenza), peramivir (Rapivab) or baloxavir (Xofluza), and may shorten the illness by a day or so and help prevent serious complications. Influenza has resulted in between nine million and 45 million illnesses each year since 2010 in the U.S., and approximately 81.6 out of 100,000 people in China were infected with the influenza virus. Currently, the overall influenza vaccination rate is extremely low, creating a massive need and tremendous potential for the influenza vaccine market.

Submental fat treatment

Submental fat is defined as a fold of fatty flesh beneath the chin, which may make the patient appear overweight or older. As a result, these patients seek treatment to address their displeasing submental fat. According to *Addressing the Double Chin: Trends in Submental Countouring*, published by *Journal of Dermatology & Cosmetology*, a survey showed that 77% of patients presenting to their dermatologist or plastic surgeon were concerned about submental fat, and 61% of patients desired it reduced. Treatments of submental fat have been limited to invasive, surgical procedures such as liposuction or fat excision and even complete neck reconstruction. Because surgery is associated with the risks of anesthesia, infection, bleeding, bruising, and scarring, as well as the possibility of poor outcome, discomfort, and the prolonged "downtime" for the patient, there is a large demand for nonsurgical alternatives. Kybella and CoolSculpting are the two FDA-approved nonsurgical treatment for submental fat. The fat reduction is processed through natural metabolic mechanisms by Kybella, while CoolSculpting uses cooling to damage the fat cells by crystallization without affecting the surrounding tissue. The drug sales possess great potential for the submental fat market. For instance, the sales of Kybella increased from US$3 million in 2015 to US$31 million in 2019 with a CAGR of 76.0%. However, these two treatments have limitations such as risk of tissue necrosis, and risk of allergic reaction for Kybella, narrow addressable patients and slower effects for CoolSculpting. Considering the limitations and huge number of targeted people, new innovative drugs with better clinical results have huge potential for the submental fat market.