

## **Lico.Health**

Prevention and Treatment of Alcoholic Liver Disease Based on Engineered Cells

# **Entrepreneurship**

**CPU\_CHINA**

2020.10

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# Products & Services

Lico.Health has been designed as a genetic-engineered, probiotic-involved prescription aimed at preventing alcohol liver disease (ALD) at early stage.

You may view the following topics in this section:

- Pain Points
- Current Treatment
- About Lico.Health
- Differentiation

## Pain Points

Alcoholic liver disease (ALD), induced by long-term heavy alcohol consumption, encompasses a progressive clinical–histological spectrum of liver injuries from simple fatty liver to alcoholic hepatitis, hepatic fibrosis and cirrhosis.

- ALD has become one of the main causes and most popular chronic liver diseases worldwide
  - The Asia-Pacific region has more than half of the world's population. According to WHO's 2015 Global Burden of Disease report, 62.6% of global liver disease deaths came from the Asia-Pacific region (1,312,480/2,095,207). (Shiv K Sarin et al., 2019)
  - At the beginning of this century, the number was 26.98% in Northeast China, and in some areas, as high as 42.76%. In South, Central and West China, the proportion of drinkers ranged from 30.9% to 43.4%. The prevalence of ALD in China as 0.5–8.55% people in their 40s showed the highest number of up to over 10%. (Youming Li et al., 2018)
- Early prevention of ALD plays a particularly important role.
  - There is no specific clinical diagnostic method for ALD, Symptoms and signs are non-specific and variable, from asymptomatic to possible complaints include right upper abdominal pain, inappetence, fatigue, weight loss and jaundice. (Youming Li et al., 2018)
  - Most patients are diagnosed at advanced stages and data on the prevalence and profile of patients with early disease are limited. AH presents with rapid onset or worsening of jaundice, and in severe cases may transition to acute on chronic liver failure when the risk for mortality, depending on the number of extra-hepatic organ failures, may be as high as 20–50% at 1 month. (Seitz et al., 2018) Alcohol is the leading risk factor for premature mortality and disability among those aged 15 to 49 years, accounting for 10 percent of all deaths in this age group.
- It is difficult to abstinance from alcohol completely.
  - The cornerstone measurement is to ensure a thorough, immediate abstinance from alcohol, which can help improve prognosis, histologically ameliorate liver injury, reduce portal pressure, retard



## Epidemiology

\*Figure 1 Liver-related deaths as proportion of overall deaths in the Asia-Pacific region

No specific symptoms at early stage

High rate of severe illness and mortality

Importance of

the progression of fibrosis and improve survival rates of ALD patients at all stages. ( O'Shea RS et al.,2010)

- With the continuous improvement of alcoholic liver disease patients' awareness of their own diseases, they have also become more and more aware of the importance of abstinence, but patients who can cause the disease have their own long-term the habit of alcoholism is often difficult to quit. In fact, many people cannot quit drinking directly due to specific social pressures. Other patients, such as those with psychological or mental problems, determine that they cannot quit drinking directly due to their physical characteristics. (Becker 2017)
- Comparing to alcohol-decomposing drug, we are in want of long-term contribution to the prevention of ALD.
- In addition, patients often have excessively optimistic trust in alcohol-decomposing drugs, which leads to retaliatory drinking. (Becker 2017)
- According to statistics, about 12 million patients are hospitalized due to excessive drinking every year. During the hospitalization period, 80% of patients may suffer from alcohol withdrawal syndrome (AWS) because they stop drinking. (Farooq and Bataller 2016)

Why not alcohol-decomposing drugs

## Current Treatment

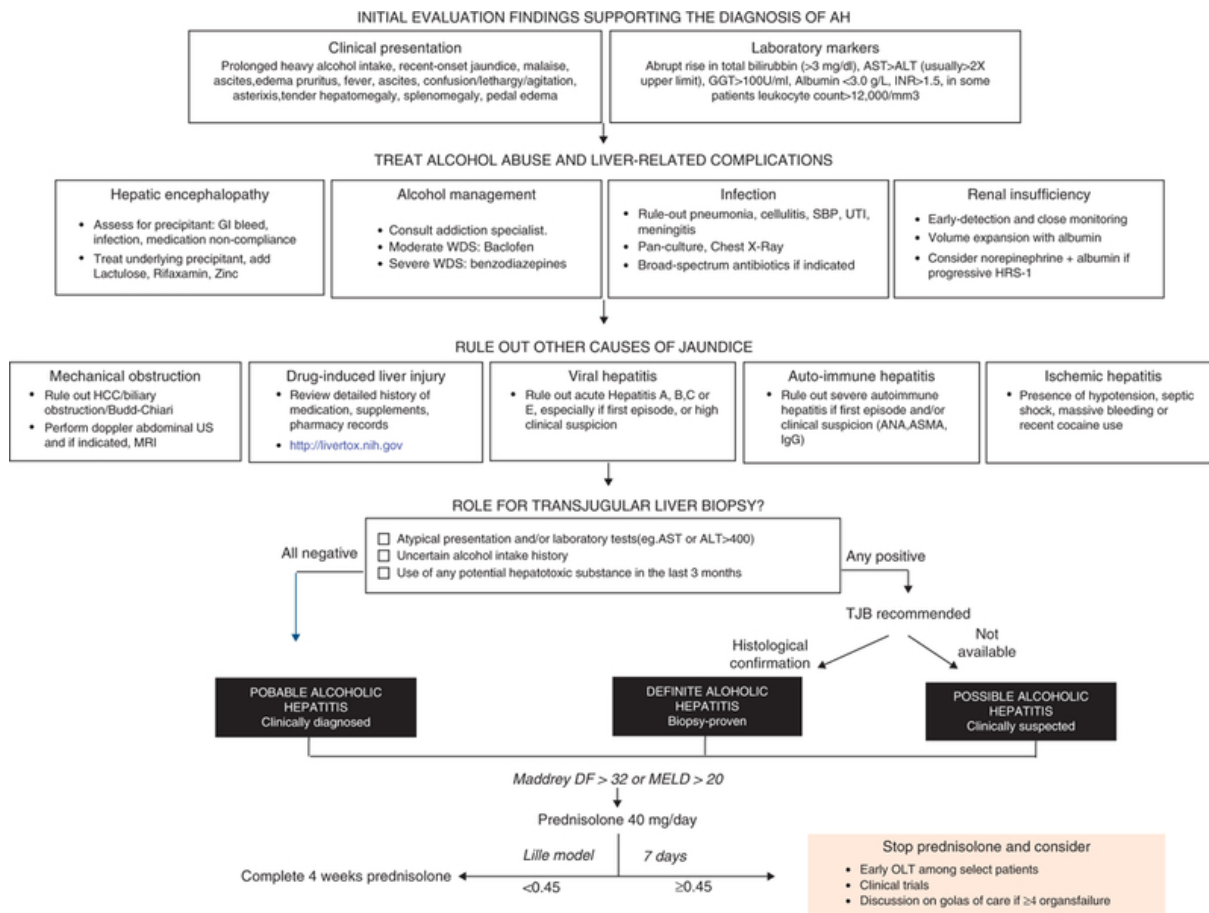
Patients with ALD are suffering from two different disorders, namely AUD and liver disease. Hence, the treatment should involve integrated management targeting both the disorders.

### ● Alcohol-use disorder(AUD)

Therapy	Introduction	Advantage	Disadvantage
Pharmacological	disulfiram, acamprosate, gabapentin, naltrexone, topiramate, sertraline, and baclofen(Leggio & Lee, 2017)		1) only baclofen has been found to be safe (Singal, Bataller, Ahn, Kamath, & Shah, 2018) 2) some larger multisite trials found no benefit over placebo 3) individual differences in the client need to be considered
Non-pharmacological	<b>behavioral interventions</b> such as motivational enhancement therapy, cognitive behavioral therapy, motivational interviewing, supportive therapy, and psychoeducation	motivational interviewing, the most commonly used intervention, is a technique that aims to be both non-judgmental and non-confrontational	1) psychologic interventions can be difficult in patients with hepatic encephalopathy, cognitive impairment, or poor performance status (2) patients with end-stage liver disease have frequent hospitalizations that preclude attendance at psychosocial interventions(Singal et al., 2018)
	<b>self-help programs</b> such as <b>Alcoholics Anonymous (AA)</b>	(1) contingency management has been shown to be effective in clients with mild alcohol use disorder, or in heavy drinkers who do not have a diagnosis of alcohol use disorder (2) improves compliance rates when used in conjunction with other treatments for alcohol and other drugs(Campbell, Lawrence, & Perry, 2018)	

Transcranial magnetic stimulation (TMS)	uses electromagnetic induction to generate targeted electrical fields on the cortical surface	a relatively novel and non-invasive technique and is currently FDA approved for clients that are resistant to antidepressant medications	the success of DBS is still debatable with some clients still experiencing short periods of relapse due to external stressful events (Campbell et al., 2018)
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- Alcohol withdrawal
  - As alcohol dependency can make it more difficult to quit drinking alcohol, it is necessary to gradually reduce alcohol intake. AWS is a common condition affecting alcohol-dependent patients who abruptly discontinue or markedly decrease alcohol consumption. Withdrawal from alcohol can be life-threatening.
  - Benzodiazepines are the most commonly used drugs to treat AWS. Long-acting benzodiazepines (e.g., diazepam and chlorthalidone) predominantly protect against seizures and delirium; short and intermediate-acting benzodiazepines (e.g., lorazepam and oxazepam) are safer for patients with poor liver function. Patients with AWS and concomitant hepatic encephalopathy should be treated for both the conditions.
- liver disease



\* Figure 2 Approach towards the diagnosis and management of alcoholic hepatitis. ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, International Normalized Ratio. (Shiv K Sarin et al., 2019)

- Liver transplantation
  - This procedure remains the standard of care for patients with end-stage liver disease. They also must abstain from alcohol for 6 months before being considered for liver transplantation. Data show that fewer than 20 percent of patients with histories of

alcohol use as the primary cause of end-stage liver disease receive liver transplants.(Dunn & Shah, 2016) In a pooled data from 50 studies on LT for alcoholic cirrhosis, annual incidence of recidivism was 5.7% and 2.5% for any alcohol use and for harmful use, respectively.(Singal et al., 2018) In conclusion, Despite the known hepatotoxic effect of alcohol use, the field lacks availability of effective safe pharmacotherapies for management of ALD patients.

- Therapies of uncertain or no benefit
  - As for therapies such as Metadoxine, Propylthiouracil, S-adenosylmethionine and Colchicine, in order to confirm the results of the subgroup analysis, more high-quality trials are needed in patients with alcoholic liver disease.

## About Lico.Health

- an engineered *E. coli* system that senses ethanol concentration signals and quorum sensing signals separately
  - there have been theories that the occurrence and development of alcoholic liver disease are closely related to the intestinal flora. The latest research shows that *Enterococcus faecalis* (*E. faecalis*) has a significant positive correlation with the mortality and poor prognosis of alcoholic liver disease. Based on this background, inhibiting local inflammation of the liver and controlling the number of *Enterococcus faecalis* are two types of treatment and prevention measures that can be tried and promising for alcoholic liver disease.
- Since it relies on ethanol to activate the promoter, it must be taken before drinking alcohol and functions as follow:
  - After receiving the ethanol signal, secrete anti-inflammatory factors that can be absorbed through the epithelial membrane of the small intestine to inhibit local liver inflammation;
  - After receiving the quorum sensing signal, secrete bactericidal peptides targeting *Enterococcus faecalis* and down-regulate the number of *Enterococcus faecalis* in the intestine;
  - After receiving the quorum sensing signal, through bacterial conjugation, the shuttle plasmid carrying the CRISPR-Cas9 system/microRNA interference system is transferred into *Enterococcus faecalis*, which interferes with the expression of cytolysin of *Enterococcus faecalis* population/interferes with the key genes for survival of *Enterococcus faecalis* , Down-regulate the number of *Enterococcus faecalis* in the intestine at an appropriate rate.
- It will be supervised by relevant departments of China, the United States, the European Union, and Japan as a gene therapy product.
  - Since 2003, there have been 10 gene therapy products on the market worldwide. As of December 2018, there have been 2,930 gene therapy product clinical trials approved globally. (Zhaojun Ma et al.,2019)
  - China has not issued a law specifically for gene therapy products. Biological products and chemical drugs are uniformly bound by the "Drug Administration Law of the People's Republic of China" and

### Operating Mechanism:

- ①Inhibiting local inflammation of the liver
- ②Controlling the number of *Enterococcus faecalis*

### Taken before drinking

### Legal Supervision: Gene Therapy (GT)

"Drug Registration Management Measures" and other laws and regulations.

- In view of the characteristics of GT product clinical trials, the U.S. Department of Health and Human Services adopted a regulatory system different from general biological products before August 2018. Led by the United States, many countries including Germany, Japan, Britain, and France have formulated administrative regulations and industry ethics codes to regulate gene therapy experiments. (Weiwei Chen et al.,2018)
- At the same time, we will pay close attention to the provisions of the laws of various countries on the patent and use of genetic engineering products
- Lico.Health is going to apply for National Science and Technology Achievement Transformation Guidance Fund in China for its application of Synthetic Biology.
- We will also strive to meet the following legal requirements to fight for international market: Regenerative Medicine Advanced Therapy(RMAT) implemented by FDA, Article 9 of the EU Directive 98/44/EG and Act on The Safety of renewable Medicine in Japan.
- 
- Lico.Health is planned to be made into probiotic capsule and beverage at this stage. Therefore, we would pay close attention to "Probiotics Health Food Application and Review Regulations (Draft for Comment)" published in 2019 by National Health Commission of China.
- We will develop more dosages, even more flavor, to meet various demand. In addition to prevention, our R&D blueprint is going to cover screening, diagnosing, curing and so on.

Legal Requirements of  
Patent and Genetic-  
engineered Products  
Worldwide

Probiotic Product

In the future

## Differentiation

- Our survey results show that it is preferable to develop an food supplement at early stage of prevention than to launch a drug, since the former can make it to soften consumer resentment. Moreover, the safety of food supplements was appraised by comparing the Adverse Effects rate(ADR) with drugs.
- Comparing to conventional food therapy such as honey and yogurt, our directional transformation could enable Lico.Health to target at specific lesions and to give full play to prevent ALD.
- While most of our competitor are Chinese medicine preparation consist of plant extract, Lico.Health, as a probiotic product, can be outstanding in competing for middle and high-end markets.
- The more sophisticated production process of this cutting-edge technology and corresponding stricter legal supervision, the higher level of quality assurance and controllability for Lico.Health.

Food supplement: safety

Genetic-engineered  
product: effectiveness

Probiotic product:  
economy

Quality assurance

# The Market

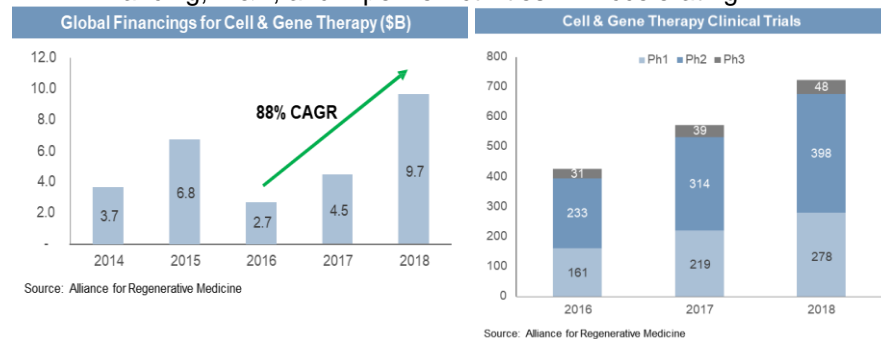
Lico.Health is aimed at people who may be in the early and middle stages of alcoholic liver injury, have certain drinking habits and cannot accept the goal of complete abstinence.

However, to some extent, they are upset with the possible alcohol-related physical harm and even in search of low-risk drinking patterns. It is Lico.Health's duty to ease their physical and mental uncomfortableness by comprehensively improving their health problems caused by alcohol Liver damage without severe alcohol withdrawal syndrome.

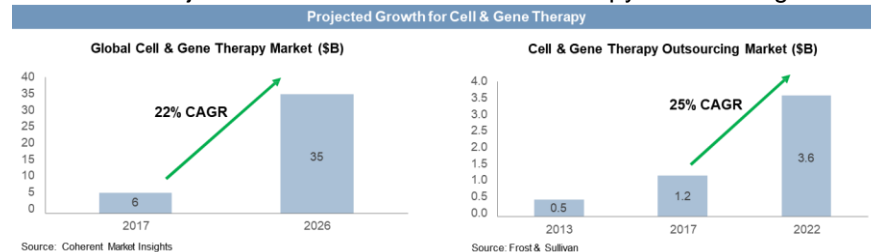
## Market Segment

### ● Market of Cell & Gene Therapy

- Financing, M&A, and Pipeline Activities All Accelerating



- 25% Projected CAGR for Cell & Gene Therapy Outsourcing



### ● Market of Food Supplements

- The scale of China's health products market continues to expand, but the industry structure is relatively fragmented.
- Affected by the tightening of regulatory policies and the "big health strategy", the industry ushered in a new round of transformation and upgrading
- In 2019, China's nutritional and health food industry has experienced a year of drastic adjustments. A number of important regulations have been implemented, including the E-commerce Law, the Implementation Regulations of the Food Safety Law, the new regulations on cross-border e-commerce retail imports, and the advertising management measures. The industry has been regulated; "Quanjian Incident", "Hundred Days Action", and pharmacy channel reform regulations have greatly affected the production and operation of enterprises. Many enterprises have fallen into a downturn, and the overall growth rate of the industry has slowed down at the same time. More and more overseas brands rely on international exchange platforms such as HNC

### Cell & Gene Therapy

\*source: J.P. Morgan

### Main competitor's market



Health Expo to continuously increase investment in the Chinese market, and rely on new models such as cross-border e-commerce retail imports, social e-commerce, and live broadcasting.

- From the perspective of the proportion of products in the health care product industry, vitamins and dietary supplements account for 91% of China's health care products market.

#### ● Market of Probiotic Products

- In recent years, the research and understanding of the health function of probiotics has continued to deepen, the consumption of probiotics has surged, and the industrial development has ushered in a window period. Survey data shows that my country's probiotics industry has a growth rate of more than 20% for three consecutive years, and it has a huge market space. It is estimated that the output value of the global probiotic industry will exceed US\$77 billion in 2025, and the Chinese market will account for more than 25%.
- As one of the fastest growing segments, the probiotic market has become a must-see for my country's nutritious food and health industries. As of 2019, the global probiotic supplement industry has reached 6.10 billion U.S. dollars, and the Chinese probiotic supplement industry has reached 4.24 billion yuan, a year-on-year increase of 18%. In the first quarter of 2020, the sales growth rate of my country's probiotics industry reached more than 20%. The industry's "rising against the trend" during a special period showed its market value related to health.

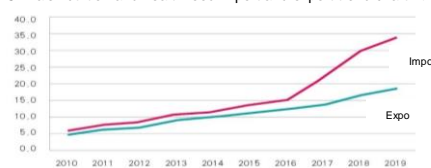
Probiotic Products

#### ● Market of medical international trade

- In 2019, despite the continued downturn of the world economy, increased international trade tensions, rising trade protectionism and other unfavorable factors, the international trade of China's nutritional and health food products still maintained a good momentum of development, with both imports and exports booming. According to statistics from the Medical Insurance Chamber of Commerce, in 2019, the total import and export volume reached 5.28 billion U.S. dollars, an increase of 12.8% year-on-year, and exports have developed steadily to 1.88 billion U.S. dollars, an increase of 12.7% year-on-year; after four years of rapid development, the import growth rate has been somewhat The growth rate was 12.8%, the import value reached 3.40 billion U.S. dollars, and the trade deficit further expanded to 1.52 billion U.S. dollars.

Medical (online)  
international trade

China's nutrition and health food import and export trend chart (Billion dollar)



Source: China Medical Insurance Chamber of Commerce

- In the export market, the United States, Hong Kong, Japan, Myanmar and Thailand are the main export regions of my country's nutritional and health food products. The export value is respectively: 300 million US dollars, 290 million US dollars, 110 million US dollars, 86 million US dollars and 82 million US dollars. The concentration ratio of the five major markets (CR5) is 46.2%. The United States is the world's largest dietary supplement market. In 2018, the market size reached 46 billion U.S. dollars. In 2019, the export value was 300 million U.S. dollars, accounting for 15.9%

of the total export value. The competitive advantage of export prices has declined, and exports to the United States have dropped by 11.7% year-on-year; Hong Kong, China, as an important global trade transit point, is also a major export destination for nutritional and health food products. In 2019, exports were US\$290 million, an increase of 71.8% year-on-year.

- On November 30, 2018, six ministries and commissions including the Ministry of Commerce issued the "Notice on Improving the Supervision and Administration of Cross-border E-commerce Retail Imports". The nutrition and healthcare industry, which is highly dependent on cross-border e-commerce retail imports, has taken a reassurance.

## Why now

- Market of Cell & Gene Therapy
  - The amount of global financing for cell & gene therapy more than doubled y/y in 2018
  - Coupled with the FDA's Regenerative Medicine Advanced Therapy designation (enacted in Dec 2016) and new guidelines to accelerate the approval of cell & gene therapies, this led to a 27% increase in the number of clinical trials in 2018
  - Large biopharma companies are increasingly seeking exposure to this new therapeutic class, with a series of acquisitions starting in 2017
- Market of Food Supplements
  - Affected by the tightening of regulatory policies and the "big health strategy", the industry has ushered in a new round of transformation and upgrading
  - In the long run, from the "Opinions on the Implementation of the Healthy China Action" issued by the State Council in 2019, "prevention" was mentioned 64 times, which clarified the country's strategy to improve people's health through disease prevention and "preventive treatment". In the long run, as an important category of "preventive treatment", health care products still have huge room for growth.
- Market of Probiotic Products
  - In January 2020, the "New Coronavirus Pneumonia Diagnosis and Treatment Plan (Trial Version 4)" issued by the National Health Commission and the State Administration of Traditional Chinese Medicine pointed out for the first time that "intestinal microecological regulators can be used to maintain intestinal microbiota. Ecological balance to prevent secondary bacterial infections." Dr. Lanjuan Li also proposed the importance of microecological therapy
  - In 2020, the outbreak of the new crown pneumonia epidemic has accelerated consumers' awareness and attention to immune nutritional products. Among them, probiotic products have become the "new favorite" of people pursuing health because of their effects on improving the gastrointestinal tract and enhancing immunity.
- Market of medical international e-commerce
  - Online channels started late, but grew the fastest. In recent years, with the popularization of the mobile Internet, online channels have captured a new round of traffic dividends and have well adapted to the long-tail needs of health care products consumers. In 2016, the

COVID-19 brings opportunities for online sales

online sales share of health products in my country exceeded the share of pharmacies for the first time, becoming the second largest health product sales channel after direct sales, and the compound growth rate in the past five years was as high as 31.2%.

- It is estimated that by 2020, China's cross-border consumer users will exceed 200 million. Online cross-border consumption has gradually become a daily life. Platform development is booming. Among them, Tmall Global has been ranked first for four consecutive years and its share continues to increase. Many consumers also choose to buy health products on Tmall Global.

# Competitive Analysis

## Overview

Drug	Indication(Function Indication)	Price	Treatment Mechanism
<b>Yishanfu (polyene phosphatidylcholine capsules)</b>	Helps to improve toxic liver damage (such as liver damage caused by drugs, poisons, chemicals and alcohol, etc.), loss of appetite, pressure in the right upper abdomen in patients with fatty liver and hepatitis.	228mg*24 capsules/65 RMB	This product is extracted from plants and has liver protection in experimental models of acute liver injury induced by ethanol, alicyclic alcohol, carbon tetrachloride, paracetamol and amino nought. In chronic models (ethanol, thioacetamide, organic solvents), the effect of inhibiting steatosis and fibrosis has also been observed. Studies have shown that this product can accelerate membrane regeneration and stabilization, inhibit lipid peroxidation, and inhibit collagen synthesis. There is no special research on human pharmacodynamics.
<b>KuiHua liver protection tablets</b>	Soothing the liver, invigorating the spleen and eliminating food. It has the effect of reducing transaminase. Used for chronic hepatitis and early liver cirrhosis.	350mg*100 tablets/45 RMB	This product has a protective effect on acute and chronic liver injury in animals caused by chemical poisons such as CCl <sub>4</sub> , thioacetamide, D-galactosamine, and paracetamol. It can reduce liver cell swelling, ballooning and necrosis, prevent fatty degeneration, and anti-fiber. It also significantly reduce the activity of serum ALT (Schisandrin B is the main enzyme-lowering component).
<b>Lecithin tablets</b>	For the adjuvant treatment of fatty liver, atherosclerosis and other diseases.	100mg*24 tablets/65 RMB	This product participates in body fat metabolism, lowers cholesterol, and excites cholinergic neurons. Phosphatidylcholine is the raw material for the synthesis of lipoproteins. Lipoproteins are the working form of fat, which can transport fat outside the liver, participate in the body's fat metabolism, and have an effect on the prevention and treatment of fatty liver. Phosphatidylcholine can also lower triacylglycerol, increase high-density lipoprotein and reduce low-density lipoprotein, and have an effect on the prevention and treatment of atherosclerosis.
<b>Ligaron (Silymarin Capsules)</b>	Toxic liver damage; supportive treatment of chronic hepatitis and cirrhosis.	140mg*10 capsules/33 RMB	This product is used for the treatment of liver disease. Pharmacological effects: It has been confirmed that in various pathological models of toxic liver damage, silymarin has an anti-toxic effect on the following substances: muscarin, $\alpha$ -ammanitin (a toxic substance found in Amanita phalloides), tetrachloride Carbon, galactosamine, thioacetamide and liver virus FV3.

In this table, there are similar drugs that currently occupy a large market share. Among them, PPC(polyene phosphatidylcholine capsules) produced by Sanofi is the largest competitor, so it is also the main object of subsequent analysis and comparison.

As for food supplements, there are 576 products currently approved as "Auxiliary protection for chemical liver injury" by National Medical Products Administration (NMPA), and most of them are Chinese medicine extracts with animal and plant extracts as the main ingredient.

## SWOT analysis

- Brief introduction of PPC
  - Polyen phosphatidylcholine (PPC) is a drug that protects liver cell membranes and protects the liver from inflammation. PPC is refined by extracting phospholipids from soybeans. Its main active ingredient is 1,2-diacyl phospholipid choline (DLPC), which accounts for about 52%. As a substance to repair damaged liver cell membrane/organelle membrane and restore membrane function, DLPC can provide the human body with endogenous phospholipids, supplement the nutrients needed by the human body, combine and enter the biological membrane, and increase

the fluidity and stability of the membrane. Clinical applications in liver disease treatment include: NAFLD, alcoholic liver disease, combined antiviral therapy, drug-induced liver injury (DILI), and autoimmune liver disease. Among them, when PPC treats alcoholic fatty liver and liver cirrhosis, it can not only improve liver biochemical indicators, but also improve liver pathological changes (fibrosis progresses more slowly and fatty change is reduced), and it can also improve blood sugar, blood lipid levels and insulin resistance. On the basis of abstinence from alcohol, patients who still have repeated abnormal liver function, liver tissue examination confirmed obvious inflammation and fibrosis, or have obvious progress of the disease, can choose PPC for treatment.

#### ● S-Strength

- The mode of action that achieves microbial intestinal colonization through oral medication will bid farewell to the traditional regular, quantitative and frequent medication. For alcohol addicts or moderate drinking enthusiasts, they may be concerned about how to improve their health while changing their lifestyle as little as possible. Our product features precisely cater to their needs
- We plan to use freeze-dried powder to solve a series of costs and risks brought by the cold chain transportation and storage of probiotic products. Compared with Yishanfu in capsule form, our products use small-package granules to achieve the purpose of early prevention and treatment of alcoholic liver disease, which can significantly alleviate consumer resistance. Genetically engineered products that sound like a sense of distance will infiltrate consumers' lifestyles like instant coffee everywhere.
- In the field of ALD prevention and early treatment, the solutions of most competitors focus on protecting the injured liver, but they have not been able to effectively resist the ongoing damage. Such treatment is usually used indiscriminately for liver damage caused by various reasons, so it is difficult to show more prominent effectiveness in clinical references of alcoholic liver disease. On the basis of studying the pathogenesis of alcoholic liver disease, Lico-Health specifically reduces the intensity of alcohol damage to the liver, and avoids the direct "decomposition of alcohol" to consumers and the consequences of excessive alcoholism and aggravation of alcoholism.
- More importantly, ethanol will have an impact on many aspects of the body, not only liver disease. Compared with simply protecting the liver, directly reducing alcohol damage has a more fundamental impact on improving the health of drinkers.

microbial intestinal  
colonization

small-package freeze-  
dried powder

Resist the ongoing  
damage

Fundamental impact

#### ● W-Weakness

- We need to invest more efforts in improving the resistance of intestinal colonization, enhancing the universality of patients with different genotypes, reducing side effects and improving safety.
- The R&D investment of genetic engineering products is relatively large. We have to choose the most cost-effective auxiliary materials, the most compatible production equipment, and the smallest but sophisticated R&D team to avoid the failure of the pricing strategy.
- At present, genetic engineering products are mostly concentrated in the area of cancer with a high return on investment, which means that we need to work harder to develop the market for patients with alcoholic liver disease.

Effectiveness and safety

Large investment

Virgin land for GT

- O-Opportunity

- Among the chemical drugs used in China for hepatitis, liver protection drugs account for nearly 40%. According to the HDM database of Menet, in 2017, the hepatitis chemical drug market in public hospitals in key cities in China was approximately 8.2 billion yuan, accounting for 6.17% of the total amount of drugs used in more than 400 public hospitals in key cities. This market is mainly composed of anti-hepatitis viruses, liver protection drugs, and immune enhancement regulators.
- Among them, the liver protection market is about 3.1 billion yuan, accounting for about 38% of the hepatitis chemical drug market in key public hospitals. Menet quoted related reports as saying that the overall consumption of liver disease drugs in China in 2017 exceeded 60 billion yuan. At the same time, it is predicted that China's liver-protecting and enzyme-lowering drug market will reach 12 billion yuan in 2020.
- At present, alcoholic liver products are mainly concentrated in health products and pharmaceutical products. Among them, pharmaceuticals are mostly small molecule drugs, including glucocorticoids, antioxidants, anti-fibrosis, and products that promote liver cell regeneration. Bacteria products are still relatively scarce in the market, so the project has a certain degree of innovation and forward-looking.
- Relying on its unique dual-system therapy theory, Lico-Health will have the opportunity to develop a combination drug regimen with other related products and even competitors. At present, with fewer products and a larger target population, the market for alcoholic liver disease prevention and early treatment products is still a blue ocean market.

Large market of liver-related drugs

Liver protection market

Innovation and forward-looking

Combination drug regimen

- T-Threat

- The laws and regulations related to gene therapy products are relatively strict, and China has not yet issued an independent standard that distinguishes them from ordinary biological products. In addition to the demanding review and approval process, ethical considerations are also a major challenge for gene therapy products.
- Currently, no gene therapy product has been approved for over-the-counter drugs or entered the national medical insurance catalogue. However, after entering China in 2017, Yishanfu, produced by Sanofi, the world's fifth-largest pharmaceutical company, has been included in the medical insurance catalog as a Class A OTC drug, which means it will gain a near-monopoly market share.

Strict legal supervision

Near-monopoly market share of Yishanfu (OTC; Food Supplement)

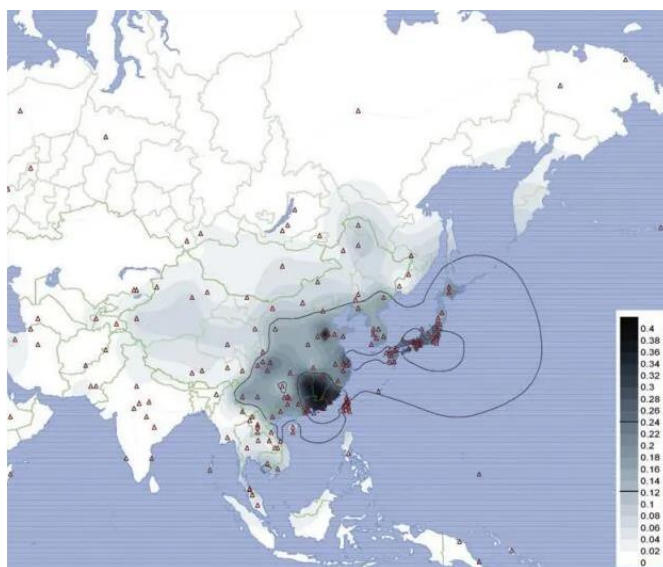
# Marketing Plan

## Target group

- Getting started: East Asian market centered on China
  - According to the research results of the world-renowned journal "Lancet", 32.5% of the world's people are current drinkers (defined as drinking in the past 12 months), that is, 2.4 billion people drink alcohol in the world, of which women It accounts for about 25% and men account for about 39%. China is the country with the most deaths from drinking in the world, with 709,000 deaths caused by drinking every year.
  - Studies have shown that people carrying the ALDH2 gene break down ethanol at about 13 times faster than other people. If the ALDH2 gene is mutated or missing, it will cause the corresponding protease activity to be greatly reduced, making acetaldehyde accumulated in the body for a long time and unable to be metabolized, which will cause the expansion of capillaries, cause flushing and inflammation of the skin, which is the so-called "drinking on the face". However, the distribution of ALDH2 gene in different populations around the world has significant differences. About 50% of Asians have genetic defects in alcohol metabolism, but such genetic defects are rare in European and American populations. Therefore, "drinking on the face" has a professional term called "Asian Flush". Unfortunately, nearly 40% of people in China have ALDH2 gene mutations.
  - But for the market, this means that "Asian Flush" makes Chinese drinkers have stronger psychological implications for the adverse effects of alcohol on the body, making them more eager to seek effective prevention and treatment of alcoholism Products for liver disease.

Most deaths from drinking in the world

Asian Flush



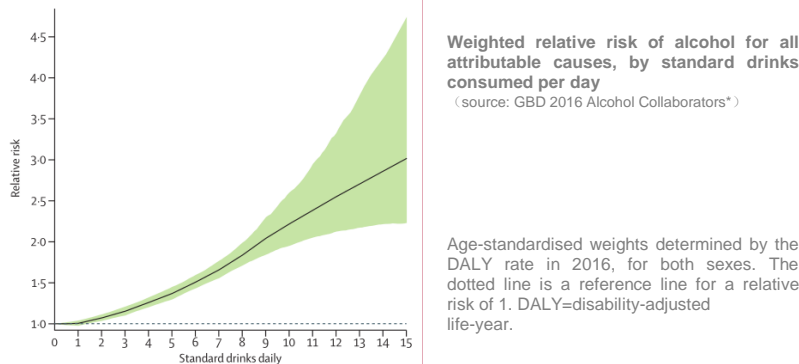
ALDH2  
Geographical distribution of 504Lys allele frequency. Gray scale represents allele distribution frequency, for example, 0.12 means that the allele frequency in the region is 12%. The open red triangle indicates the position of the overall sample. The surrounding black lines indicate the frequency boundaries of the 0.12 and 0.24 distributions.

Li H, Borinskaya, S, Yoshimura, K, et al. Refined Geographic Distribution of the Oriental ALDH2\*504Lys (nee487Lys) Variant. *Annals of Human Genetics*. 2009. doi:10.1111/j.1469-1809.2009.00517.x



- People aged 15-49 who have the habit of drinking, mainly men
  - The target population of Lico-Health is those who have the habit of drinking (that is, those who cannot completely quit alcohol) and those who have mild symptoms of alcoholic liver disease or other alcohol-related diseases
  - Alcohol use is a leading risk factor for disease burden worldwide, accounting for nearly 10% of global deaths among populations aged 15–49 years, and poses dire ramifications for future population health in the absence of policy action today.
  - In estimating the weighted relative risk curve, we found that consuming zero (95% UI 0.0–0.8) standard drinks daily minimised the overall risk of all health loss. The risk rose monotonically with increasing amounts of daily drinking.

10% of global deaths



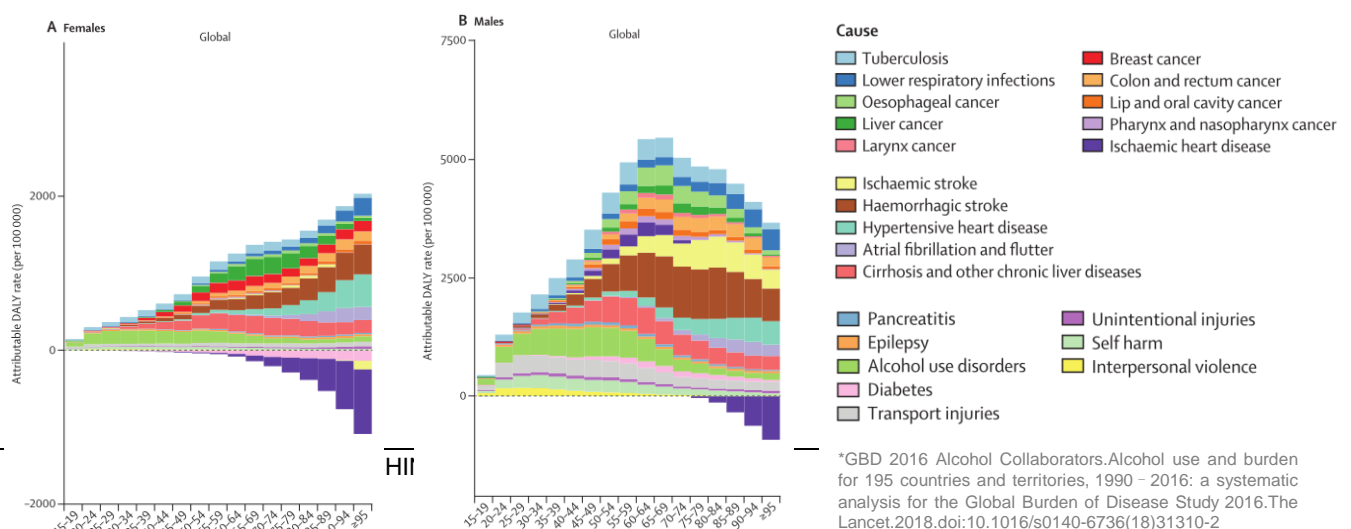
## Product exposure strategy

Article 16 of the Advertising Law of the People's Republic of China:  
*Prescription drugs that meet the requirements can only be advertised in medical and pharmaceutical publications jointly designated by the health administration department of the State Council and the drug regulatory department of the State Council.*

Prescription drugs  
advertised in medical  
publications only

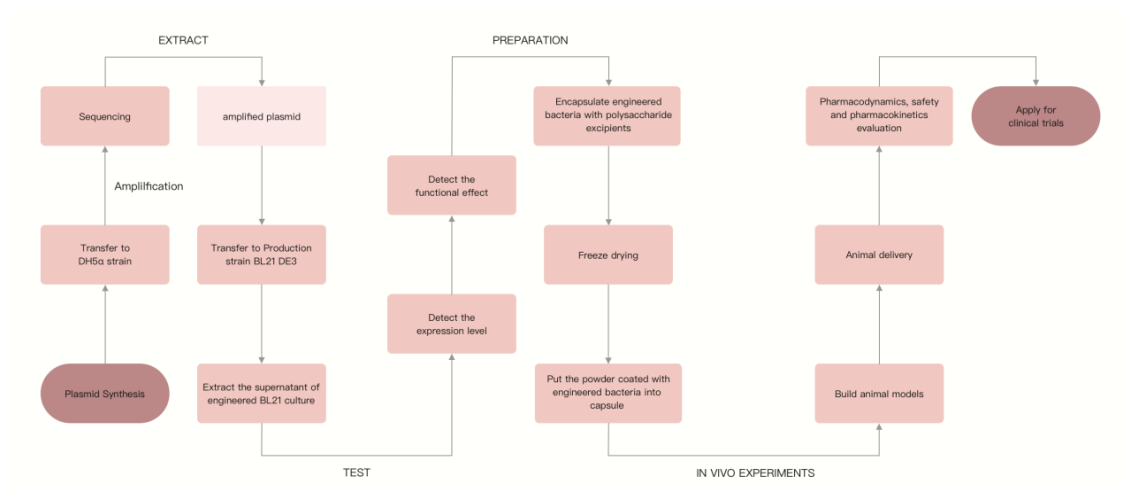
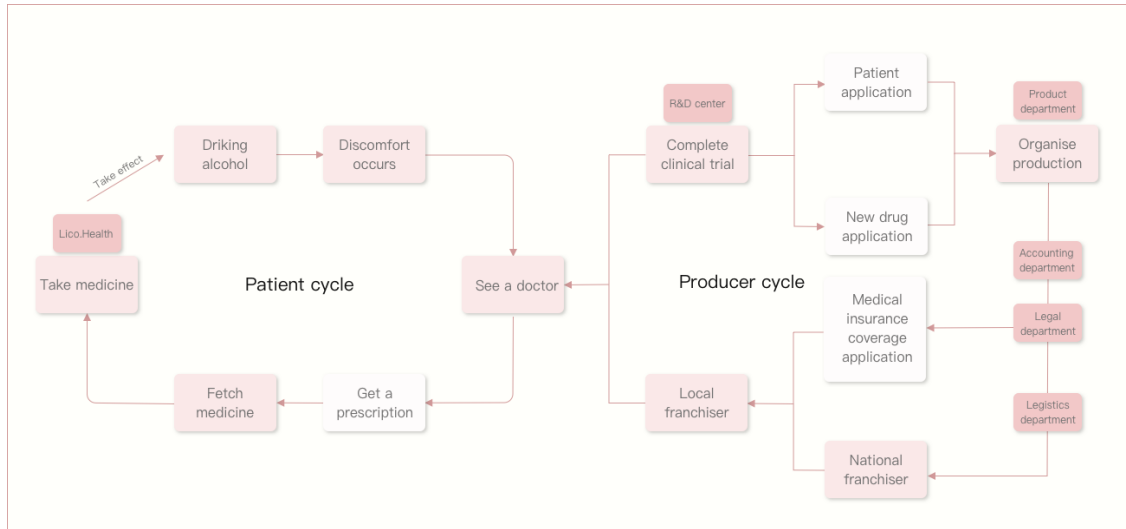
- As shown above, in order to comply with legal requirements, we will use hospitals to purchase drugs and doctors to issue prescriptions as the main sales channels.
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- Considering that in addition to alcoholic liver disease, ethanol is also a predisposing factor for many other diseases, so our sales plan may not be limited to liver disease departments.

Ethanol-related disease





## Operation cycle



# Risk Management

You may view the following topics in this section:

- Production risk
- Risks of technology
- Security risks
- Financial risk
- Management risk
- Market risk
- Competitive risk

## Production risk

- Resource supply: the production of drugs in the design mainly involves raw materials such as E. coli, target genes and required reagents. Before the formal production, at least one alternative partner should be identified, and another raw material supplier should also be contacted if there is any problem with the raw material.
- Process equipment: production equipment and process technology should be synchronized with new drug innovation technology. Timely maintenance of instruments and equipment, timely repair if problems occur.
- Operators: the technical level and proficiency of the production operators shall meet the corresponding requirements of GMP. The most important aspect of drug production is quality. Therefore, strict requirements should be imposed on the workers, checks on the process layer by layer and strictly checks whether the finished products meet the quality standards. In case of production failure, the bidder shall be severely punished.

Raw materials alternative

Timely maintenance of equipments

Operators

## Risks of technology

- The technical problems appeared in the drug development process bring risks to the production process, and excellent technicians are the only way to solve these technical problems.
- Life of technology: For example, due to the rapid pace of technology update, the new technology research and development application will soon be replaced by the updated technology, resulting in a short technology life cycle and the initial investment funds not be recovered. We should pay close attention to the development trend of the production industry.

Sharpen the Saw

## Security risks

- Strictly check every aspect in the process of production and check the production safety of the production workshop regularly. Once problems such as bacterial contamination and bacterial liquid leakage occur, the production in the contaminated area should be stopped immediately and cleaned up.

Strict requirement

Reliable staff

## Financial risk

- Select reliable staff to strictly manage the company's finances:timely liquidate the company's profit and loss, and ensure that there is sufficient liquidity for the daily operation of the company and the needs of the company.

- According to the different development stages and the characteristics of funds required for new drug projects, capital should be timely and correctly financed in a timely manner at important moments such as effectiveness verification, industrialization construction and pre-clinical evaluation to ensure the liquidity of funds and avoid the financial risks improper financing brought. If the funds are scarce, considering the problems of high risk of anti-hepatocarcinoma drug development and long development cycle, joint development of multiple enterprises can be chosen.
- Transnational development may have exchange rate risk.

In a timely manner

### Management risk

- Management of talent and organizational structure are the main factors affecting management risk. Persons with high ability and personal quality should be selected as managers to plan a reasonable organizational system, so as to maintain the operational sensitivity and information dissemination in the production and marketing stages, and improve the coordination of the organization system.

Selecting the Worthy and Promoting the Capable

### Market risk

- As a new treatment, gene therapy, has played an important role in the medical field in recent years. Even so, the related technology is still not mature, and the virus vector still has security problems. Adverse reactions are the key factors that restrict the stable presence of drugs in the market. Therefore, we should always insist on innovation and constantly improve our technology and products. At the same time, the quality of drugs should be strictly controlled and the long-term status of products in the market should be stabilized.
- Gene drugs require high R&D costs. From this perspective, this product may not have an advantage over chemotherapy-targeted drugs led by sorafenib. Therefore, as a latecomer, we should not be overly demanding and profitable on the premise of high costs. Instead, we should adopt a strategy of winning sales to occupy the market.
- The country has strict management over the listing of drugs, and there are many related laws and regulations. Unreasonable marketing channels and marketing methods may cause risks. Therefore, it should be legally advertised. In short, we should do more market research, clarify market trends and strengths(or weaknesses) of the product, grasp market opportunities, and make the most use of its advantages. Meanwhile, we should clarify its disadvantages and improve as much as possible in these areas.

Quality controllability

Winning sales

Abide by the law

### Competitive risk

- Research on gene therapy has been very popular in recent years. It is not excluded that competitors have proposed similar projects. Therefore, the pace of industrialization should be accelerated so that we could win the opportunities. After acquiring the core patent for conditional RNAi, the team should begin to develop new targets and new diseases to expand the use of the therapy. In this way, even if there appears similar therapies, we can be familiar with the market trend and stay in the dominant position in the competition. In

Expand the use of therapy

addition, competition for other liver cancer drugs may also have a certain impact on our products. Therefore, under the premise of ensuring the advantages of our products (good targeting, high controllability, and low side effects), we should lower the selling price as much as possible, thus occupying a market position in the competition for similar drugs.