



图源：果果麻插画设计

参与人员：Involved：Writing Department: Ray Liu, Katherine, Jan
Zhiyuan, Leona Xie, Polaris Zhao, Olivia, Arrietty, Edith, Rachel,
Icey: Design Department: Wakanda, Vanessa, Rachel, Cylinda;
General Planner: Cylinda Wang

SMART MAGAZINE 04



SMART月刊

on-Stream Medical Academy Research and Translation

关注SMART，一键获取生物领域最新研究信息

Efficiency | Accurate | Influencial



1

ENGLISH VERSION

Chinese version is in the back

SMART magazine

WORD BANK

Bispecifics: a class of engineered antibody and antibody-like proteins that, in contrast to 'regular' monospecific antibodies, combine two or more different specific antigen binding elements in a single construct.

Inflammation: a red, painful, and often swollen area in or on a part of your body

Oedema: an unhealthy condition in which liquid collects in the body tissues between the cells

SITUATION

On September 19, 2022, Roche announced that the European Commission (second) approved Vabysmo (faliximab) for the treatment of vision damage caused by neovascular or wet senile macular degeneration (AMD) and diabetes macular edema (dimethyl ether). Wabismo is the only approved ophthalmic injection drug in Europe.

FARICIMAB: THE FIRST DUAL ANTIBODY OPHTHALMIC DRUG INTRODUCTION

Faricimab (product name: Vabysmo), developed by Roche Pharmaceuticals, is a bispecific antibody that can bind and inhibit vascular endothelial growth factor A (VEGF-A) and angiopoietin 2 (Ang-2). Faricimab is the first dual anti ophthalmic drug that has been reviewed and approved by many countries. At present, the drug has been approved by the European Union and nine other countries, including the United States and Japan, to treat patients with wet macular disease (nAMD) and diabetes macular edema (DME). Faricimab only needs to receive treatment every four months to improve eye problems, and as time goes by, the number of injections can be reduced later.

MACULA

In the human eye, there is a tissue located at the center of the retina that contains the highest amount of lutein in the human body. Under normal circumstances, when light is refracted through the cornea and lens, it will focus on a point, which is the macula, and its working principle is similar to a camera's film. The macula contains a large number of cone cells, which are photosensitive cells responsible for receiving and converting light signals and have the ability to distinguish colors.

WHAT'S AMD

AMD (age related macular degeneration) refers to age-related macular degeneration. Senile macular lesions can be divided into dry macular lesions and wet macular lesions (nAMD). Wet macular lesions are mainly caused by fundus hemorrhage and are more common in the elderly population. Senile macular degeneration may be caused by factors such as genetics, human aging, and underlying eye diseases. People with macular degeneration may experience symptoms such as decreased vision and blurred central field of vision. In severe cases, irreversible damage may occur.

WHAT'S DME

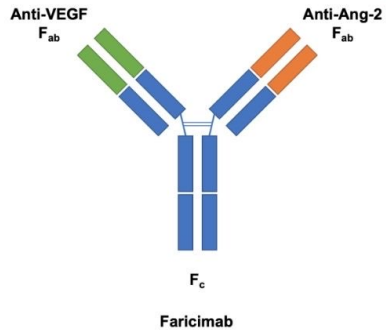
DME (Diabetic Macular Edema) is diabetes macular edema. DME is a complication that affects the eyes of patients with severe diabetes. The common symptoms of the disease include floaters, ghosting, vision loss, etc. If it is not treated early, it may cause blindness.

Whether suffering from AMD or DME, it can lead to excessive activity of various cytokines such as vascular endothelial growth factor (VEGF), promoting abnormal growth of new blood vessels. New blood vessels are usually fragile and can easily cause damage or rupture of the inner wall of the vessels, leading to the appearance of blood and osmotic substances inside and around the vessels. When a large amount of blood or osmotic fluid accumulates in the fundus of the eye, it can cause compression and swelling of the macula, leading to retinopathy.

Both of the above diseases can be treated through methods such as laser therapy or injection of drugs. In terms of injection drugs, anti VEGF treatments are usually used for treatment, and anti VEGF drugs will be injected into the vitreous cavity to inhibit VEGF activity and reduce the growth of new blood vessels. According to clinical data, the use of anti vascular endothelial growth factor therapy is more effective in improving vision, and it has now become a mainstream treatment option.

ABOUT FARICIMAB

There are two important components in Faricimab, namely anti vascular endothelial growth factor (Anti VEGF-A) and anti angiopoietin (Anti Ang-2). Anti vascular endothelial growth factor (Anti VEGF-A) can inhibit endothelial cell growth, reduce vascular permeability, and inhibit the formation of new blood vessels, while anti angiopoietin (Anti Ang-2) can improve vascular stability and reduce vascular sensitivity to VEGF-A. When the two specifically bind, it helps to inhibit endothelial growth factor (VEGF-A) and angiopoietin (Ang-2) in blood vessels, thereby increasing patient vascular stability, reducing the formation of new blood vessels, and inflammation.



PICTURE: STRUCTURE OF FIGURE FARICIMAB

GLOBAL PHASE III CLINICAL TRIALS

There are four clinical trials related to the global phase III, namely TENAYA and LUCERNE, YOSEMITE and RHINE. The four trials are aimed at studying the safety and durability of Faricimab. TENAYA and LUCERNE are mainly aimed at studying wet macular disease (nAMD), while YOSEMITE and RHINE are aimed at studying diabetes macular edema (DME).

According to the data, in the global double-blind experiment of TENAYA and LUCERNE, patients receiving treatment were randomly assigned to the control groups of faricimab and aflibercept, and BCVA scores (Best Corrected Vision Score) were performed at week 48. The results showed that approximately 45% of patients received medication every four months in the first year, while over 60% of patients received medication every four months in the second year. In the global double blind experiment of YOSEMITE and RHINE, the approach was similar to that of TENAYA and LUCERNE studies, except that YOSEMITE and RHINE studies compared the average change in baseline BCVA score after one year, and the results showed that about half of the people receiving treatment achieved once every four months in the first year.

CONCLUSION

Both AMD and DME are relatively common eye diseases in the world. Especially with the development of society, more and more elderly people or diabetes patients have the opportunity to suffer from this disease. As a bispecific antibody drug, Faricimab can effectively treat these patients. Meanwhile, according to research data, patients receiving treatment can generally maintain medication administration every four months and reduce the number of doses over time. Its safety and tolerance have also been certified.

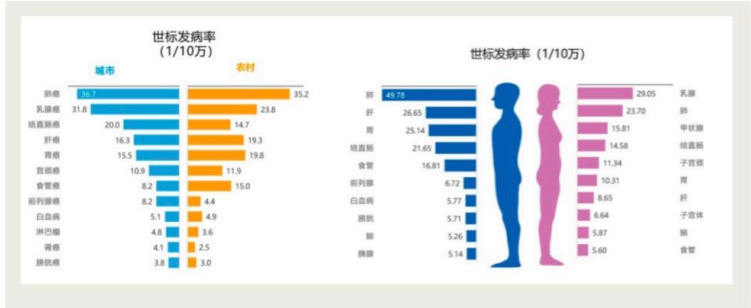
REFERENCE

1. Cris Martin P. Jacoba. Diabetic Macular Edema. EyeWiki. American Academy of Ophthalmology. June 6, 2022 [Diabetic Macular Edema - EyeWiki \(aao.org\)](#)
2. Azeem Khan. Faricimab. EyeWiki. American Academy of Ophthalmology. March 12, 2023. [Faricimab - EyeWiki \(aao.org\)](#)Roche | Vabysmo (faricimab-svoa)
3. Jeffrey S Heier. Efficacy, durability, and safety of intravitreal faricimab up to every 16 weeks for neovascular age-related macular degeneration (TENAYA and LUCERNE): two randomized, double-masked, phase 3, non-inferiority trials. PubMed. National Library of Medicine. [Efficacy, durability, and safety of intravitreal faricimab up to every 16 weeks for neovascular age-related macular degeneration \(TENAYA and LUCERNE\): two randomised, double-masked, phase 3, non-inferiority trials - PubMed \(nih.gov\)](#)
4. Nicole Eter. YOSEMITE and RHINE: Phase 3 Randomized Clinical Trials of Faricimab for Diabetic Macular Edema: Study Design and Rationale. PubMed. National Library of Medicine. [YOSEMITE and RHINE: Phase 3 Randomized Clinical Trials of Faricimab for Diabetic Macular Edema: Study Design and Rationale - PubMed \(nih.gov\)](#)
5. Yasser M. Elshatory. Age-Related Macular Degeneration. EyeWiki. American Academy of Ophthalmology. December 19, 2022. [Age-Related Macular Degeneration - EyeWiki](#)

According to the data released by China's National Cancer Center, in 2022 alone, the number of lung cancer cases in China will be 828 thousand and the number of deaths will be 657 thousand, which means that there will be 13 lung cancer patients die every ten minutes. The same situation has also occurred in other countries around the world, including the United States. In the US, approximately 350 people die from lung cancer every day in 2022. Lung cancer tops the list in terms of both mortality and incidence rate. Although many countries have been promoting regular physical examinations and early detection and treatment for cancer. Unfortunately, the 5-year survival rate of resectable lung cancer patients from stage IB to stage IIIA is only 68% to 36%, which means that despite postoperative tumour resection, there are still many lung cancer patients who fail treatment. With the development of tumour treatment technology, there are now various tumour treatment methods, including chemotherapy radiation therapy, surgery, targeted therapy, biological therapy, immunotherapy, and new monoclonal antibody therapy.

NEW TREATMENT METHODS FOR NON-SMALL CELL LUNG CANCER

Chemotherapy, one of the most traditional treatment methods, achieves therapeutic goals by using chemotherapy drugs to kill cancer cells. Chemotherapy is more suitable for malignant tumours that are sensitive to chemotherapy, such as SCLC, while the NSCLC mentioned in this article does not belong to the tumour type that is



sensitive to chemotherapy, so chemotherapy is not the first choice when treating NSCLC. Meanwhile, as a cytotoxic drug, the occurrence of side effects is inevitable. Digestive system reactions such as nausea and diarrhoea; Bone marrow suppression such as reduction of white blood cells and platelets; Hair loss is also the most common side effect.

Radiotherapy and surgery: Radiotherapy is a local treatment method that uses radiation to treat tumours. Radiation, including those generated by radioactive isotopes α 、 β 、 γ X-rays and various types of X-rays. Approximately 70% of cancer patients require radiation therapy during the treatment process. Like surgery, radiotherapy belongs to local treatment and is only effective for tumours at the treatment site. It is difficult to effectively treat potential metastatic lesions (cancer cells have actually metastasized but cannot be detected and detected clinically due to technical limitations) and cancers that have already undergone clinical metastasis. Traditional chemotherapy methods have only improved 5-year survival rates by 5.4% and 5%, respectively, in terms of NSCLC adjuvant therapy and neoadjuvant therapy

ARTIFICIAL INTELLIGENCE IN DRUG DISCOVERY

CYLINA WANG

ABSTRACT

Artificial intelligence (AI) is revolutionizing the field of drug discovery by enabling researchers to design and test new drugs more speedily and accurately than ever before. This article explores the latest developments in AI-based drug discovery, including its potential applications and implications for society and the pharmaceutical industry.

INTRODUCTION

The process of developing new drugs is lengthy, complex, and expensive. Trial-and-error experimentation, which is one of the past's typical methods for drug discovery can take years and cost billions of dollars. On the other hand, technological advancements recently have enabled researchers to use AI algorithms to design new drugs with greater efficiency and accuracy. In this article, we will explore the cutting-edge field of AI-based drug discovery and explore how it is transforming the world of medicine.



HOW AI IS USED IN DRUG DISCOVERY:

AI is being used in drug discovery in a number of ways. These include predicting the properties of molecules, identifying potential drug targets, and designing new compounds. For instance, using deep learning neural networks to predict the effectiveness of potential drug candidates based on their chemical structures is one of the most promising applications of AI in this field. From this application, researchers can be enabled to identify promising compounds much more quickly than traditional methods.

Virtual screening, which is another key application of AI in drug discovery, where people use computer simulations to screen large databases of molecules and predict which ones are most likely to be effective against a particular disease. By using AI, researchers can easily filter out molecules that are unlikely to be effective, so that they can focus their efforts on a smaller set of compounds, saving time and resources.





BENEFITS OF AI IN DRUG DISCOVERY:

There are many potential benefits of using AI in drug discovery.

First, AI can greatly reduce the time and cost, like bringing new drugs to market. Just to take an example, identify promising compounds more quickly is a great benefit and proved to us that AI has the potential to accelerate the drug development process and bring life-saving treatments to patients faster.

In addition, AI-based drug discovery has the potential to improve the safety and efficacy of new drugs. By using computer simulations to predict the behavior of molecules in the body, researchers can identify potential safety concerns early on in the drug development process. This can help prevent costly and potentially dangerous setbacks in the future.

Challenges and Future Directions:

Despite the many benefits of AI-based drug discovery, there are also significant challenges that must be addressed. For example, AI algorithms are only as good as the data they are trained on, and there are concerns about bias and the quality of the data used to develop these algorithms.

Looking to the future, AI's potential in this field is continuing to boost and it could continue transforming the field of drug discovery. As AI algorithms become more sophisticated and data becomes more abundant, researchers may be able to design entirely new classes of drugs that were previously impossible to develop using traditional methods.

CONCLUSION:

In conclusion, the use of AI in drug discovery is an exciting area of research with enormous potential for improving human health and wellbeing. By enabling researchers to design and test new drugs more efficiently and accurately than ever before, AI has the potential to revolutionize the pharmaceutical industry and bring life-saving treatments to patients faster. However, it is important to address the challenges associated with AI-based drug discovery and ensure that these technologies are used responsibly and ethically.

REFERENCE:

- Aliper, A., et al. "Artificial intelligence for drug discovery, biomarker development, and generation of novel chemistry." *Molecular Pharmaceutics*, vol. 13, no. 8, 2016, pp. 2524-2530.
- Chen, H., et al. "Artificial Intelligence in Healthcare: Past, Present and Future." *Seminars in Cancer Biology*, vol. 70, 2021, pp. 4-11.
- Ekins, S., et al. "Machine learning models identify molecules active against the Ebola virus in vitro." *F1000Research*, vol. 5, 2016, p. 1045.
- Kell, D. B., and Goodacre, R. "Metabolomics and systems pharmacology: why and how to model the human metabolic network for drug discovery." *Drug Discovery Today*, vol. 19, no. 2, 2014, pp. 171-182.
- Ragoza, M., et al. "Protein-ligand scoring with convolutional neural networks." *Journal of Chemical Information and Modeling*, vol. 57, no. 4, 2017, pp. 942-957.
- Schwab, M., et al. "AI in healthcare." *Nature Machine Intelligence*, vol. 1, no. 1, 2019, pp. 1-3.
- Stokes, J. M., et al. "A deep learning approach to antibiotic discovery." *Cell*, vol. 180, no. 4, 2020, pp. 688-702.
- Wang, L., et al. "Deep learning enables efficient selection of antiviral compounds." *bioRxiv*, 2019, pp. 693143.

INTRO

Meat is an indispensable part of our diet. Most people purchase their meat from supermarkets, but have you ever pondered whether the raw meat sold in supermarkets contains any contaminants? People may underestimate the potential for contamination that meat encounters during farming, transportation, and processing in supermarkets, from the farm to the point where it is sold in supermarkets.

On-farm

On farms, the sources of environmental contamination that are most frequently taken into consideration by management are the air and the soil. When it comes to the pollution of the atmosphere, dioxins are a relatively new type of air pollutant that has garnered a lot of attention in the past few years. Dioxins are typically created as a byproduct of industrial processes and combustion, and they typically make their way into the body through the food chain. It has been demonstrated through research that in regions of maximum deposition near incinerators, the rate of dioxin uptake by animals can be anywhere from two to 10 times higher than the rate at which plants take it (Fries et al., 1990). PCBs are released into the atmosphere by combustion facilities as a byproduct of their waste emissions, facilities in the environment can also take up PCBs from the atmosphere and pass them on to herbivorous animals (Weber et al., 2018). The levels of pollutants in plants are directly influenced by the levels of contaminants in the soil; as a result, soil contamination may be an essential component of agricultural production. In some regions, the levels of the heavy metal lead present in beef have been shown to be many times greater than what is considered typical in recent research. It has been hypothesised that pesticides are a common source of heavy metals and that the improper use of pesticides such as insecticides and herbicides in the vicinity of farms may have caused excessive heavy metals in the soil. Additionally, some of the heavy metals accumulate in plants and provide a food chain to be passed on to herbivores (Kasozzi et al., 2018). However, it is important to take note of a few sources of contamination that are less common. Because feed is so tightly associated with the rest of the animal feeding process, feed contamination can often present a more significant challenge. This was found in the pork recall from Ireland, where feed production facilities used hot gases from the burning of tainted fuel oil to dry animal feed. This activity raised the possibility of millions of metric tonnes of pork being contaminated with PCBs (Marnane, 2012).



Transportation process

Supermarket processing

When customers shop for groceries at supermarkets, they will find that different kinds of meat are packaged in plastic bags or other materials like cling film and trays. However, very few shoppers are aware that these types of packaging may leave behind residues that generate dangerous compounds. Plastic wrapping films have been shown to contain chemical pollutants, according to a study that used molecular dynamics simulations (Silva et al., 2007). These contaminants have a propensity to move into meat products. The movement of pollutants in food oftentimes takes into consideration the presence of microplastics. Microplastics are particles of plastic that are smaller than 5 millimetres, and nanoplastics are plastic particles that are smaller than 1 micrometre and can be easily absorbed by animals. One study found XPS microplastics (MP-XPS) in packed meat with food trays, demonstrating the real migration of plastic packaging to meat products (Kedziarski et al., 2020). The majority of food trays are made of polystyrene (XPS), and this study found XPS microplastics in the meat. Plastic cutting boards are currently a widespread type of chopping board that is used in kitchens; however, it was just recently discovered that these boards are a direct source of microplastic contamination in ground beef that is sold in supermarkets (Habib et al., 2022). When people buy meat in supermarkets, they frequently ask the staff to cut it up for them. However, it is during the process of cutting the meat on these plastic chopping boards that the plastic boards are worn down and produce microplastics that are not visible to the naked eye. The meat itself causes microplastic contamination during the processing stage.



CONCLUSION

We found that there are many potential opportunities for meat to be contaminated with contaminants throughout the process of travelling from the farm to the shop after it has been purchased, which means that there are many potential possibilities. At the source, the quantity of pollutants in live animals can be affected by a variety of factors, including those related to the atmosphere and the soil. During shipment, microbiological contamination is the most common problem that we think about; nevertheless, we should also pay attention to the unique route of contamination, which is the crate, and we should devote attention to cleaning it. Consideration should also be given to the possibility that plastic cutting boards and other packaging materials could directly contaminate meat during the processing that takes place in supermarkets. On the other hand, there is no reason to be unduly concerned about the impact of pollutants on human beings caused by the processing of meat. In the meat supply chain, appropriate regulation and control can help cut down on contaminant residues to some extent; nevertheless, supply chain managers should also be aware of the possible risks posed by contamination and make adjustments as necessary.

Corry, J. E., Allen, V., Hudson, W., Breslin, M., & Davies, R. J. J. O. A. M. (2002). Sources of *Salmonella* on broiler carcasses during transportation and processing: modes of contamination and methods of control. 9(2/3), 424-432.

Fries, G. F., Paustenschlag, D. J. J. J. O. T., & Environmental Health, P. A. C. I. (1990). Evaluation of potential transmission of 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin-contaminated incinerator emissions to humans via foods. 29(1), 1-43.

Habib, R. Z., Podosek, V., Alkadi, R., Al Kendi, R., Iftikhar, S. H., Mourad, A. H. I., Kittanow, W. F., Thiemann, T. J. F. A., & A. C. P. (2022). Plastic cutting boards as a source of microplastics in meat. 39(3), 609-619.

Kasozzi, K. I., Natabwo, P. C., Namubiru, S., Tayebwa, D. S., Tamale, A., Baramya, P. H. J. O. E., & Health, P. (2018). Food safety analysis of milk and beef in southwestern Uganda. 2018.

Kedziarski, M., Leicht, B., Sims, O., Le Magnier, G., Le Tilly, V., Bittanaki, S. J. P. & Life, S. (2020). Microplastic contamination of packaged meat: Occurrence and associated risks. 24, 100489.

Marnane, I. J. J. O. E. M. (2012). Comprehensive environmental review following the pork PCB/dioxin contamination incident in Ireland. 14(10), 2551-2556.

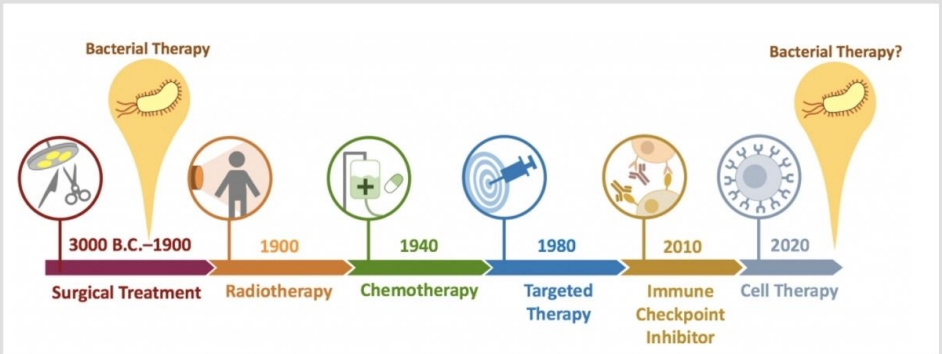
Niyonzima, E., Ongoli, M. P., Kimonyo, A., & Stadic, M. (2015). Risk factors and control measures for bacterial contamination in the bovine meat chain: a review on *Salmonella* and pathogenic *E. coli*.

Silva, A. S., Cruz, J., Garcia, R. S., Frantz, R., & Losada, P. P. J. M. S. (2007). Kinetic migration studies from packaging films into meat products. 77(2), 248-245.

Weber, G., Herold, C., Hölter, H., Kamphuis, J., Blopp, M., & Ballechmann, K. J. E. S. F. (2018). Reviewing the relevance of dioxin and PCB sources for food from animal origin and the need for their inventory, control and management. 30, 1-42.

IMMUNOTHERAPY

A N E W T H E R A P Y F O R C A N C E R



author: Katherine

Cancer is also known as a malignant tumor. As the first of the top ten causes of death for human beings, it has always been a problem that has troubled us very much. Since the beginning of the development of medicine, human beings have been trying many ways to treat cancer. There are currently five major methods for cancer treatment: surgery, chemotherapy, radiation therapy, targeted drugs, and the latest immunotherapy that drives human immune function, which can be subdivided into four primary methods: immune drugs, immune cell therapy, cancer vaccines, and bacterial therapy.

I. How do cancer cells avoid the search of immune cells?

As everyone knows, the occurrence of cancer is the continuous proliferation of cells caused by abnormal mutations in human genes, and it is extremely difficult for human immune cells to recognize cancer cells, which often leads to people finding it after seeking medical treatment due to discomfort. Normally, such abnormal cells should be discovered and killed by immune cells. However, cancer cells evade the search of immune cells by relying on his three tricks. Therefore, understanding the principle of cancer cell evasion is the key for humans to find corresponding treatment methods.

Trick 1: Pretend to be a transparent person

Almost all nucleated cells in vertebrates contain a very important protein—Major histocompatibility complex class I (MHC-I). MHC-I is the key for immune cells to distinguish between friend and enemy. When a cell is infected by a virus or becomes cancerous, it will present virus or tumor antigens through the MHC-I on the cell surface, allowing immune cells to kill the mutated cells. Cancer cells will reduce the concentration of their own MHC-I and turn themselves into "transparent people" to avoid the search of immune cells.

Trick 2: I am a good person

There is another protein on the surface of normal cells in the human body -- CD47. When CD47 binds to the signal regulatory protein α (SIRPα) on the surface of immune cells, it will display a "don't eat me" signal to immune cells. Normally, CD47 is only present on the surface of normal cells, but the researchers found that cancer cells also have CD47 on the surface. In other words, when immune cells encounter cancer cells, they think the cancer cells are good people.

Trick 3: Stop immune cells from attacking

In order to prevent immune cells from being crazy and causing a cytokine storm in patients, immune cells have some unique "brake mechanisms" called "immune checkpoints". There are currently three known T cell immune checkpoints, namely PD-1, CTLA-4, and LAG-3; and there are also special proteins on the surface of cancer cells that can bind to immune checkpoints, reducing the ability of T cells to attack.

III. Immunotherapy

In 2007, Nature magazine published a paper confirming the connection between cancer cells and the immune system. And the paper further pointed out that T cells have the highest correlation with the occurrence of cancer. Therefore, humans have started research on T cells and cancer treatment.

1. Immunological drugs

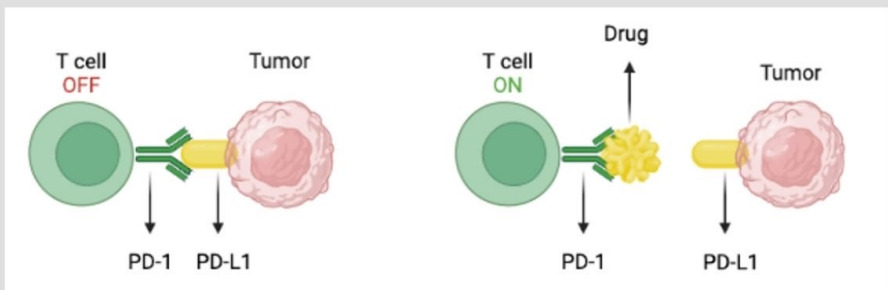
The full name of immune drugs is commonly known as immune checkpoint inhibitors, which subdue cancer cells by using the third trick mentioned above. Taking PD-1 on the surface of T cells as an example, PD-1 will bind to PD-L1 on the surface of cancer cells, resulting in a decrease in the attacking ability of T cells. Immunopharmaceuticals use drug molecules to preempt cancer cells and bind to PD-1; however, this combination does not lead to a decrease in the attacking ability of T cells and only avoids the possibility of combining PD-1 and PD-L1.

Immunopharmaceuticals can be applied to 17 types of cancer, including lung cancer, gastric cancer, esophageal cancer, head and neck cancer, cervical cancer, and hepatocellular carcinoma, with mild side effects, and the activation effect on the immune system can be preserved for 3 to 5 years after stopping the drug. However, with current technology, the success rate of this therapy is not high, and only 15% to 30% of solid tumor cancers respond to immune drugs.

Doctors currently use three indicators to judge whether a patient is suitable for immunotherapy, namely the expression of PD-L1, microsatellite instability (MSI), and tumor mutation load (TMB).

II. The development of cancer treatment

Humans can't understand cancer overnight. Actually, it takes us thousands of years. According to historical records, as early as 3000 BC, doctors at that time had used surgical resection to treat cancer, but it was not until 1891 AD that new treatments appeared. In 1891, American physician William Curley first used bacteriotherapy, which uses bacteria to treat cancer in the human body. However, at that time, Dr. Curley could not explain the principle of the therapy, so he was widely opposed by the academic community. Through time came the 20th century, when radiation therapy, chemotherapy, and targeted therapy appeared one after another. And at the beginning of the 21st century, was the time when immunotherapy (immune drugs, cell therapy, etc.) flourished. However, as scientists have understood the principles of bacterial therapy in recent years, perhaps bacterial therapy will become another new trend.



C. The side effects of CAR-T cell therapy

Although CAR-T cell therapy drives the body's immune response to fight cancer cells, it also has a chance of causing side effects. Because a large number of T cells are injected into the human body in a short period of time, the immune system will still be disturbed to a certain extent. And when CAR-T cells attack cancer cells, a violent immune response will also occur. However, the length of time and symptoms of side effects are not the same for each person, and the side effects can be roughly divided into three categories. The first type is Inflammatory factors, leading to a series of symptoms such as fever, chills, rapid heartbeat, shortness of breath, dizziness, nausea, vomiting, diarrhea, and joint pain. In the most severe cases, coma may also occur. The second type is neurotoxic syndrome, a symptom which caused by immune cells "accidentally injuring" the central nervous system. When the nervous system carries the same type of antigen as the cancer cells, or the cancer cells are near the nervous system, the nervous system will be accidentally injured. The patient will develop headaches, tremors, muscle stiffness, convulsions, unresponsiveness, poor balance, or unconsciousness. The third type is side effects from other treatments, such as allergic reactions during infusions, or immune system reactions after treatment. weaken. All in all, CAR-T cell therapy has the risk of acute side effects, so it needs to be observed in the hospital for several days after treatment.

3. Cancer vaccines

Cancer vaccines are the direction that many biotechnology companies have invested in research in recent years, such as Moderna and BNT, the two biotechnology companies that have developed COVID-19 vaccines. The initial research directions of these two companies were both cancer vaccines. During the process, they just developed mRNA technology. As a result, they happened to meet the outbreak of COVID-19, so the two companies turned to research COVID-19 vaccines. The reason why the COVID-19 vaccine can be launched in just one year can be said to rely on previous research results in the field of cancer vaccines. It is not an exaggeration to say that the COVID-19 vaccine is an additional product of cancer vaccines.

The cancer vaccines are different from vaccines that the general public is familiar with. Vaccination is not to "prevent" disease, but to prevent the "relapse" of disease. Take the hepatitis B vaccine as an example. Everyone is exposed to the same virus, so the ingredients of the vaccine are also the same. But in the case of cancer, the gene mutation of each cancer cell is different. It is tailor-made for each patient, so it is impossible to make a vaccine for the general public.

D. The latest research direction of CAR-T cell therapy

Since CAR-T cell therapy is a new technology developed in 2019, there are still many technical problems waiting to be overcome, which has attracted many scientists to invest in research. This article selects two recent breakthrough studies to share with you.

- Science Advances, April 8, 2022: CAR-T cells are encapsulated in a special hydrogel containing cell-stimulating factors that increase cell activity. Encapsulating CAR-T cells in hydrogel allows the body to maintain a certain concentration of cells and maintain cell activity.
- Science, December 16, 2022: Make CAR-T cells have their own stimulants, and add a gene to CAR-T cells so that they can secrete substances that stimulate their own excitement when they come into contact with cancer cells.

(1) TCR-T cell therapy

The name of TCR-T cell therapy is similar to CAR-T cell therapy. TCR is the abbreviation of T cell receptor, which is a protein that can help T cells distinguish friend from enemy. By means of computer algorithms (guess how to modify the genes of T cells) and gene editing technology (Crispr-Cas9), humans can make T cells exhibit TCR. Even if MHC-I is reduced, immune cells can navigate proteins to find cancer cells. In addition to the similar naming methods, TCR-T cell therapy and CAR-T cell therapy also have the same side effects to be overcome. However, this new technology published in Nature in November 2022, is expected to treat cancers with solid tumors such as lung cancer, breast cancer, and colorectal cancer.

However, cancer vaccines are not a research direction that has only emerged in the past few years. As early as 13 years ago, in 2010, the world's first cancer vaccine, Provenge vaccine, which also known as Sipuleucel-T vaccine was born. This vaccine is mainly used to treat prostate cancer. But it is a pity that the development of cancer vaccines hit the wall in the next ten years, no second vaccine has been on the market.

Having said that, if broadly defined, there are two vaccines that are familiar to the public can also be positioned as cancer vaccines, namely the human papillomavirus (HPV) vaccine and the hepatitis B vaccine. HPV vaccine can effectively reduce the risk of cancer because it can prevent viral infection. The hepatitis B vaccine can prevent hepatitis and cirrhosis, and indirectly reduce the chance of liver cancer.

(1) The expression of PD-L1

The higher the expression of PD-L1 on cancer cells, the higher the probability of effective immunotherapy. According to the latest ESMO Guidelines in 2019, when a patient's PD-L1 expression is $\geq 50\%$, immunotherapy is suitable for first-line treatment; if the patient's PD-L1 expression is $< 50\%$, it is recommended to use Chemotherapy and immunological drugs together.

(2) Microsatellite instability (MSI)

Microsatellites refer to DNA repeats in cancer cells. The higher a patient's MSI is, the more unstable his DNA is, making it easier for the immune system to identify abnormal cells.

(3) Tumor mutation load (TMB)

The principle of TMB is similar to that of MSI. The more mutated a tumor is, the more likely it is to produce mutated proteins and trigger the body's immune response.

B. The limitations of CAR-T cell therapy

There are currently only six CAR-T cell preparations approved by the US Food and Drug Administration (FDA), all of which are used to treat blood and lymphoid cancers. Among them, CAR-T cells are most effective in the treatment of Acute B Lymphocytic Leukemia (ALL), with an effective rate of more than 90% for advanced patients. But CAR-T cell therapy is less effective for cancers with solid tumors, and there are three reasons. The first reason is the heterogeneity of solid tumors. From a microscopic perspective, each tumor is composed of many kinds of mutated cancer cells. That is to say, the location of the mutation in the cancer cells in the tumor is not the same. But CAR-T cell therapy is to find "commonly owned" antigens on the surface of cancer cells. So obviously, the heterogeneity of solid tumors has a great conflict with the fundamental principle of CAR-T cell therapy. If the mutations between cancer cells are different, the antigens presented on their surface will also be different. If CAR-T cells are administered, there will always be some cancer cells that are not killed, and these surviving cancer cells will multiply rapidly and occupy the position of the dead cancer cells. The second reason is that the blood vessels in the tumor cannot keep up with the proliferation of cancer cells, resulting in the tumor being always in a state of hypoxia. Even if the immune cells successfully enter the tumor, they will not be able to function due to hypoxia. Third, cancer cells secrete chemicals that suppress the activity of immune cells and also make immune cells unable to function. Of course, this is not completely insurmountable. Researchers are now trying to make more CAR on the surface of T cells, but the concept is still experimental.

2. Immune cell therapy

At present, researchers have discovered two methods of immune cell therapy, CAR-T cell therapy invented in 2019, and TCR-T cell therapy invented at the end of 2022. Both of these cell therapies "strengthen" T cells in the body through gene editing. The following will introduce the two therapies separately.

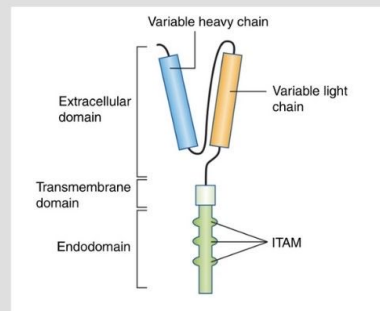
(1) CAR-T cell therapy

A. The secret weapon to strengthen T cells - CAR

CAR is the abbreviation of Chimeric Antigen Receptor. As the name suggests, CAR-T cell therapy is to add chimeric antigen receptors on the surface of T cells through gene editing.

The CAR can be regarded as a protein composed of three parts. The protein outside the T cell is an antibody molecule with high specificity and strong affinity for the surface antigen of the cancer cell; the middle block is responsible for maintaining the stability of the CAR so that it can maintain on the surface of T cells; and the block in T cells can be used to trigger intracellular signaling pathways. When a CAR antibody attached to the surface of a T cell comes into contact with a cancer cell, the CAR activates the T cell, causing it to kill the cancer cell. Therefore, in theory, as long as the antibody at the top of the CAR protein is replaced, various cancers can be attacked, which is also the biggest incentive for major pharmaceutical companies to develop one after another.

However, in addition to being unable to overcome solid cancers, CAR-T cell therapy has another dilemma waiting for a breakthrough. Since the current technology uses the patient's own T cells, this allows CAR-T cells to be reinfused into the patient without rejection. However, this production method also makes CAR-T cell therapy an extremely personalized therapy, which cannot be mass-produced, which makes the cost of treatment unaffordable. Therefore, the next step of CAR-T cell therapy is to find a way to find T cells that can be used by several people, so as to reduce the cost of the customization process, but so far, humans still cannot overcome the rejection of allogeneic transplantation.



All in all, because of the failure experience of more than ten years, many researchers or scientists still doubt the feasibility of cancer vaccines, but many people are optimistic. According to a review report in *Lancet Oncology* in October 2022, there are many mRNA vaccines underway or about to undergo clinical trials, covering cancers such as lung cancer, colorectal cancer, pancreatic cancer, prostate cancer, ovarian cancer, and head and neck cancer.

At present, there are many data pointing out the brilliant performance of cancer vaccines. When cancer vaccines are combined with immunotherapy, the risk of recurrence or death of patients with advanced melanoma is reduced by 44%. On May 10, 2023, *Nature* magazine published the results of a phase I human clinical trial of a pancreatic cancer vaccine, showed that some of the subjects produced cancer cells that could fight tumors. Pancreatic cancer is very difficult to treat, and it is also known as the "cancer king", so this result is very important and fell exhilarating. And in April 2023, *Moderna* told the *British Guardian* that they are confident that mRNA vaccines for cancer, cardiovascular disease and autoimmune diseases will be made before 2030. The chief of the medical officer even says the the cancer vaccines may be possible ready within five years.

4. Bacterial therapy **"Bacteria are not necessarily enemies, they may be allies"**

In 1891, American doctor William Coley injected *Streptococcus pyogenes* into the tumor for the first time, completely eliminating the cervical sarcoma cancer in the patient. In the following 30 years, Dr. Coley used bacterial therapy to save more than 1000 patients. However, at that time, Dr. Coley could not explain the principle of the therapy, and even the cause of the tumor could not be explained at that time, so he was opposed by the academic circles. In modern times, 100 years later, the academic community was finally able to explain the principles of bacterial therapy, and called Ke Lizun the father of immunotherapy.

In the past 10 to 20 years, as the relationship between cancer and immunity has gradually become clear, bacterial cancer therapy has made a comeback, and scientists have used their favorite strains to conduct cancer treatment experiments. In this article, three kinds of bacteria that are more popular and have been clinically tested are selected to share with you.

(3) *Mycobacterium tuberculosis*

Mycobacterium tuberculosis is an aerobic microorganism, which is the culprit that causes tuberculosis in humans. In 1882, German microbiologist Robert Koch was awarded the Nobel Prize in Physiology or Medicine in 1905 for his discovery of *Mycobacterium tuberculosis* as the causative agent of tuberculosis.

In 1900, Albert Calmette and Camille Guérin began research on a tuberculosis vaccine. The research process can be said to be full of twists and turns, and the experiment process was interrupted many times due to the First World War. In the end, it took them nearly 20 years to develop a vaccine to overcome tuberculosis - *Bacille Calmette-Guérin* (BCG). The BCG vaccine is an active vaccine made from weakened tuberculosis bacteria, which can produce resistance to tuberculosis.

(1) *Listeria monocytogenes*

Listeria monocytogenes is an intracellular pathogen that can grow inside human cells. Phagocytes that invade the human body, grow and multiply inside the cell, and present specific antigens on the surface. Humans use gene transfer to make *Listeria* show specific antigens, such as mesothelin, which only appears in pancreatic cancer and ovarian cancer. Use the specific antigens displayed by bacteria to exercise the immune cells of the human body, so that the immune cells can respond to the antigens carried by cancer. In 2015, researchers successfully used *Listeria* that had been weakened to express mesothelin to treat patients with end-stage pancreatic cancer.

(2) *Clostridium butyricum*

Clostridium butyricum is a probiotic bacteria developed in Japan in 1933, also known as "butyric acid bacteria" or "CB bacteria". As a probiotic, *Clostridium butyricum* not only maintains gut health and relieves depression, but also significantly increases the response rate of immune checkpoint inhibitors (enhancing the effect of immune boosters). On February 28, 2022, a paper published in *Nature* pointed out that in patients with end-stage kidney cancer, if thalidomide butyrate is used together with immune checkpoint inhibitors, the patient's response rate can increase by 58%. Compared with the 20% response rate of immune checkpoint inhibitors alone, it is clear that the combination of the two is more effective.

In 1959, a *Nature* paper accidentally discovered that mice given BCG could greatly delay the growth of tumors. So on the basis of BCG, the researchers developed another drug, Onco-BCG. If Onco-BCG is injected into the bladder, it can treat early bladder cancer or prevent bladder cancer recurrence. After Onco-BCG is injected into the human body, it can call more white blood cells to the bladder and stimulate the activity of white blood cells to kill cancer cells. Onco-BCG itself also has the effect of directly inhibiting tumor growth.

V. Conclusion

After introducing so many kinds of immunotherapy, I believe everyone has realized the importance of immunotherapy for the treatment of cancer. Scientists are also optimistic that under the treatment of immunotherapy, cancer may have the opportunity to transform the deadly killer of human beings into a common chronic disease. However, no matter what kind of immunotherapy, there is still a long way to go, especially the high cost of treatment is also a difficulty waiting for researchers to overcome.

Citations

AACR News: mRNA Vaccine Added to Immunotherapy Reduces Melanoma Recurrence. (2023, April 17). Genetic Engineering & Biotechnology News. <https://www.genengnews.com/topics/cancer/aacr-news-mrna-vaccine-added-to-immunotherapy-reduces-melanoma-recurrence/>

Rojas, L. A., Sethna, Z., Soares, K. C., Olcese, C., Pang, N., Patterson, E., ... & Balachandran, V. P. (2023). Personalized RNA neoantigen vaccines stimulate T cells in pancreatic cancer. *Nature*, 1-7.

Lorentzen, C. L., Haanen, J. B., Met, Ö., & Svane, I. M. (2022). Clinical advances and ongoing trials on mRNA vaccines for cancer treatment. *The Lancet Oncology*, 23(10), e450-e458.

Tokarew, N., Ogonek, J., Endres, S., von Bergwelt-Baildon, M., & Kobold, S. (2019). Teaching an old dog new tricks: next-generation CAR T cells. *British journal of cancer*, 120(1), 26-37.

牟昀. (2022, July 28). The Good(免疫細胞), the Bad(癌細胞), and the Ugly(細菌) – 淺談細菌癌症療法. 中研院訊. <https://newsletter.sinica.edu.tw/28204/>

Le, D. T., Wang-Gillam, A., Picozzi, V., Greten, T. F., Crocenzi, T., Springett, G., ... & Jaffee, E. M. (2015). Safety and survival with GVAX pancreas prime and *Listeria monocytogenes*-expressing mesothelin (CRS-207) boost vaccines for metastatic pancreatic cancer. *Journal of clinical Oncology*, 33(12), 1325.

Dizman, N., Meza, L., Bergerot, P., Alcantara, M., Dorff, T., Lyou, Y., ... & Pal, S. K. (2022). Nivolumab plus ipilimumab with or without live bacterial supplementation in metastatic renal cell carcinoma: a randomized phase 1 trial. *Nature medicine*, 28(4), 704-712.

Ledford, H. (2022). CRISPR cancer trial success paves the way for personalized treatments. *Nature*.

Foy, S. P., Jacoby, K., Bota, D. A., Hunter, T., Pan, Z., Stawiski, E., ... & Mandl, S. J. (2023). Non-viral precision T cell receptor replacement for personalized cell therapy. *Nature*, 615(7953), 687-696.

Grosskopf, A. K., Labanieh, L., Klysz, D. D., Roth, G. A., Xu, P., Adebowale, O., ... & Appel, E. A. (2022). Delivery of CAR-T cells in a transient injectable stimulatory hydrogel niche improves treatment of solid tumors. *Science Advances*, 8(14), eabn8264.

Allen, G. M., Frankel, N. W., Reddy, N. R., Bhargava, H. K., Yoshida, M. A., Stark, S. R., ... & Lim, W. A. (2022). Synthetic cytokine circuits that drive T cells into immune-excluded tumors. *Science*, 378(6625), eaba1624.

Fehervari, Z. (2015). Don't eat me, activate me. *Nature Immunology*, 16(11), 1113-1113.

Luca, S., & Mihaescu, T. (2013). History of BCG vaccine. *Maedica*, 8(1), 53-58.

Green tea against liver disease

Keyword definition:

Liver fibrosis: Condition that occurs when scar tissue forms in the liver and ultimately affects the liver to function properly.

Intro:

Liver, as one of the organs that plays an essential role in the body, has a proper function is essential for good health. Viral infections, alcohol consumption, or lifestyle factors, just to list a few factors that leads to liver dysfunction. As a growing problem globally, liver malfunction is spot by researchers and proves us the need for effective therapies which can help prevent or treat liver diseases (cirrhosis, fatty liver disease, liver cancer, etc.). While, one promising avenue of research is the use of natural compounds such as EGCG, found in green tea, to protect and improve liver health. In the following paragraphs, potential benefits of EGCG on liver health will be explored.

Benefits of EGCG for Liver Health:

Green tea is found to include a type of flavonoid, specifically EGCG (Epigallocatechin Gallate), which is known for the antioxidant properties it possesses and potential health benefits such as reducing the risk of cardiovascular disease and certain types of cancer. This shows the link between EGCG and tea. Several benefits of EGCG are mentioned below: To begin, EGCG is able to improve liver function by reducing inflammation and oxidative stress. To explore its ability of improving liver's function, we shall first focus on the two key factors that drives people to liver damage. A study conducted on mice with non-alcoholic fatty liver disease (NAFLD) demonstrated that treatment with EGCG

and it have shown a significant improvement in liver function and reduction of liver inflammation. Considering the fact that NAFLD is a growing problem worldwide, and these findings lightens the hope for the prevention and treatment of this disease. On the other hand, EGCG is also capable of reducing the risk of liver fibrosis. Moreover, a study conducted on rats with liver fibrosis showed that EGCG could reduce the activation of cells that produce scar tissue. This significant result suggests that it may be an effective therapy for preventing or treating liver fibrosis. Furthermore, studies have shown that EGCG possesses anti-cancer properties that could make it a useful tool in preventing and treating liver cancer.

According to reliable sources, researchers have found that EGCG inhibited the growth of liver cancer cells in vitro, while another study showed that EGCG reduced the size and number of liver tumors in mice.

Other Potential Health Benefits of Green Tea: Additionally, green tea has been linked to numerous other health benefits. For instance, studies have shown that green tea can help lower the risk of heart disease, stroke, and certain types of cancer. It may also improve brain function, promote weight loss, and reduce the risk of type 2 diabetes.

Conclusion: In short, EGCG helps protect against liver damage, reduce inflammation, prevent liver fibrosis, and inhibit the growth of liver tumors. While further research is necessary to determine the optimal dosage and duration of treatment, these findings offer hope for the prevention and treatment of liver diseases such as cirrhosis, fatty liver disease, and liver cancer. Nevertheless, it is important to understand that green tea should not be used as an alternative for professional medical treatments.

References:

- Chen, Y., Zhang, L., Tian, J., Xu, Q., & Liang, Y. (2018). Green Tea Compounds in Breast Cancer Prevention and Treatment. *Nutrients*, 10(12), 1841. doi: 10.3390/nu10121841
- Chuangngsarnam, S., Rattanamongkolgul, S., Phonrat, B., Tungtrongchitr, R., & Jirawatnotai, S. (2018). Epigallocatechin-3-Gallate and Alpha-Lipoic Acid Improve Hepatic Steatosis in Obese Type 2 Diabetic Mice. *Advances in Nutrition*, 9(2), 240-252. doi: 10.1093/advances/nny009
- Du, G. J., Zhang, Z., Wu, X. D., Yu, C., Caiway, T., Yuan, C. S., & Wang, C. Z. (2013). Epigallocatechin Gallate (EGCG) is the most effective cancer chemopreventive polyphenol in green tea. *Nutrients*, 5(10), 4184-4202. doi: 10.3390/nu5104184
- Li, Y., Yan, J., Han, C., Yang, J., Chaubry, M. Y., & Wang, S. (2017). Quercetin, Inflammation and Immunity. *Nutrients*, 9(6), 1-14. doi: 10.3390/nu9060462
- Molanouri Shamsi, M., Mohammadi, M., Nasiri Toosi, M., Hekmatdoost, A., & Rashidkhani, B. (2018). Beneficial effects of green tea on liver - a review article. *Journal of Nutrition and Food Security*, 3(3), 155-160. doi: 10.29252/foods.3.3.155
- Norouzi, S., Adulrahman, J., & Sohal, S. S. (2019). Prooxidant and antioxidant properties of epigallocatechin-3-gallate (EGCG) in vitro: implications for oxidative stress. *Biochemical Pharmacology*, 184, 169-177. doi: 10.1016/j.bcp.2019.03.012
- Saeedi-Boroujeni, A., Mahmoudian-Sani, M. R., Asadi-Samani, M., & Yang, Q. (2020). Green tea and its anti-inflammatory, antioxidant and hepato-protective effects. *Journal of Hermed Pharmacology*, 9(2), 91-98.
- Tang, W., Jiang, Y. F., Ponnusamy, M., Diallo, M., & Zhou, X. L. (2019). Hepatoprotective effects of green tea catechins: A mechanistic review. *Food Science and Human Wellness*, 9(2), 239-247. doi: 10.1016/j.fshw.2019.07.003



2

CHINESE VERSION

English version is in the front

SMART magazine

WORD BANK

双特异性：一类工程抗体和抗体样蛋白，与“常规”单特异性抗体不同，它们在单个构建体中结合了两种或多种不同的特异性抗原结合元件。

炎症：身体或某个部位的红色、疼痛且经常肿胀的区域

水肿：一种不健康的情况，液体聚集在细胞之间的身体组织中

SITUATION

2022年9月19日，罗氏宣布，欧盟委员会（EC）批准Vabysmo（faricimab）用于治疗新生血管性或湿性老年性黄斑变性（AMD），以及糖尿病性黄斑水肿（DME）导致的视力损害。Vabysmo 是欧洲唯一获批的眼科注射药物。

FARICIMAB: 第一款双抗眼科药物

简介 由Roche(罗氏药厂)所研发的Faricimab (产品名称: Vabysmo)是一种双特异性抗体，可以通过结合并抑制血管内皮生长因子A(VEGF-A)以及血管生成素2(Ang-2)。Faricimab是第一款获得多国审核并通过的双抗眼科药物，目前，该药物已获欧盟以及其他九个国家，包括美国以及日本等，批准使用于治疗患有湿性黄斑部病变(nAMD)以及糖尿病性黄斑水肿(DME)的患者，Faricimab只需每四个月接受一次治疗便可改善眼部问题，而随着时间的推移，之后可以减少注射次数。

黄斑部 在人的眼球当中，有一个组织位于视网膜的中心上，并含有人体内最高量的叶黄素。正常情况下，当光线经过角膜及水晶体折射后会聚焦在一点上，而该点就是黄斑部，其作用原理有点像照相机的底片。黄斑部当中含有大量视锥细胞，视锥细胞是一种感光细胞，负责接收和转换光信号，具有辨别颜色的能力。

什么是AMD? AMD(age-related macular degeneration)即是指老年性黄斑部病变。老年性黄斑部病变又可以分为干性黄斑部病变和湿性黄斑部病变(nAMD)，湿性黄斑部病变以眼底出血为主，并以老年人居多。老年性黄斑部病变可能是由于遗传、人体衰老、眼部基础疾病等因素造成，而患上黄斑性病的人可能会出现视力下降、中心视野模糊等症状，严重者则会发生不可逆的损伤。

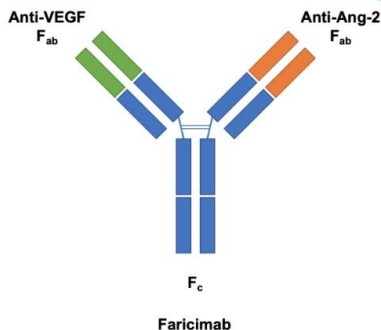
什么是DME? DME(Diabetic Macular Edema)即是糖尿病性黄斑水肿。DME是患有重度糖尿病患者中一种影响眼部的并发症疾病，该疾病常见的症状包括飞蚊症、重影、视力下降等，如果不及早治疗的话，可能会失明。

无论是患上AMD还是DME，都会导致血管内皮生长因子(VEGF)等多种细胞激素过度活跃，促使异常新生血管生长，而新生血管通常比较脆弱，很容易会造成血管内壁受损或破裂，从而引起血管内部和周围出现血液及渗透物，当大量血液或渗透液累积在眼底时，便会使黄斑部受压而肿胀，引起视网膜病变。

以上两种疾病都可以通过激光疗法或注射药物等方法来治疗。在注射药物方面，通常会使用抗血管内皮生长因子疗法(Anti-VEGF treatments)来治疗，而抗VEGF药物将会注射在玻璃体内，抑制VEGF的活跃度，同时减少新生血管的增长。由临床数据显示，使用抗血管内皮生长因子疗法更能改善视力，现在该疗法已成为较主流的治疗方案。

有关FARICIMAB

Faricimab当中有两种重要的份子，分别是抗血管内皮生长因子(Anti VEGF-A)以及抗血管生成素(Anti Ang-2)，抗血管内皮生长因子(Anti VEGF-A)可以抑制内皮细胞的生长，降低血管的通透性以及抑制新生血管的形成，而抗血管生成素(Anti Ang-2)则可以改善血管的稳定性及降低血管对于VEGF-A的敏感度。当两者特异性结合时，有助抑制血管内的内皮生长因子(VEGF-A)以及血管生成素(Ang-2)，从而达到增加患者的血管稳定性，减少新生血管的形成以及炎症等。



全球三期臨床實驗

有关全球三期的临床实验一共有四项，分别是TENAYA和LUCERNE以及YOSEMITE和RHINE，四项实验旨在研究Faricimab的安全性以及耐久性，其中TENAYA和LUCERNE主要针对研究湿性黄斑部病变(nAMD)，而YOSEMITE和RHINE则是针对糖尿病性黄斑水肿(DME)。

由数据得出，在TENAYA和LUCERNE的全球双盲实验中，接受治疗的患者会被随机分配到faricimab和aflibercept两组对照组当中，并在第48周进行BCVA评分(最佳矫正视力评分)，结果显示大约45%的患者在第一年每四个月给药一次即可，而第二年则有超过60%的患者每四个月给药一次。在YOSEMITE和RHINE的全球双盲实验中，做法和TENAYA以及LUCERNE两项研究差不多，只是YOSEMITE和RHINE的研究是比较一年后与基线BCVA评分的平均变化，结果显示大约一半接受治疗的人在第一年实现每四个月给药一次。

結論

无论是AMD还是DME在全球都是属于较为常见的眼部疾病，尤其随着社会的发展，越来越多老年人或者糖尿病患者都有机会患上该疾病，而Faricimab作为一种双特异性抗体药物，可以有效地治疗这些患者。同时，由研究数据得出，接受治疗的患者基本上可以维持在每四个月给药一次，并可以随着时间的推移减少给药次数，其安全性以及耐受性也得到了认证。

REFERENCE

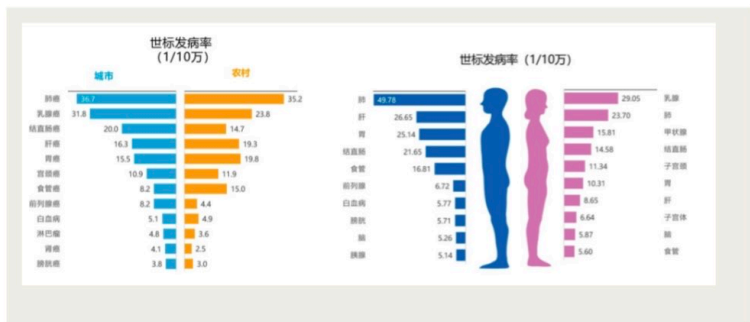
1. Cris Martin P. Jacoba. Diabetic Macular Edema. EyeWiki. American Academy of Ophthalmology. June 6, 2022. [Diabetic Macular Edema - EyeWiki \(aao.org\)](#)
2. Azeem Khan. Faricimab. EyeWiki. American Academy of Ophthalmology. March 12, 2023. [Faricimab - EyeWiki \(aao.org\)](#)Roche | Vabysmo (faricimab-svoa)
3. Jeffrey S Heier. Efficacy, durability, and safety of intravitreal faricimab up to every 16 weeks for neovascular age-related macular degeneration (TENAYA and LUCERNE): two randomized, double-masked, phase 3, non-inferiority trials. PubMed. National Library of Medicine. [Efficacy, durability, and safety of intravitreal faricimab up to every 16 weeks for neovascular age-related macular degeneration \(TENAYA and LUCERNE\): two randomised, double-masked, phase 3, non-inferiority trials - PubMed \(nih.gov\)](#)
4. Nicole Eter. YOSEMITE and RHINE: Phase 3 Randomized Clinical Trials of Faricimab for Diabetic Macular Edema: Study Design and Rationale. PubMed. National Library of Medicine. [YOSEMITE and RHINE: Phase 3 Randomized Clinical Trials of Faricimab for Diabetic Macular Edema: Study Design and Rationale - PubMed \(nih.gov\)](#)
5. Yasser M. Elshatory. Age-Related Macular Degeneration. EyeWiki. American Academy of Ophthalmology. December 19, 2022. [Age-Related Macular Degeneration - EyeWiki](#)

根据中国国家癌症中心发布数据，仅在2022年间，中国肺癌发病人数为82.8万，死亡人数65.7万，这意味着每十分钟就有13位肺癌患者去世「1」。同样的情况也出现在全球其他国家包括美国。在美国，2022年间约有每天350人死于肺癌。无论是死亡率还是发病率，肺癌都高居榜首。虽然国家一直在大力提倡规律体检，早发现早治疗。但是令人遗憾的是IB期到IIIA期可切除肺癌患者5年生存率仅有68%至36%，也就是意味着尽管手术后肿瘤以及切除，但仍然有许多肺癌患者治疗失败「2」。随着肿瘤治疗技术的发展，现如今已经有多种多样的肿瘤治疗方法包括化学疗法（化疗），放射疗法（放疗），手术切除，靶向疗法（靶向），生物治疗，免疫治疗和新单抗疗法。

化疗，最为最传统的治疗方法之一，它通过使用化学治疗药物杀灭癌细胞达到治疗目的。化疗更适用于对化疗敏感的恶性肿瘤如小细胞肺癌，而本文所提及的非小细胞肺癌则不属于对化疗敏感的肿瘤类型，所以在治疗非小细胞肺癌时化疗不是首选。同时，化疗作为细胞毒物药物，副作用的出现是无法避免的。消化系统的反应如恶心腹泻等；骨髓抑制如白细胞和血小板的减少；脱发也是最常见的副作用「3」。

非小细胞肺癌全新治疗方法

放射疗法和手术：放射治疗是利用放射线治疗肿瘤的一种局部治疗方法。放射线包括放射性同位素产生的 α 、 β 、 γ 射线和各类x射线。大约70%的癌症患者在治疗癌症的过程中需要用放射治疗「4」。和手术一样，放疗属于局部治疗，只对治疗部位的肿瘤有效，对于潜在的转移病灶（癌细胞实际已经发生转移，但因为技术手段的限制在临床上还不能发现和检测到）和已经发生临床转移的癌症就难以发挥有效治疗了。



放射疗法和手术：放射治疗是利用放射线治疗肿瘤的一种局部治疗方法。放射线包括放射性同位素产生的 α 、 β 、 γ 射线和各类x射线。大约70%的癌症患者在治疗癌症的过程中需要用放射治疗「4」。和手术一样，放疗属于局部治疗，只对治疗部位的肿瘤有效，对于潜在的转移病灶（癌细胞实际已经发生转移，但因为技术手段的限制在临床上还不能发现和检测到）和已经发生临床转移的癌症就难以发挥有效治疗了。

传统化疗手段在传统化疗手段在NSCLC辅助治疗和新辅助治疗方面仅分别提高5.4%和5%的5年生存率。随着研究的进展，奥希替尼成为首个获批用于辅助治疗的靶向治疗药物，纳武利尤单抗和阿替利珠单抗分别成为首个获批用于新辅助治疗和辅助治疗的免疫药物。在2023AACR大会，AEGEAN作为首个公布结果的“新辅助免疫+手术+辅助免疫”治疗模式的III期研究，为非小细胞肺癌的治疗提供了新的思路，并且有望大大提高患者生存率。

AEGEAN的研究是一项随机、对照、双盲、国际多中心 III 期临床试验，评估无EGFR及ALK突变的可切除 IIA - IIIB (N2) 期NSCLC患者使用度伐利尤单抗进行“新辅助免疫治疗+手术切除+术后辅助免疫治疗”方案的疗效与安全性

人工智能在制药领域

CYLINA WANG

文摘：

人工智能(AI)正在彻底改变药物发现领域，使研究人员能够比以往更快、更准确地设计和测试新药。本文探讨了人工智能药物发现的最新进展，包括其潜在的应用和对社会和制药工业的影响。

介绍

新药的开发过程漫长、复杂并且昂贵。作为过去药物发现的典型方法之一，试错实验可能需要数年、耗资数十亿美元来完成。另一方面，最近的技术进步使研究人员能够使用人工智能算法以更高的效率和准确性设计新药。本文，我们将探讨人工智能药物发现的前沿领域并探索它是如何改变医学世界的。

人工智能在药物发现中的益处

人工智能正以多种方式用于药物研发。这些方法包括预测分子的性质，识别潜在的药物靶点，以及设计新的化合物。例如，使用深度学习神经网络来预测潜在候选药物的有效性——基于他们化学结构是人工智能在这方面最有前途的应用之一。从这个应用中，研究人员可以识别出有前途的比传统方法快得多的化合物。

虚拟筛选，这是人工智能在药物发现中的另一个关键应用，人们使用计算机模拟来筛选大型分子数据库，并预测哪些分子最有可能对特定疾病有效。通过使用人工智能，研究人员可以很容易地过滤掉不太可能有效的分子，这样他们就可以把精力集中在研究更少的化合物上，节省时间和资源。





人工智能在制药领域的益处

在药物发现中使用人工智能有许多潜在的好处。

首先，人工智能可以大大减少时间和成本，就像把新药带到市场。更快地识别有前途的化合物是一个很大的好处，并向我们证明了人工智能有可能加速药物开发过程，更快地为患者带来挽救生命的治疗。

此外，人工智能药物发现具有提高新药安全性和有效性的潜力。通过使用计算机模拟来预测分子在体内的行为，研究人员可以在药物开发过程的早期发现潜在的安全问题——这可以帮助防止未来出现代价高昂且潜在危险的挫折。

挑战和未来方向

尽管人工智能的药物发现有许多好处，但也存在着亟待解决的重大挑战。例如，人工智能算法的好坏取决于它们所训练的数据，人们担心产生数据信息偏见和用于开发这些算法的数据质量问题。

未来，人工智能在这一领域的潜力将继续增强，它可能会继续改变药物发现领域。随着人工智能算法越来越复杂，数据越来越丰富，研究人员几乎不会再使用传统方法进行开发，也许能够设计出以前无法设计的全新的药物类别

结论

总而言之，在药物发现中使用人工智能是一个令人振奋的研究领域，其具有改善人类健康和福祉的巨大潜力。通过使研究人员能够比以往更有效、更准确地设计和测试新药，人工智能有可能彻底改变制药行业，并更快地为患者带来挽救生命的治疗。然而，重要的是要解决与基于人工智能的药物发现相关的挑战，并确保这些技术得到负责任和有效的使用符合伦理道德的行为。

REFERENCE:

- Aliper, A.等。“用于药物发现、生物标志物开发和新化学生成的人工智能。”《分子药剂学》，第13卷，第2期。2016年第8期，第2524-2530页。
- Chen, H., 等。《医疗保健中的人工智能:过去、现在和未来》。《癌症生物学研讨会》，vol. 70, 2021, pp. 4-11。
- Ekins, S.等人。“机器学习模型识别对其有活性的分子体外的埃博拉病毒。”《F1000Research》2016年第5卷，第1045页。
- Kell, D. B., Goodacre, R.。“代谢组学和系统药理学:为什么以及如何为药物发现建立人类代谢网络模型。”《今日药物发现》，第19卷，第2期。2014年第2期，第171-182页。
- Ragoza, M.等。“用卷积神经网络进行蛋白质配体评分。”Journal of Chemical Information and Modeling, vol. 57, no. 5。2017年第4期，第942-957页。
- Schwab, M., 等。“医疗保健中的人工智能。”《自然机器学习》，vol. 1, no. 1。1, 2019, pp. 1-3。
- Stokes, J. M., 等。“抗生素发现的深度学习方法。”《细胞》，第180卷，第2期。4, 2020, pp. 688-702。
- Wang, L.等。“深度学习可以有效地选择抗病毒化合物”，bioRxiv, 2
-

介绍

在饮食中，肉类是我们必不可少的选择。人们购买肉类的途径大多都是在超市，但是你有没有思考过，在超市里购买的生肉类是否也含有一些污染物？在养殖场、运输过程中，超市加工处理等步骤中，人们可能低估了从养殖场到超市被售卖前肉类所面对的被污染的可能性。

养殖场

在养殖场中，大气、土壤是最常被管理者考虑到的环境污染来源。提到大气污染，二噁英是近年来备受关注的新型大气污染物。二噁英通常通过在工业和燃烧中产生，常通过食物链进入体内。有文献证明，在焚化炉附近沉积最高地区，动物对二噁英的吸收量可能是植物吸收量的2到10倍。燃烧厂在排放废弃物中，将多氯联苯排放到大气中沉积，大气中的多氯联苯也会被植物吸收并通过植物迁移到食草动物中。土壤中的污染直接影响植物中的污染物含量，因此在养殖场中，土壤污染可能是至关重要的因素。最近的文献发现，一些地区中牛肉中重金属铅的含量高出正常值数倍。有学者认为，农药是常见的重金属来源，养殖场附近的杀虫剂、除草剂等农药的使用不当可能引起了土壤的重金属超标，而植物中积累了部分重金属，并提供食物链传递到食草动物体中。然而，一些不常见的污染源也应该被注意到。饲料与整个动物饲养过程息息相关，因此饲料污染可能是较为严重的问题。来自爱尔兰的猪肉召回事件中就揭示了这一点，饲料生产设施使用受污染燃料油燃烧产生的热气体来干燥动物饲料，这一行为造成了上百万吨猪肉被多氯联苯污染的风险。



运输过程

在肉类的运输过程中，微生物是近几年多次被提到的生物性污染物。肉类具有较高的含水量和丰富的营养物质，适于微生物繁殖。因此，肉类对运输条件较为严苛，需要较低的温度和湿度。冷链运输是解决这种问题的有效途径，但是建成冷链运输的设备成本较高，因此肉类的运输条件往往达不到抑制大部分微生物生长的环境。有研究发现，在牛肉的运输过程中，温度滥用是牛肉屠宰后被沙门氏菌和致病性大肠杆菌污染的重要因素。潜在的被污染危险却不止于此，运输材料可能是被人忽视的一点。在肉鸡的运输过程中，板条箱是一种便宜和可以重复使用的运输材料，大多数商家都会使用板条箱作为运输活体动物的材料。然而，重复利用的消毒杀菌等卫生清洁操作的不规范可能也会带来潜在的微生物污染危害，有研究发现用来运输的板条箱在清洗和消毒后被沙门氏菌污染，并由此引起了肉鸡在运输过程中沙门氏菌的感染。

超市加工处理

在超市购买产品时，各种形式的肉类使用塑料袋或者保鲜膜、托盘等材料进行包装，但是很少有消费者注意到这些包装是否可能产生残留物产生有害物质。有研究利用分子动力学模拟发现，塑料包装含有的化学污染物有向肉制品迁移的趋势。微塑料是在食品中污染物迁移经常被考虑到的问题。微塑料是小于5毫米的塑料颗粒，包括小于1微米的纳米塑料，容易被动物吸收。食品托盘大多成分为聚苯乙烯（XPS），有研究在有食品托盘的包装肉中检测到了XPS微塑料（MP-XPS），证明了塑料包装向肉制品的实际迁移。塑料砧板是现在厨房中常用的砧板类型，但是最近被发现塑料砧板是超市销售的碎肉中微塑料污染的直接来源，人们往往在超市购买肉类时要求工作人员切块，然而正是在这些塑料砧板上的切割过程中，塑料砧板被磨损而产生肉眼不可见的微塑料，肉类在加工过程中造成了微塑料污染。



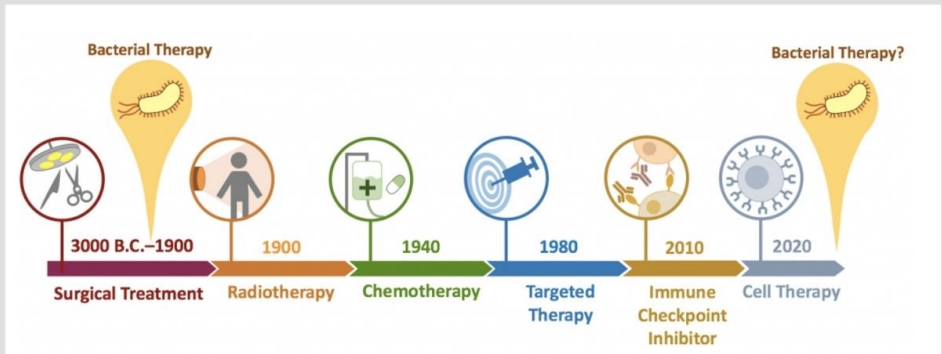
结论 CONCLUSION

在从农场到超市购买后的过程中，我们发现肉类被污染物污染的可能有很多。在养殖场中大气、土壤因素都会影响源头活体动物中的污染物含量。在运输过程中，微生物污染是我们最常考虑的问题，然而我们也应该重视特殊的污染途径——板条箱，板条箱的清洁问题应当被给予重视。最后，超市加工过程中，塑料材质的砧板和包装材料中产生的污染物残留对于肉类的直接污染也应该被给予一些思考。不过也不可以过分担忧肉类过程中的污染物对人体的影响，在肉类制品的供应链中加以适当的监管和控制可以在一定程度上减轻污染物的残留，但是供应链管理者也应警醒过程中的潜在污染风险并且做出改变。

- Cory, J. E., Allen, V., Hanson, W., Breslin, M., & Davies, R. J. J. (2002). Sources of Salmonella on broiler carcasses during transportation and processing: modes of contamination and methods of control. 92(3), 424-432.
- Frost, G. F., Pantonbach, D. J. J., & T., & Environmental Health, P. A. C. I. (1990). Evaluation of potential transmission of 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin-contaminated incinerator emissions to humans via foods. 29(1), 14-43.
- Habib, R. Z., Postole, V., Akandi, R., Al Kendi, R., Bikhar, S. H., Moudar, A. H. I., Kattam, W. F., Thiemann, T. J. F. A., & A. C. P. (2022). Plastic cutting boards as a source of microplastics in meat. 39(3), 609-619.
- Katou, K. I., Nishida, P. G., Nishimura, S., Togejima, D. S., Tamate, A., Bando, P. H. J. F. O., & Health, P. (2018). Food safety analysis of milk and beef in south-eastern Ujssah. 2018.
- Kozlowski, M., Lech, B., Siro, O., Le Magnier, G., Le Tiby, V., Burzard, S. J. P. O., & Life, S. (2020). Microplastic contamination of packaged meat: Occurrence and associated risks. 34, 100459.
- Miyamae, I. J. J. O. E. M. (2012). Comprehensive environmental review following the peck PCB/dioxin contamination incident in Ireland. 14(10), 2551-2556.
- Nyström, E., Öngül, M. F., Kınıyaya, A., & Şimşek, M. (2015). Risk factors and control measures for bacterial contamination in the bovine meat chain: a review on Salmonella and pathogenic E. coli.
- Singh, A. S., Chui, J., Garek, R. S., Fiana, R., & Kosloski, P. P. J. M. S. (2007). Kinetic migration studies from packaging films into meat products. 7(2), 238-245.
- Weber, R., Harold, C., Holtz, H., Kampfers, J., Bleep, M., & Balchmann, K. J. E. S. E. (2018). Reviewing the relevance of dioxin and PCB sources for food from animal origin and the need for their inventory, control and management. 30, 1-42.

免疫治疗

癌症的新兴疗法



作者: Katherine

癌症，又称为恶性肿瘤。身为人类十大死因之首的它，一直都是让人类十分困扰的难题。自医学开始发展以来，人类不断的想方设法想攻破癌症所带来的魔咒。关于癌症治疗，目前总共有五大方法，分别是外科手术、化学治疗、放射线治疗、标靶药物以及最新的免疫疗法。而本篇文章将着重在驱动人体免疫功能的免疫疗法，其中又可细分为免疫药物、免疫细胞治疗、癌症疫苗以及细菌疗法四大方法。

一、癌细胞如何躲避免疫细胞的搜查？

众所周知，癌症的发生是起源于人类基因的不正常突变所造成的细胞不断增生，而人类的免疫细胞极难识别癌细胞，进而常常导致人们因不适而就医之后才发现它。正常来说，这种不正常的细胞应该会被免疫细胞发现并且杀死。然而，癌细胞靠着他的三大绝招，躲避免了免疫细胞的搜查。因此，了解癌细胞躲避的原理，也就是人类寻找对应治疗方法的关健。

招式一：假装自己是透明人

脊椎动物体内的有核细胞几乎都含有一种很重要的蛋白质——第一型主要组织相容性复合物（Major histocompatibility complex class I），简称 MHC-I。MHC-I 正是免疫细胞分辨敌我的关键，当细胞被病毒感染或癌化时，会透过细胞表面的 MHC-I 呈现病毒或肿瘤的抗原，使免疫细胞杀死已变异的细胞。而癌细胞会降低自身 MHC-I 的浓度，将自己变成“透明人”，以躲过免疫细胞的搜查。

招式二：我是好人

人体内的正常细胞表面还有另一种蛋白质——CD47。当 CD47 与免疫细胞表面的信号调节蛋白 α （Signal regulatory protein α ），简称 SIRP α 结合时，会向免疫细胞表现“别吃我”的讯号。正常来说，CD47 只会出现在正常细胞的表面，然而研究员发现癌细胞的表面也有 CD47。也就是说，当免疫细胞遇见癌细胞时，会认为癌细胞是好人。

招式三：让免疫细胞停止攻击

为了避免免疫细胞杀红了眼，使患者体内发生细胞激素风暴（又称细胞激素症候群），免疫细胞有一些独特的“煞车机制”即“免疫检查点”。目前已知的 T 细胞免疫检查点有三个，分别是 PD-1、CTLA-4 及 LAG-3；而癌细胞表面也有些可与免疫检查点结合的特殊蛋白，使 T 细胞的攻击能力降低。

二、癌症治疗的发展

人类对癌症的了解并非一蹴可几，而是经过了上千年的研究才有如今的成果。根据史书的记载，早在公元前 3000 年，当时的医生就已经采用手术切除来治疗癌症了，不过直到西元 1891 年，才有新疗法的出现。1891 年，美国医生威廉·柯立首次采用细菌疗法，以细菌来治疗人体内的癌症。不过在当时，因为柯立医生无法解释该疗法的原理，所以遭到学术界的大规模反对。紧接着，时间来到 20 世纪，放射治疗、化学治疗及标靶治疗等疗法相继出现，而 21 世纪初，更是免疫疗法（免疫药物、细胞疗法等）蓬勃发展的时间。不过随着近几年科学家了解细菌疗法的原理后，或许细菌疗法又将成为另一种新趋势。

三、免疫疗法

2007年《自然》杂志刊登了一篇文章，证实癌细胞与免疫系统的关联性。并且该论文进一步指出，T细胞与癌症的发生与否关联性最高。因此，人类就此开启有关T细胞与癌症治疗的研究。

(一) 免疫药物

大家俗称的免疫药物全名为免疫检查点抑制剂，正是利用前面提到的招式三来制服癌细胞。以T细胞表面的PD-1为例，PD-1会与癌细胞表面的PD-L1结合，造成T细胞的攻击能力下降。而免疫药物则是利用药物分子，抢先癌细胞一步，与PD-1结合；但这种结合并不会导致T细胞的攻击能力下降，仅避免PD-1与PD-L1结合的可能。

免疫药物可以应用在肺癌、胃癌、食道癌、头颈癌、子宫颈癌、肝细胞癌等共17种癌症，且副作用轻微，停药之后对免疫系统的活化效果可保存3~5年。不过以目前的技术而言，该种疗法的成功率并不高，只有15%~30%的固态肿瘤癌症对免疫药物有反应。

医生目前共使用三种指标来判断患者是否适合使用免疫药物治疗，分别是PD-L1的表现量、微卫星不稳定性MSI以及肿瘤突变负荷量TMB。

1. PD-L1的表现量

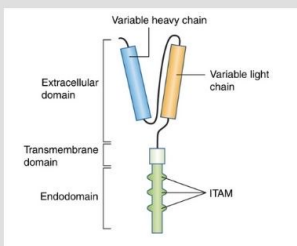
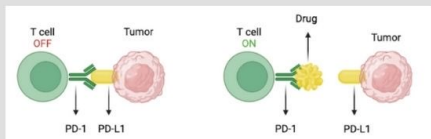
若癌细胞上的PD-L1表现量愈高，免疫药物治疗有效的机率也愈高。根据2019年最新的欧洲治疗指引（ESMO Guidelines），当患者的PD-L1表现量 $\geq 50\%$ ，第一线治疗就适合使用免疫药物；若患者的PD-L1表现量 $< 50\%$ ，则建议使用化疗配合免疫药物治疗法进行。

2. 微卫星不稳定性（Microsatellite Instability, MSI）

微卫星系指癌细胞的DNA重复片段，当患者的MSI愈高，代表他的DNA愈不稳定，使免疫系统较容易识别为异常细胞。

3. 肿瘤突变负荷量（Tumor Mutation Burden, TMB）

TMB的原理与MSI相似，若肿瘤的突变程度愈高，则愈有机会生成突变的蛋白质，并引发人体的免疫反应。



(二) 免疫细胞治疗

目前研究员们共发现两种免疫细胞治疗的方法，分别是于2019年发明的CAR-T细胞疗法，以及2022年底发明的TCR-T细胞疗法。这两种细胞疗法皆是透过基因编辑“强化”体内的T细胞，以下将分别针对这两种疗法进行介绍。

1. CAR-T细胞疗法

(1) 强化T细胞的秘密武器——CAR

CAR为嵌合抗原受体（Chimeric antigen receptor）之简称。顾名思义，CAR-T细胞疗法便是透过基因编辑，在T细胞表面加入嵌合抗原受体。

CAR受体可视为由三个部分的蛋白质组成，T细胞外的蛋白质对癌细胞表面抗原有高度专一性和强亲和力的抗体分子；中间的区块负责维持CAR的稳定，使其可以维持在T细胞表面；而T细胞内的区块，则可用来触发细胞内的讯息传递路径。当附着在T细胞表面的CAR抗体接触到癌细胞时，CAR就会活化T细胞，使其杀死癌细胞。因此理论上，只要更换CAR蛋白质最上端的抗体，就能攻击各种癌症，这也是各大药厂相继开发的最大诱因。

(2) CAR-T细胞疗法的局限

目前经美国食品及药物管理局（FDA）核准的CAR-T细胞制剂只有六种，且都是用于治疗血液以及淋巴癌症。其中，CAR-T细胞在治疗急性B淋巴细胞白血病（Acute lymphoblastic leukemia, 简称ALL）时效果最为显著，对晚期患者有效率达百分之九十以上。但CAR-T细胞疗法对于具有固态肿瘤的癌症效果较差。CAR-T细胞疗法还无法治疗固态肿瘤有三大原因，第一个原因是因为实体肿瘤的异质性，从微观层面来看，每一颗肿瘤它是由许多种突变的癌细胞所组成，也就是说肿瘤内的癌细胞发生突变的位置不尽相同。很明显的，实体肿瘤的异质性与CAR-T细胞疗法的根本原理有极大的冲突，CAR-T细胞疗法是想找到癌细胞表面「共同拥有」的抗原。而癌细胞之间的突变如果不同，其表面呈现出的抗原也会有所差异。如果施打CAR-T细胞，总会有一部分癌细胞没有被杀死，而这些活下来的癌细胞会快速繁殖，占领已死亡的癌细胞的位置。第二个原因是肿瘤内的血管跟不上癌细胞繁殖速度，导致肿瘤内总是处于缺氧状态，纵使免疫细胞成功进到肿瘤内，也会因缺氧而无法发挥作用。第三，癌细胞会分泌抑制免疫细胞活性的化学物质，也会使免疫细胞无法发挥作用。当然，这也不是完全无法克服。目前研究员们正试图让T细胞表面带有更多种CAR嵌合蛋白质，不过此概念仍在实验中。

不过除了无法克服实体癌症之外，CAR-T细胞疗法还有另一个窘境等待突破。由于目前的技术皆取用患者本人的T细胞，这可以使CAR-T细胞重新注入患者体内时，不会发生排斥反应。但这个制作方法也导致CAR-T细胞疗法是一项极端个性化的疗法，无法大规模生产，因而导致治疗费用压不下来。因此CAR-T细胞疗法的下一步，便是想办法找出说数人可以通用的T细胞，这样便可以降低客製化过程的费用，不过到目前为止，人类仍无法克服实体移植的排斥问题。

(三) CAR-T 细胞疗法的副作用

CAR-T 细胞疗法虽然是驱动人体的免疫反应对抗癌细胞，但也是有机率产生副作用的。因为在短时间内注射了大量的 T 细胞进入人体，所以对免疫系统还是会产生一定程度的扰动。并且在 CAR-T 细胞攻击癌细胞时，也会发生剧烈的免疫反应。不过每个人副作用出现时间的长短以及症状皆不太相同，而副作用可大致分为三类，第一类是细胞激素症候群（又称细胞激素风暴），这是因为免疫细胞在短时间内大量释出发炎因子，导致患者发烧、畏寒、心跳加快、呼吸急促、头晕目眩、恶心、呕吐、腹泻及关节疼痛等一系列症状，最严重的情况也可能导致昏迷；第二类是神经毒性症候群，这是因为免疫细胞“误伤”了中枢神经系统所导致的症状，当神经系统携带与癌细胞同种类的抗原，或是癌细胞在神经系统附近时，便会导致神经系统被误伤，患者会出现头痛、手脚颤抖、肌肉僵硬、抽搐、反应迟钝、平衡感差或是意识不清楚等症状；第三类是其他治疗过程产生的副作用，例如输血过程中产生的过敏反应，或是治疗之后免疫系统变弱。总而言之，CAR-T 细胞疗法有发生急性副作用的风险，因此在治疗之后还需住院几日观察。

(四) CAR-T 细胞疗法的最新研究方向

由于 CAR-T 细胞疗法是 2019 年才开发的新技术，因此还有很多技术问题等待克服，吸引了许多科学家投入研究。本篇文章选取了两篇近期十分具有突破性的研究来与大家分享。

- 2022 年 4 月 8 日《Science Advances》：将 CAR-T 细胞封装在特制的水凝胶中，且水凝胶中含有能提高细胞活性的细胞刺激因子。将 CAR-T 细胞封装在水凝胶中，可让人体维持一定的细胞浓度，并且维持细胞活性。
- 2022 年 12 月 16 日《Science》：使 CAR-T 细胞自带兴奋剂，在 CAR-T 细胞中再加入一段基因，使其在接触癌细胞时，能自行分泌刺激自己兴奋的物质。

2. TCR-T 细胞疗法

TCR-T 细胞疗法的取名与 CAR-T 细胞疗法有着异曲同工之妙。TCR 为 T 细胞受体（T cell receptor）之简称，这是一种可以帮助 T 细胞分辨敌我的蛋白质。藉由电脑演算法（推测如何修改 T 细胞的基因）以及基因编辑技术（CRISPR-Cas9），人类可使 T 细胞表现出 TCR，在即使 MHC-I 减少的情况下，免疫细胞藉由人工设计的导航蛋白质，找出癌细胞。除了取名方式相似以外，TCR-T 细胞疗法与 CAR-T 细胞疗法也有着相同的副作用等待克服。不过这项于 2022 年 11 月刊登于《Nature》的新技术，有望治疗肺癌、乳癌、大肠癌等具有实体肿瘤的癌症。

(四) 细菌疗法

「细菌不一定是敌人，也可能是盟友」

1891 年，美国医生威廉·柯立（William Coley），首次将化脓性链球菌打入肿瘤内，完全消除患者身上的颈部肉瘤癌，在此后的 30 年间，柯立医生使用细菌疗法拯救超过 1000 位病人。不过当时，柯立医生无法解释该疗法的原理，且在当时连肿瘤的发生原因都无法解释，因此遭到学术界的反对。而在 100 年后的现代，学术界终于能解释细菌疗法的原理，并将柯立尊称为免疫疗法之父。

近 10 到 20 年来，由于癌症与免疫之间的关系渐渐清楚，细菌癌症疗法又卷土重来，科学家们纷纷使用自己最喜欢的菌种来进行癌症治疗的实验。本篇文章共选择了三种较热门且已做过临床实验的细菌与大家分享。

(三) 癌症疫苗

癌症疫苗是近年来许多生技公司投入研究的方向，例如研发 COVID-19 疫苗的莫德纳以及 BNT 两家生技公司。这两家公司最初的研究方向皆是癌症疫苗，过程中恰好研发出 mRNA 技术，结果又刚好遇上 COVID-19 的爆发，因此两家公司纷纷转而研究 COVID-19 疫苗。之所以 COVID-19 疫苗能在短短一年内推出，可说是依赖癌症疫苗领域先前的研究成果，如果说 COVID-19 疫苗是癌症疫苗的附加产物，一点也不为过。

值得注意的是，癌症疫苗跟与一般大众所熟知的疫苗不同。施打疫苗不是为了“预防”疾病，而是防止疾病“复发”。以 B 型肝炎疫苗为例，每个人接触的病毒都一样，所以疫苗成分也一样；但以癌症来说，每个人癌细胞的基因突变不一样，癌症疫苗必须等到病患发病后，再为病患量身打造，所以无法制造大众通用的疫苗。

不过严格来说，癌症疫苗并不是近几年才兴起的研究方向。早在 13 年前的 2010 年，就已经诞生世界上第一款癌症疫苗——Provenge 疫苗，又称 Sipuleucel-T 疫苗，此款疫苗主要用于治疗摄护腺癌。但可惜的是，此后十年癌症疫苗的开发陷入极大的瓶颈期，一直没有第二款疫苗上市。

话虽如此，若以广义的定义来说，有两款大众所熟悉的疫苗，也可以被定位为癌症疫苗，分别是人类乳头病毒（HPV）疫苗与 B 型肝炎疫苗。HPV 疫苗因为可预防病毒感染，所以能有效减少癌症罹患机率。而 B 型肝炎疫苗，可预防肝炎以及肝硬化，也间接降低肝癌发生的机率。

总而言之，也因为十多年来的失败经验，目前仍有许多研究员或科学家在怀疑癌症疫苗的可行性，不过也有许多人乐观看待。根据 2022 年 10 月《Lancet Oncology》的回顾报告，有许多 mRNA 疫苗正在或即将进行临床实验，疫苗范围包括肺癌、大肠直肠癌、胰脏癌、摄护腺癌、卵巢癌及头颈癌等癌症。

目前已有许多数据指出癌症疫苗的亮眼表现，当癌症疫苗配合免疫药物治疗之后，中晚期黑色素癌病人的复发或死亡风险降低了 44%；2023 年 5 月 10 日，《自然》杂志刊登了一篇有关胰腺癌疫苗的人体临床一期实验结果，结果显示部分受试者产生能对抗肿瘤的癌细胞，要知道胰腺癌十分难治疗，又称为“癌王”，因此这个结果十分令人振奋。且 2023 年 4 月，莫德纳向英国卫报表示，他们有信心在 2030 年以前做出癌症、心血管疾病和自体免疫疾病的 mRNA 疫苗，且医疗长也乐观地认为，有可能在五年内准备就绪。

1. 李斯特菌 (*Listeria monocytogenes*)

李斯特菌是一种可在人体细胞内部生长的细胞内病原体。会入侵人体的吞噬细胞，在细胞内部生长、繁殖，并在表面呈现特殊抗原。人类利用基因转殖，使李斯特菌表现出特定的抗原，如只在胰腺癌和卵巢癌等才出现的特定抗原——间皮素。利用细菌表现出的特定抗原，锻炼人体的免疫细胞，使免疫细胞对癌症所携带的抗原有反应。在 2015 年，研究员已成功使用已弱化并可表现间皮素的李斯特菌，治疗胰腺癌末期的病人。

2. 丁酸梭菌 (*Clostridium butyricum*)

丁酸梭菌是一种日本于 1933 年研发的益生菌，又称“酪酸菌”或“CB菌”。身为一种益生菌的丁酸梭菌不仅可维护肠道健康并缓解忧郁症，还可大幅增加免疫检查点抑制剂的反应率（加强免疫促进剂的效果）。2022 年 2 月 28 日，一篇发布于《Nature》的论文指出，在肾脏癌末期的病人中，若使用丁酸梭菌配合免疫检查点抑制剂，患者的反应率可上升之 58%，相较于单独使用免疫检查点抑制剂的 20% 反应率，由此可见，两者搭配后的效果更佳。

3. 结核分枝杆菌 (*Mycobacterium tuberculosis*)

结核分枝杆菌即结核菌，是一种需氧微生物，为导致人类罹患肺结核的元凶。西元 1882 年，德国微生物学家罗伯·柯霍凭着发现结核菌为肺结核的病原体，获得了 1905 年诺贝尔生理学或医学奖。

西元 1900 年，阿尔伯特·卡尔梅特和卡米尔·介兰开始了肺结核疫苗的研究。研究过程可说是一波三折，实验过程中还多次因第一次世界大战而中段。最终，他们花费了近 20 年的光阴，终于研发出克服结核菌的疫苗——卡介苗（BCG）。而卡介苗正是由结核菌弱化后所制成的活性疫苗，可产生对结核病的抵抗力。

1959 年，一篇《Nature》论文意外发现，施打过卡介苗的小鼠，可以大大延缓肿瘤生长的速度。于是在卡介苗的基础上，研究员研发出另一只药物 Onco-BCG；若将 Onco-BCG 经由膀胱内注射，可治疗早期膀胱癌或是预防膀胱癌复发。简单来说，Onco-BCG 在注射到人体后，可号召更多白血球到膀胱，并刺激白血球的活性来杀死癌细胞，且 Onco-BCG 本身也有直接抑制肿瘤生长的效果。

五、结论

在介绍了这么多免疫疗法之后，相信大家已经意识到免疫疗法对于治疗癌症的重要性。科学家们也乐观地认为，在免疫疗法的治疗之下，癌症或许有机会重人类的致命杀手转变为普通的慢性疾病。不过不论是哪种免疫疗法，仍有很长一段路要走，特别是高昂的治疗费用也是等待研究员们克服的难关。

引用

AACR News: MRNA Vaccine Added to Immunotherapy Reduces Melanoma Recurrence. (2023, April 17). Genetic Engineering & Biotechnology News. <https://www.genengnews.com/topics/cancer/aacr-news-mrna-vaccine-added-to-immunotherapy-reduces-melanoma-recurrence/>

Rojas, L. A., Sethna, Z., Soares, K. C., Olcese, C., Pang, N., Patterson, E., ... & Balachandran, V. P. (2023). Personalized RNA neoantigen vaccines stimulate T cells in pancreatic cancer. *Nature*, 1-7.

Lorentzen, C. L., Haanen, J. B., Met, Ö., & Svane, I. M. (2022). Clinical advances and ongoing trials on mRNA vaccines for cancer treatment. *The Lancet Oncology*, 23(10), e450-e458.

Tokarew, N., Ogonek, J., Endres, S., von Bergwelt-Baildon, M., & Kobold, S. (2019). Teaching an old dog new tricks: next-generation CAR T cells. *British journal of cancer*, 120(1), 26-37.

牟昀. (2022, July 28). The Good(免疫細胞), the Bad(癌細胞), and the Ugly(細菌) – 淺談細菌癌症療法. 中研院訊. <https://newsletter.sinica.edu.tw/28204/>

Le, D. T., Wang-Gillam, A., Picozzi, V., Greten, T. F., Crocenzi, T., Springett, G., ... & Jaffee, E. M. (2015). Safety and survival with GVAX pancreas prime and *Listeria monocytogenes*-expressing mesothelin (CRS-207) boost vaccines for metastatic pancreatic cancer. *Journal of clinical Oncology*, 33(12), 1325.

Dizman, N., Meza, L., Bergerot, P., Alcantara, M., Dorff, T., Lyou, Y., ... & Pal, S. K. (2022). Nivolumab plus ipilimumab with or without live bacterial supplementation in metastatic renal cell carcinoma: a randomized phase 1 trial. *Nature medicine*, 28(4), 704-712.

Ledford, H. (2022). CRISPR cancer trial success paves the way for personalized treatments. *Nature*.

Foy, S. P., Jacoby, K., Bota, D. A., Hunter, T., Pan, Z., Stawiski, E., ... & Mandl, S. J. (2023). Non-viral precision T cell receptor replacement for personalized cell therapy. *Nature*, 615(7953), 687-696.

Grosskopf, A. K., Labanieh, L., Klysz, D. D., Roth, G. A., Xu, P., Adebowale, O., ... & Appel, E. A. (2022). Delivery of CAR-T cells in a transient injectable stimulatory hydrogel niche improves treatment of solid tumors. *Science Advances*, 8(14), eabn8264.

Allen, G. M., Frankel, N. W., Reddy, N. R., Bhargava, H. K., Yoshida, M. A., Stark, S. R., ... & Lim, W. A. (2022). Synthetic cytokine circuits that drive T cells into immune-excluded tumors. *Science*, 378(6625), eaba1624.

Fehervari, Z. (2015). Don't eat me, activate me. *Nature Immunology*, 16(11), 1113-1113.

Luca, S., & Mihaescu, T. (2013). History of BCG vaccine. *Maedica*, 8(1), 53-58.

绿茶对肝脏疾病的防治

关键字:

肝脏纤维化: 当肝脏内形成瘢痕组织并最终影响肝脏正常功能时发生的疾病。

介绍: 肝脏, 作为在身体中起着重要作用的器官之一, 具有适当的功能是健康的关键。病毒感染、饮酒或生活方式因素, 以上列举了导致肝脏功能失调的几个因素。作为全球范围内一个日益严重的问题, 肝功能失调被研究人员发现, 并证明我们需要有效的疗法, 以帮助预防或治疗肝病(肝硬化、脂肪肝、肝癌等)。

虽然, 一个有希望的研究途径是使用天然化合物, 如绿茶中的EGCG, 来保护和改善肝脏健康。在以下段落中, 我们将探讨EGCG对肝脏健康的潜在益处。

EGCG对肝脏健康的好处: 绿茶中含有一种类黄酮, 特别是EGCG(表没食子儿茶素), 因其所具有的抗氧化特性和潜在的健康益处而闻名, 如降低心血管疾病和某些类型癌症的风险。根据一些研究, EGCG是茶叶中最丰富的儿茶素之一, 被认为是负责其健康促进作用的主要成分之一。这已经表明了两者之间的联系: EGCG和茶。

下面提到EGCG的几个好处:

首先, EGCG能够通过减少炎症和氧化压力来改善肝功能。为了探索它改善肝脏功能的能力, 我们首先要关注促使人们肝脏受损的两个关键因素。

对患有非酒精性脂肪肝(NAFLD)的小鼠进行的一项研究表明, 用EGCG和它治疗后, 肝功能得到了明显的改善, 肝脏炎症也得到了减少。考虑到非酒精性脂肪肝在全球范围内是一个日益严重的问题, 这些发现为预防和治疗这种疾病点燃了希望。

另一方面, EGCG也能够降低肝脏纤维化的风险。

此外, 对患有肝纤维化的大鼠进行的一项研究表明, EGCG能够减少产生疤痕组织的细胞的激活。这一重要结果表明, 它可能是一种预防或治疗肝脏纤维化的有效疗法。

研究表明, EGCG具有抗癌特性, 可以使其成为预防和治疗肝癌的有用工具。据可靠消息, 研究人员发现, EGCG在体外抑制了肝癌细胞的生长, 而另一项研究表明, EGCG减少了小鼠肝肿瘤的大小和数量。

绿茶的其他潜在健康益处: 此外, 绿茶还与许多其他健康益处有关。例如, 研究表明, 绿茶可以帮助降低患心脏病、中风和某些类型癌症的风险。它还可能改善大脑功能, 促进减肥, 并减少2型糖尿病的风险。

结论: 简而言之, EGCG有助于保护肝脏免受损害, 减少炎症, 防止肝脏纤维化, 并抑制肝脏肿瘤的生长。虽然需要进一步研究以确定最佳剂量和治疗时间, 但这些发现为预防和治疗肝脏疾病, 如肝硬化、脂肪肝和肝癌提供了希望。尽管如此, 重要的是要明白, 绿茶不应该被用作专业医疗的替代品。

参考文献:

- Chen, Y., Zhang, L., Tian, J., Xu, Q., & Liang, Y. (2018). 绿茶化合物在乳腺癌预防和中的作用。Nutrients, 10(12), 1841. doi: 10.3390/nu10121841
- Chuengsamarn, S., Rattanamongkolgul, S., Phonrat, B., Tungtrongchitr, R., & Jirawatnotai, S. (2018). Epigallocatechin-3-Gallate和 α -硫辛酸可改善肥胖的2型糖尿病小鼠的肝脏脂肪沉积。《营养学进展》, 9(3), 240-252. doi: 10.1093/advances/nmy005
- Du, G. J., Zhang, Z., Wen, X. D., Yu, C., Calway, T., Yuan, C. S., & Wang, C. Z. (2013). Epigallocatechin Gallate (EGCG)是绿茶中最有效的癌症化学预防多酚。doi: 10.3390/nu5104184.
- Li, Y., Yao, J., Han, C., Yang, J., Chaudhry, M. T., & Wang, S. (2017). 槲皮素、炎症和免疫力。Doi: 10.3390/nu9040402
- Molanri Shamsi, M., Mohammadi, M., Nasiri Toosi, M., Hekmatdoost, A., & Rashidkhani, B. (2018). 绿茶对肝脏的有益影响——一篇评论文章。《营养与食品安全杂志》, 3(3), 155-160. Doi: 10.29252/jnfs.3.155
- Norouzi, S., Adulcikas, J., & Sohal, S. S. (2019). 表没食子儿茶素-3-植酸盐 (EGCG) 在体外的氧化和抗氧化特性: 对氧化压力的影响。Biochemical Pharmacology, 164, 169-177. doi: 10.1016/j.bcp.2019.03.012
- Saeedi-Boroujeni, A., Mahmoudian-Sani, M. R., Asadi-Samani, M., & Yang, Q. (2020). 绿茶及其抗炎、抗毒和保护肝脏的作用。《草药药理学杂志》, 9(2), 91-98.
- Tang, W., Jiang, Y. F., Ponnusamy, M., Diallo, M., & Zhou, X. L. (2019). 绿茶儿茶素的肝脏保护作用: A mechanistic review. Food Science and Human Wellness, 8(3), 238-247. doi: 10.1016/j.fshw.2019.07.003



图源：果果麻插画设计

SMART MAGAZINE 04

参与人员：Involved：Writing Department: Katherine, Jan Zhiyuan,
Leona Xie, Polaris Zhao, Icey, Cylinda; Design Department:
Wakanda, Vanessa, Rachel, Cylinda, Katie; General Planner:
Cylinda Wang



SMART月刊

on-Stream Medical Academy Research and Translation

关注SMART，一键获取生物领域最新研究信息

Efficiency | Accurate | Influential