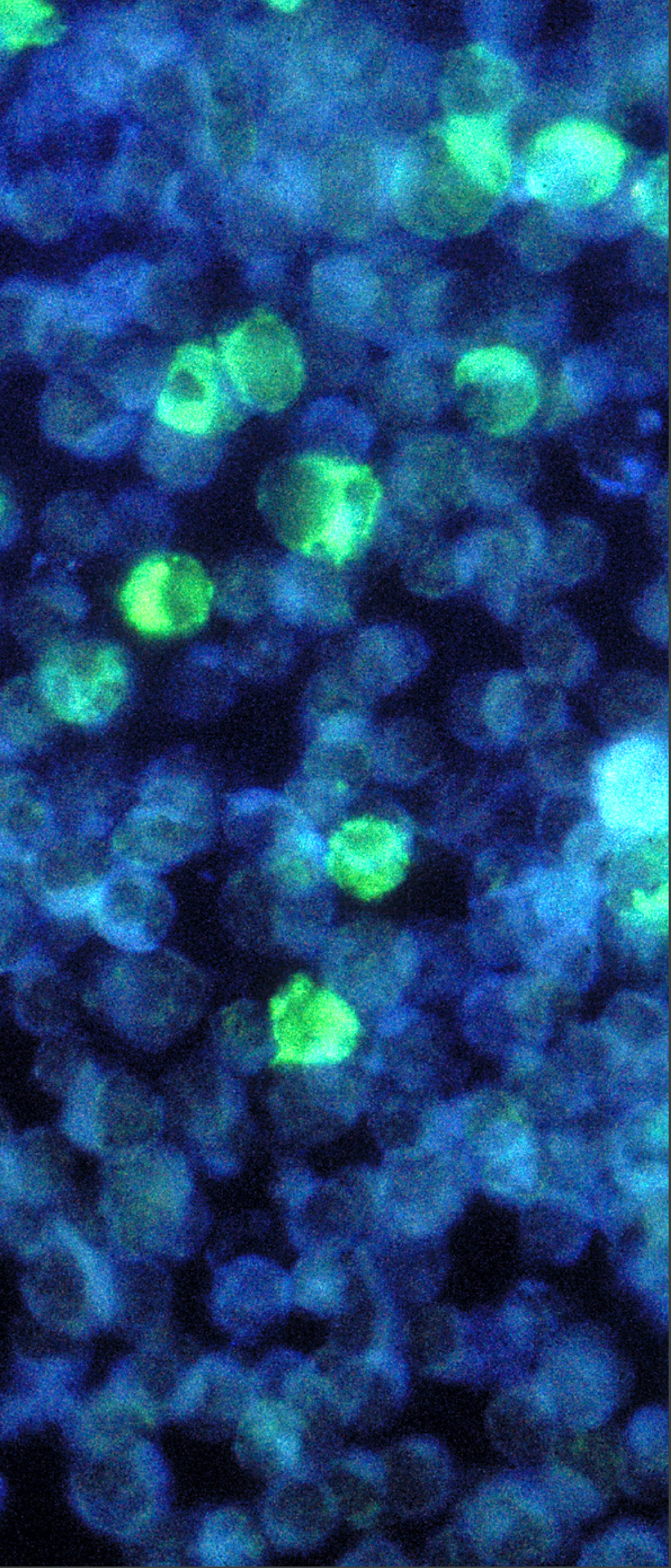

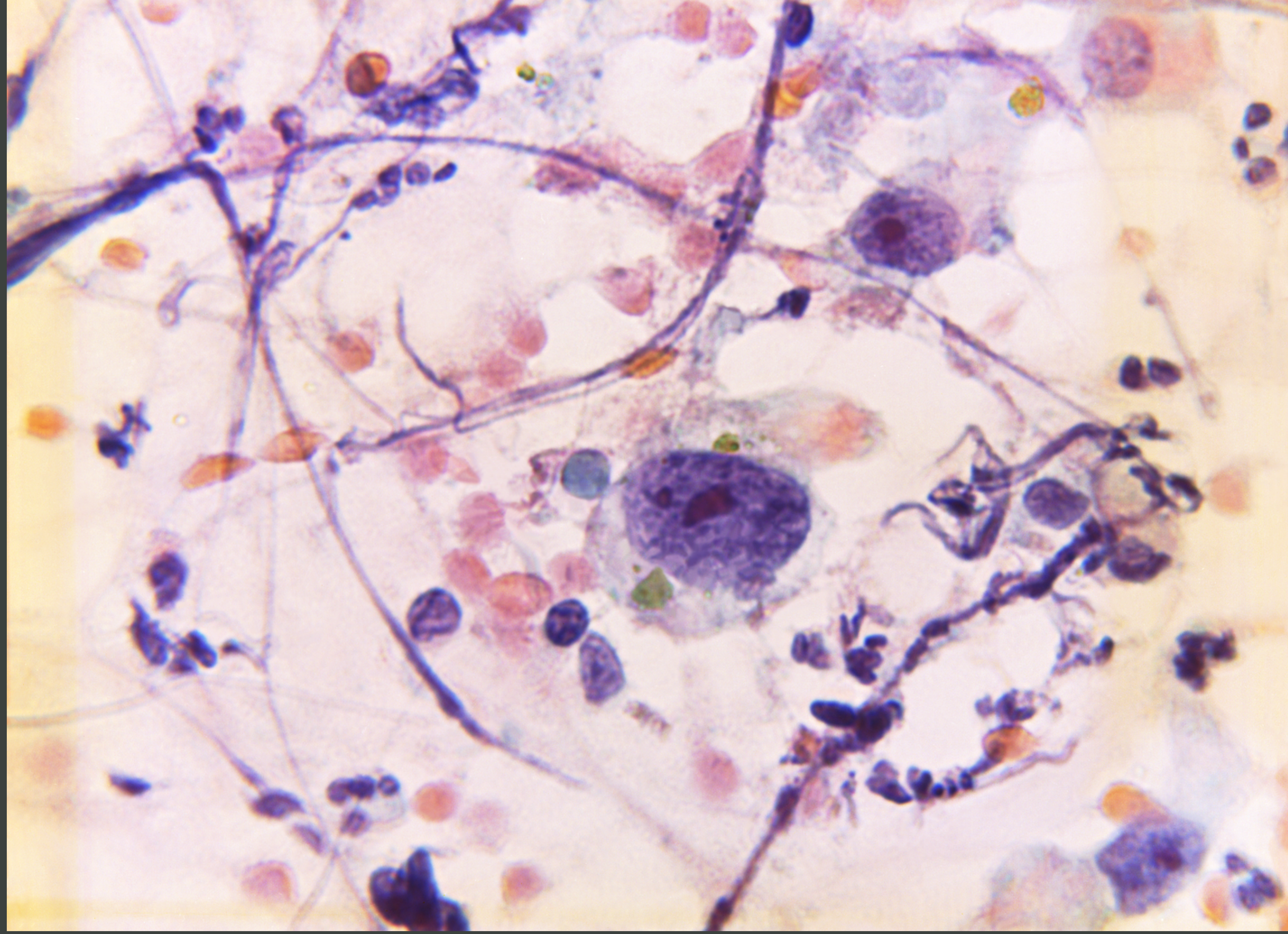

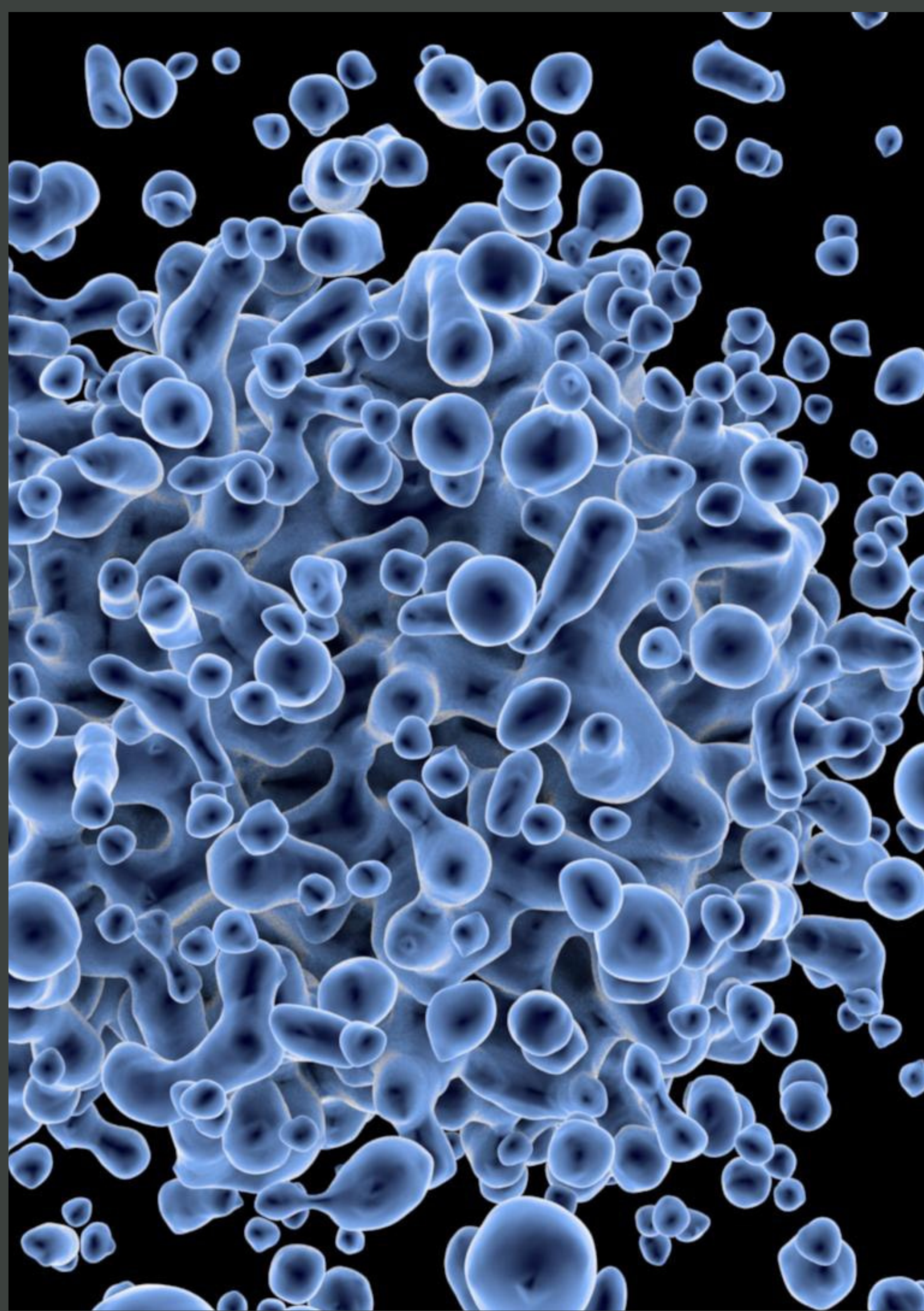

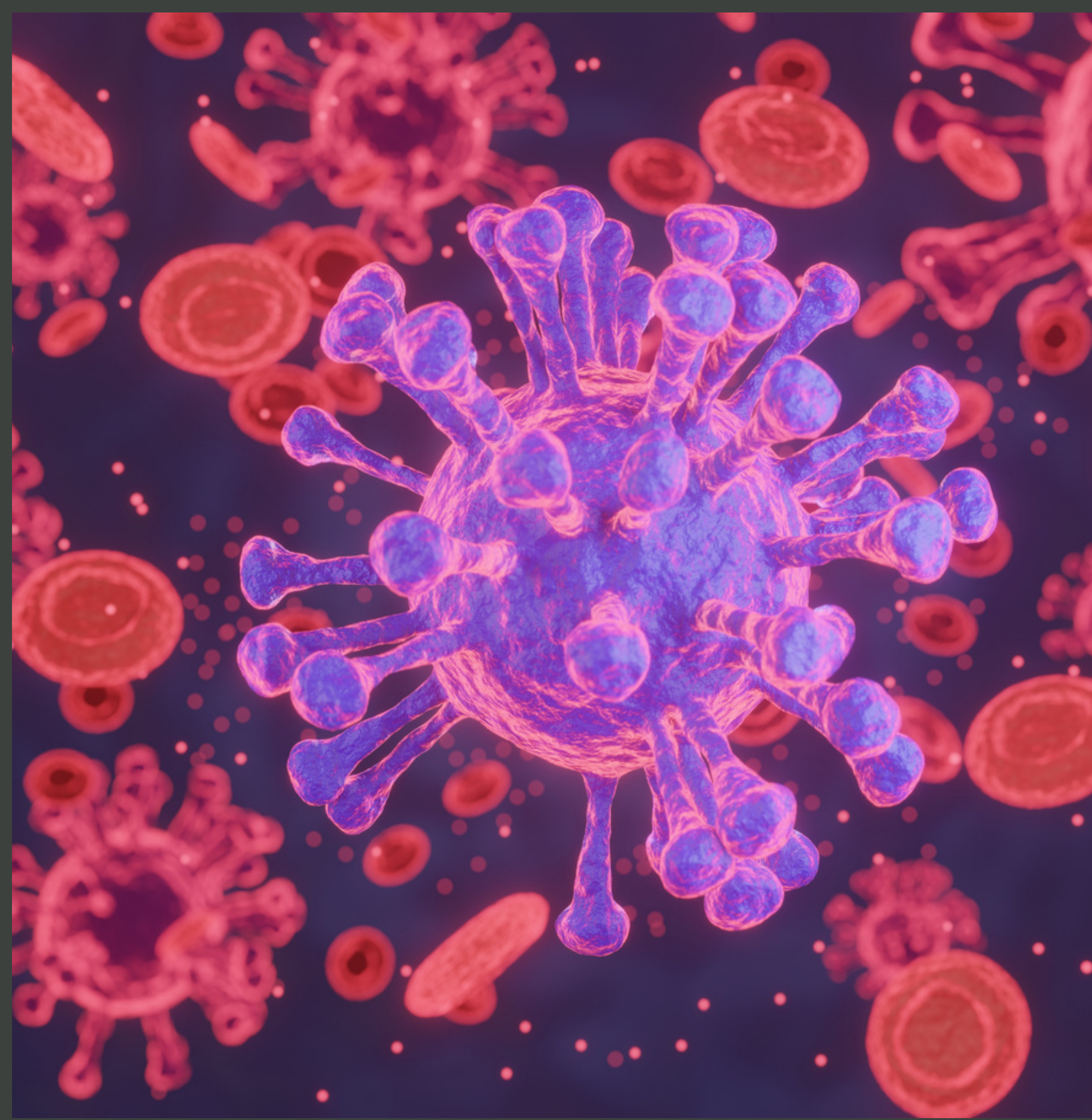

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SMART

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The ENGLISH VERSION

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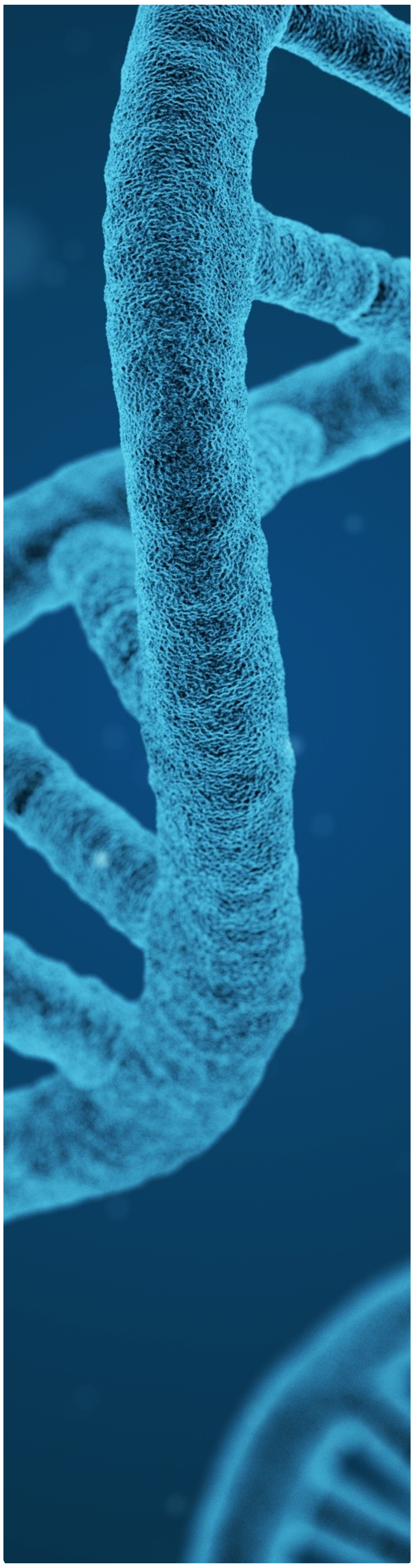
AUTHOR: RACHELLE WU

SMARCB1 DELETION UNDIFFERENTIATED CARCINOMA



Some time ago, doctoral students suffered from cancer events have received widespread attention, including one student with undifferentiated pancreatic cancer, diagnosed as "pancreas SMARCB1/INI1 deletion type of undifferentiated cancer." Undifferentiated pancreatic carcinoma is a rare subtype of pancreatic cancer, accounting for only 2% of malignant exocrine pancreatic tumors, and the prognosis of most patients is very poor. It is a kind of malignant tumor which is difficult to treat and the effect is not obvious. Many people may ask, what is the meaning of undifferentiated cancer in cancer? What does SMARCB1/INI1 stand for?

First of all, the classification, grading and staging of tumors are the three most important indicators to evaluate the biological behavior and diagnosis of tumors. The grading and staging are mainly used to evaluate the biological behavior and prognosis of malignant tumors. The "degree of differentiation" we are talking about is a grading. Grading determines the degree to which cancer cells differ from normal cells, and there are five grades to describe the degree of these differences: Gx (grade unknown), G1 (low grade highly differentiated), G2 (medium grade moderately differentiated), G3 (high grade poorly differentiated), and G4 (high grade undifferentiated). The higher the degree of differentiation, the lower the grade proves that the cancer cells are more similar to surrounding normal cells, the slower they grow, and the more difficult it is to spread to other parts of the body. Conversely, the less differentiated the cancer cells, the higher the grade, the more dangerous. [2]

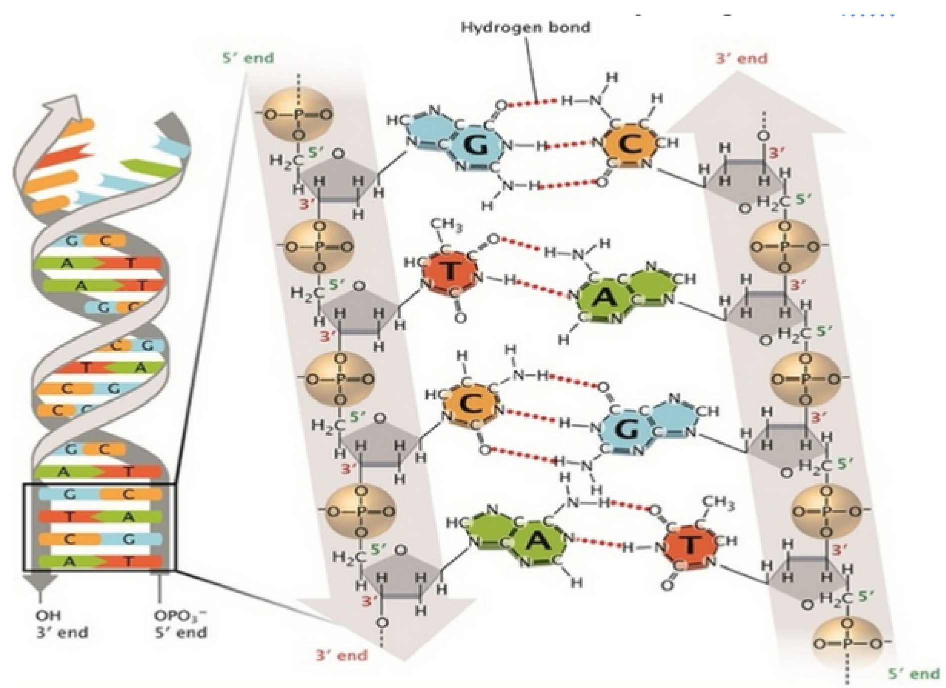


Figure 2

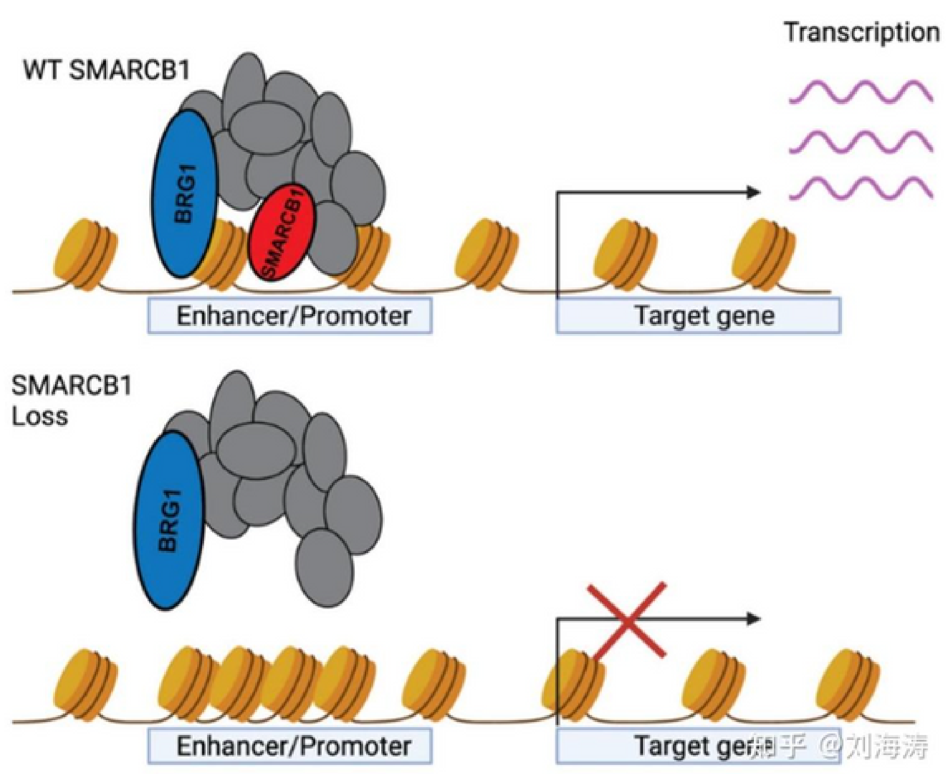


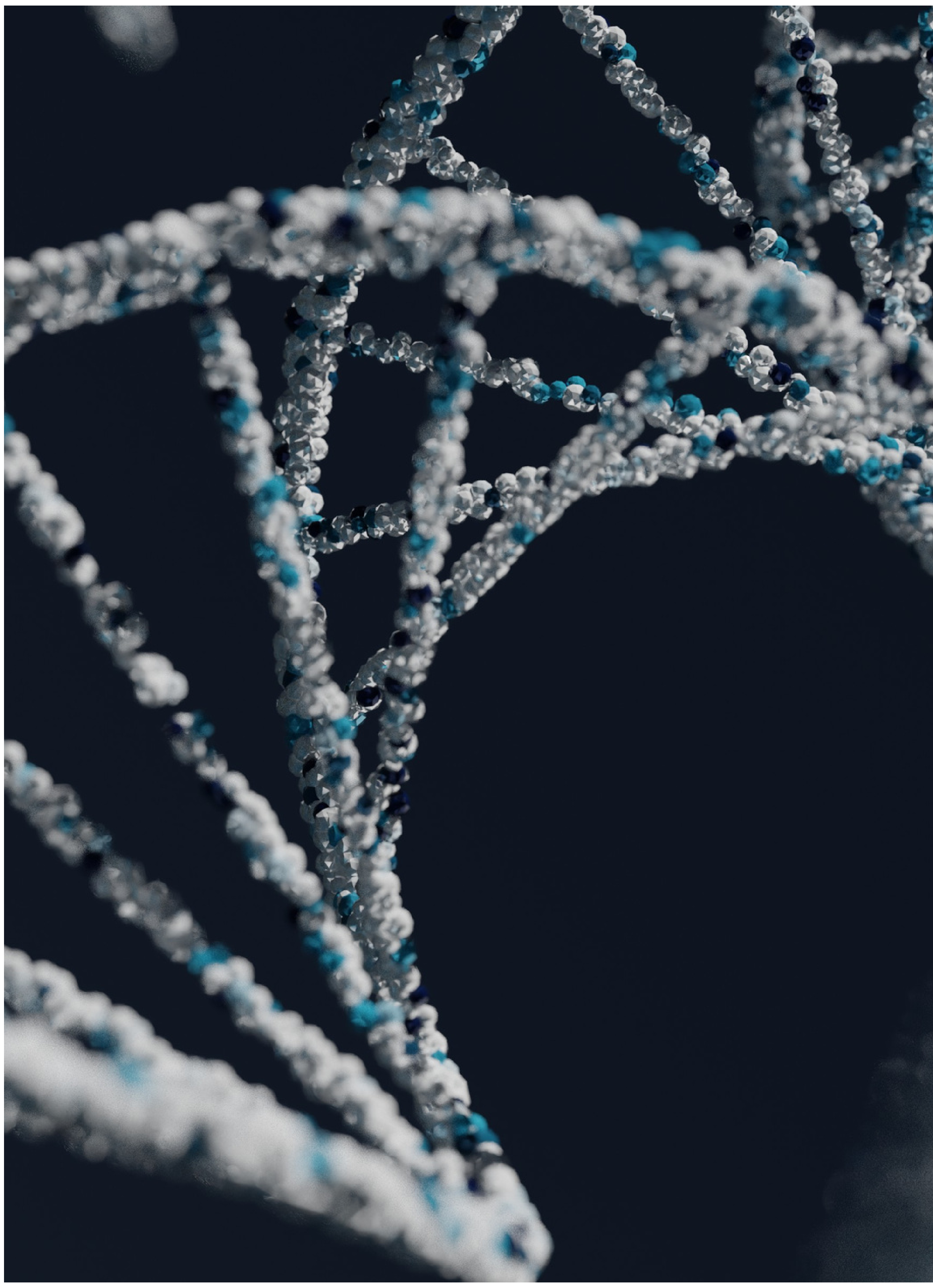
Figure 3

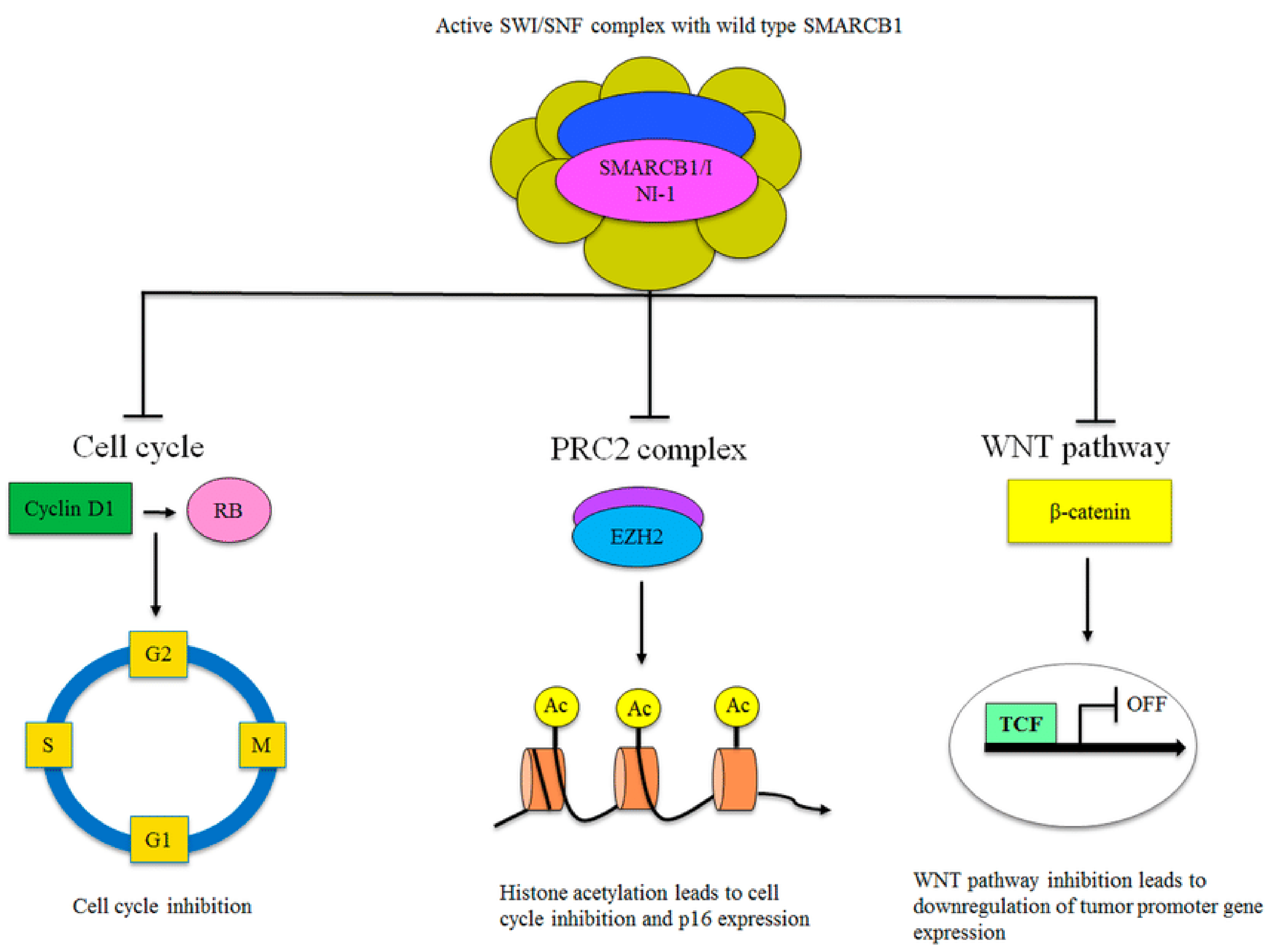
Poorly differentiated cancer cells are too different from surrounding normal cells to function as cells. We all know that the DNA in the nucleus carries the cell's genetic information. In the DNA double helix structure (see Figure 2), there are many bases. If all the bases are in the right place, there is no difference between cells. Poorly differentiated cancer cells are cells with incorrect base arrangements (insertion, amplification, deletion), that is, genetic mutations. So cells with these mutations take on a different shape than normal cells. As you can imagine, undifferentiated cells with genetic mutations are more uncertain, do not know what direction they will go, and has almost no function. [3]

The full name of SMARCB1 in the diagnosis conclusion "consistent with SMARCB1/ Ini1-deficient undifferentiated cancer of the pancreas" mentioned at the beginning is SAI/SNF-related, matrix associated, actin-dependent regulae of chromatin. SWI/ SNF-associated stroma-associated actin-dependent regulators of chromatin subfamily B member 1 (SMARCB1), also known as integrase interactor 1 (INI1), are key components of the chromatin remodeling protein complex. [5] The SWI/SNF complex is a very important chromatin modification protein that regulates gene transcription in organisms, responsible for loosening dense chromosomes and exposing DNA for transcription. Cells need transcription to make the proteins the body needs. Without this complex, humans can die even as embryos. [6] Therefore, the importance of SMARCB1 can be seen, and SMARCB1 is considered to be a true tumor suppressor, which plays a very important role in inhibiting tumor formation and replication. Figure 3 shows how the SMARCB1 gene plays a role in transcription.

The SMARCB1/INI1 gene was first identified in yeast in the late 1980s. [5] By 1994, the human homologous of this gene was isolated in fibroblasts. Although people have long discovered that this genetic defect can cause cancer, but because of the few cases and other reasons have not yet developed an effective way to cure it. Tumors due to SMARCB1 defects are primarily sarcomas [5]. These aggressive tumors usually have a poor prognosis. In addition, refractory and relapsing progressive diseases are also common. [5]

In the past, people often used doxorubicin and ifosfamide as the main drugs for the first-line treatment of advanced disease. The most commonly used treatment for soft tissue sarcomas today is called AIM and consists of doxorubicin (Doxorubicin) plus ifosfamide and Mesa sodium [5]. All of these programs are more or less likely to lead to refractory and progressive diseases (diseases that are difficult to treat, such as cancer cells that are resistant to drugs)[5] At present, biologists are studying more drugs and therapies for SmarCB1-deficient tumors, looking forward to the birth of more effective therapies to bring a line of life to patients in desperate situations.





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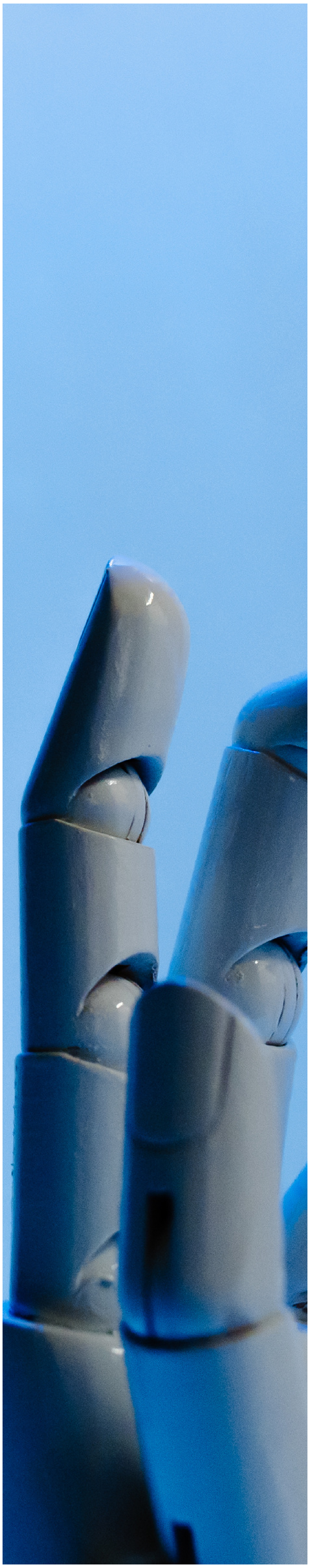

AUTHOR： OLIVIA
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EDITOR: HECATE YE

AI THROAT

The team at Tsinghua University developed an intelligent artificial throat to assist individuals who have.

KEY WORDS

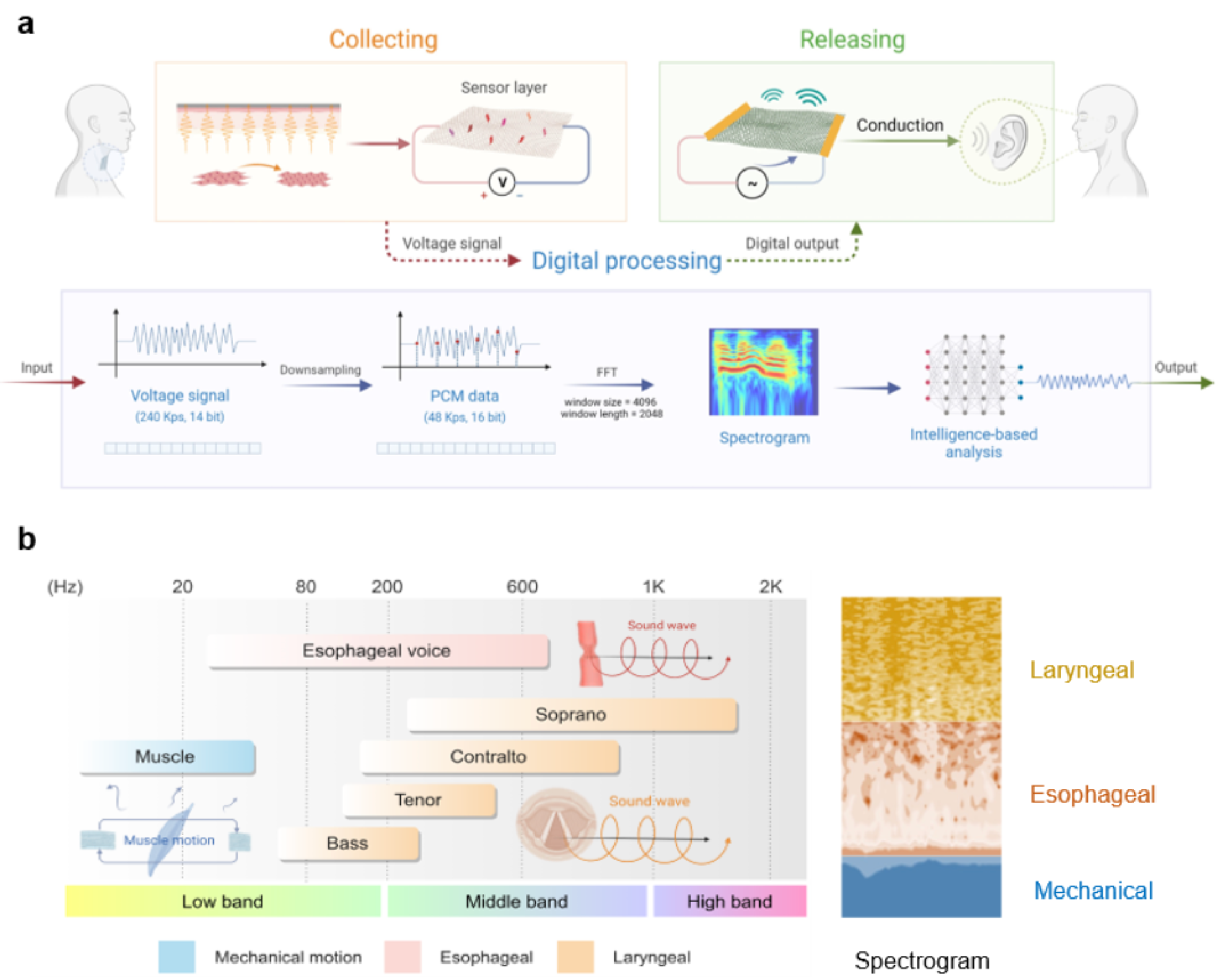
Artificial throat(AT), Amyotrophic Lateral Sclerosis (ALS), Graphene, Wearable Artificial Graphene Throat (WAGT)

SCOPE OF APPLICATION

The causes of speech impairment include diseases that damage the speech center, such as cerebrovascular disease, traumatic brain injury, and neurodegenerative diseases like Alzheimer's. Other causes include conditions like lung-related brain disease, non-ketotic hyperosmolar coma, hypoglycemia, carbon monoxide poisoning, and more. These patients are unable to produce speech voluntarily and require external assistance.

APPLICATION EXAMPLES

A notable example is the trial of the wearable artificial throat by Cai Lei, former Vice President of JD.com and an ALS patient. Cai Lei became the world's first ALS patient to use this wearable artificial throat, which successfully captured and reproduced his pre-illness voice by converting signals from his throat.



INTRODUCTION

Graphene is a two-dimensional crystal composed of carbon atoms with a thickness of only one atom. It possesses extremely high electron mobility, thermal conductivity, and low heat capacity. Therefore, it exhibits high sensitivity to muscle movement, esophageal vibrations, and high-frequency sound waves. It can distinguish various human actions such as low moans, screams, coughs, swallowing, and nodding.

In 2017, the research team first proposed an integrated acoustic device based on graphene that functions as both a receiver and transmitter: utilizing the piezoresistive effect to receive signals and emit sound based on the thermoacoustic effect, achieving simultaneous sound reception and transmission within a single structure.

Researchers utilized a unique laser writing technique in the device fabrication process, which can directly transform a highly cost-effective polyimide film into graphitized porous graphene material.

In their latest achievement, the team developed a smaller, more convenient integrated "artificial throat." This film is connected to a microcontroller measuring only 2 square centimeters, linked by conductors, which can be placed in a pocket. It is equipped with a button-sized battery, making it simple and convenient.

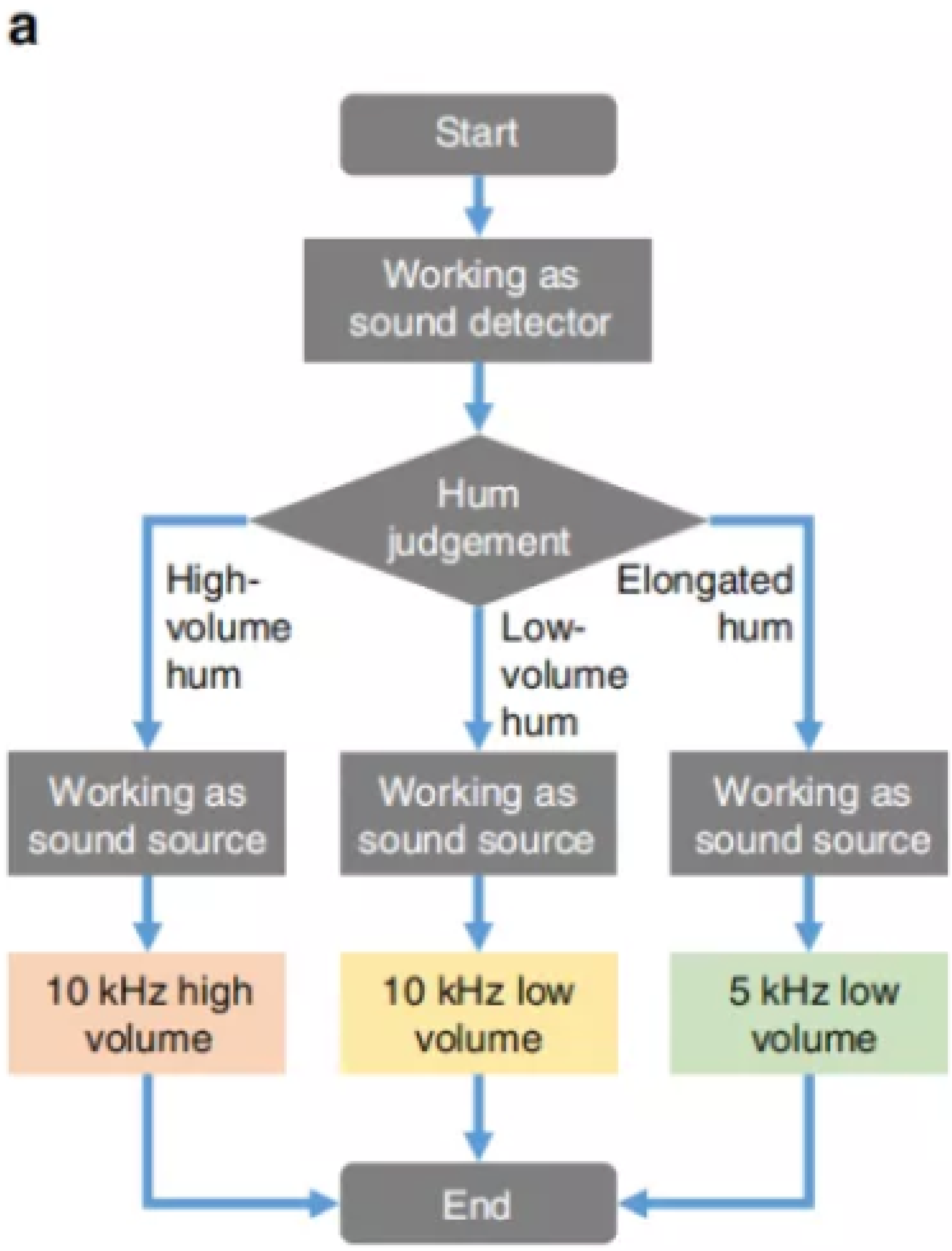
When the graphene film is placed on the patient's throat, the film can detect subtle vibrations in the throat and translate these vibrations into various sounds.

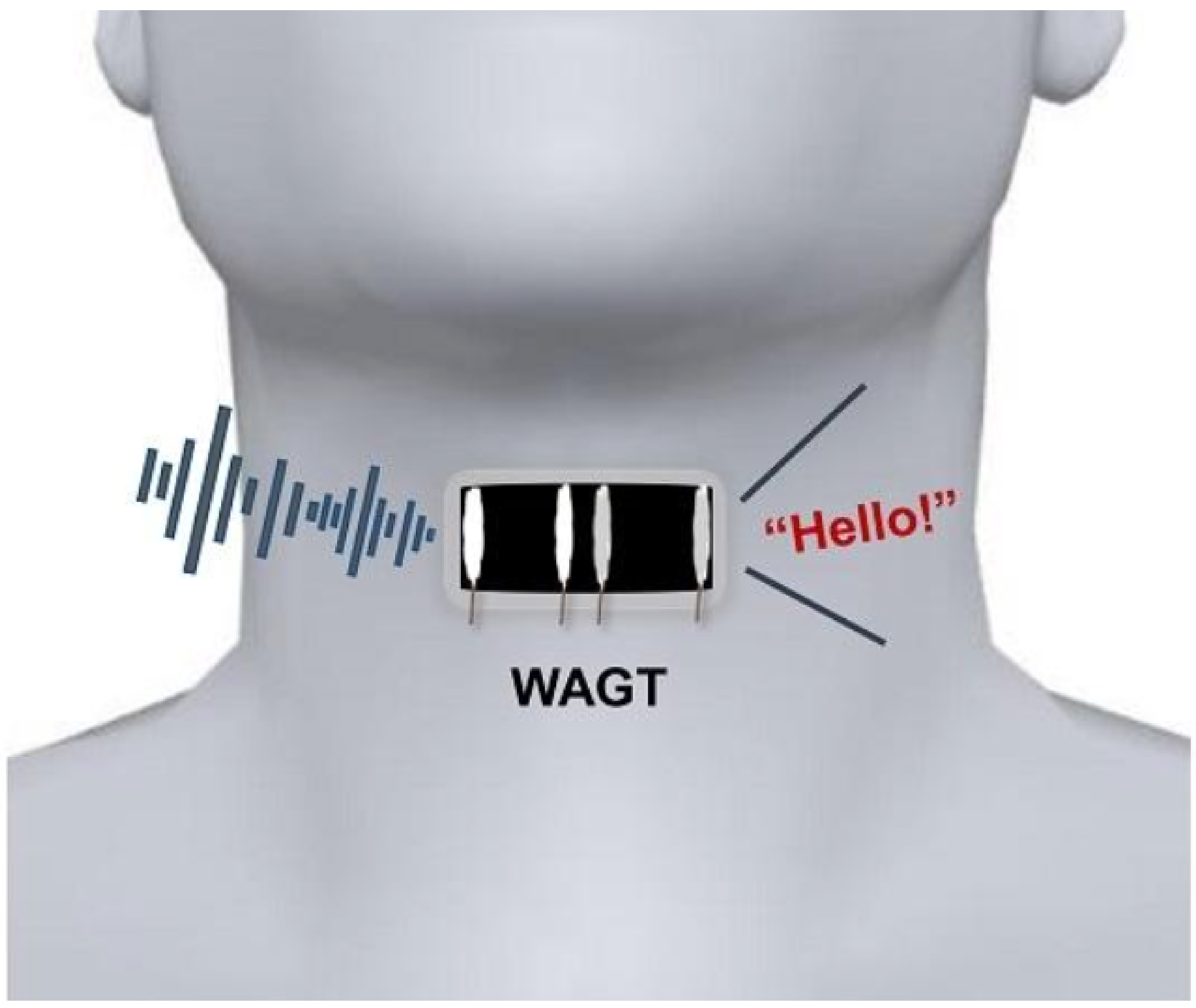
Regarding the underlying principle, the research team stated, "Although deaf-mute individuals cannot speak, the throat can vibrate. We can detect throat vibrations by placing this (graphene material black film) on the outside of the throat. After detecting the vibrations, the next step is to identify different vibrations and then convert them into a 'language code' for deaf-mute individuals."

RESULTS

The experimental results indicate that the artificial throat can detect basic speech elements with an average accuracy of 99.05%. For a laryngectomy patient using this tool to articulate everyday vocabulary, the accuracy exceeds 90%.In summary, although there is significant room for optimization and expansion, such as improving the quality and volume of the sound, enhancing the diversity of speech, and incorporating expressions, the artificial throat, in terms of manufacturing processes, stability, and integrated sound production, has the potential to become a valuable assistive tool for the next generation of speech recognition and interaction systems.

Let the artificial throat benefit more individuals with speech impairments and users of speech interaction!





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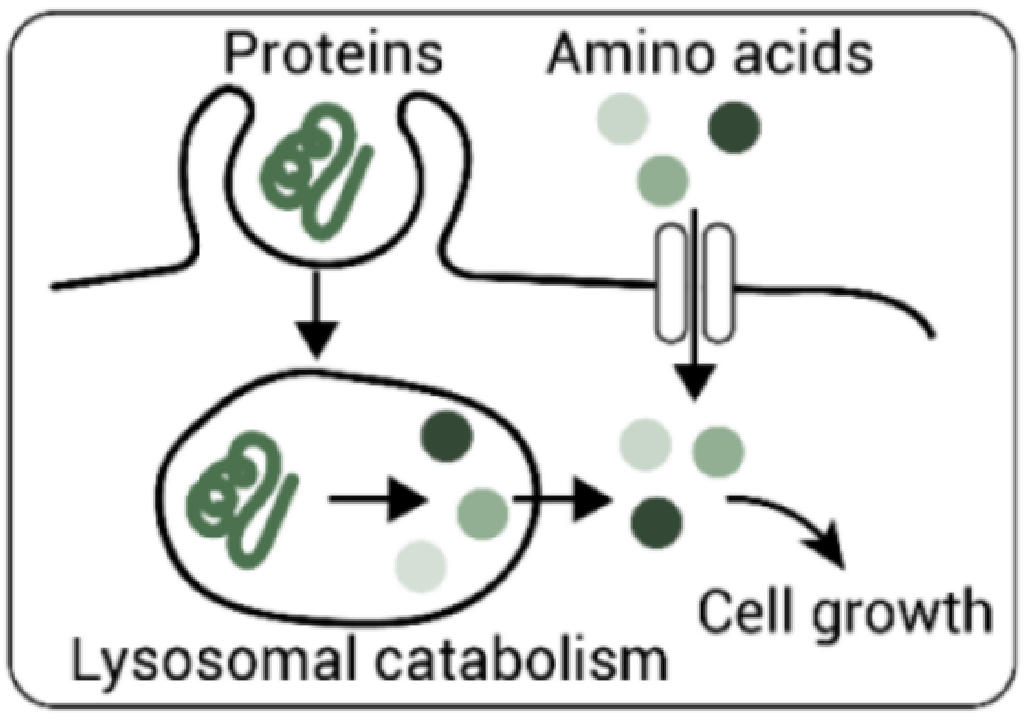
An intelligent artificial throat with sound-sensing ability based on laser-induced graphene | Nature Communications

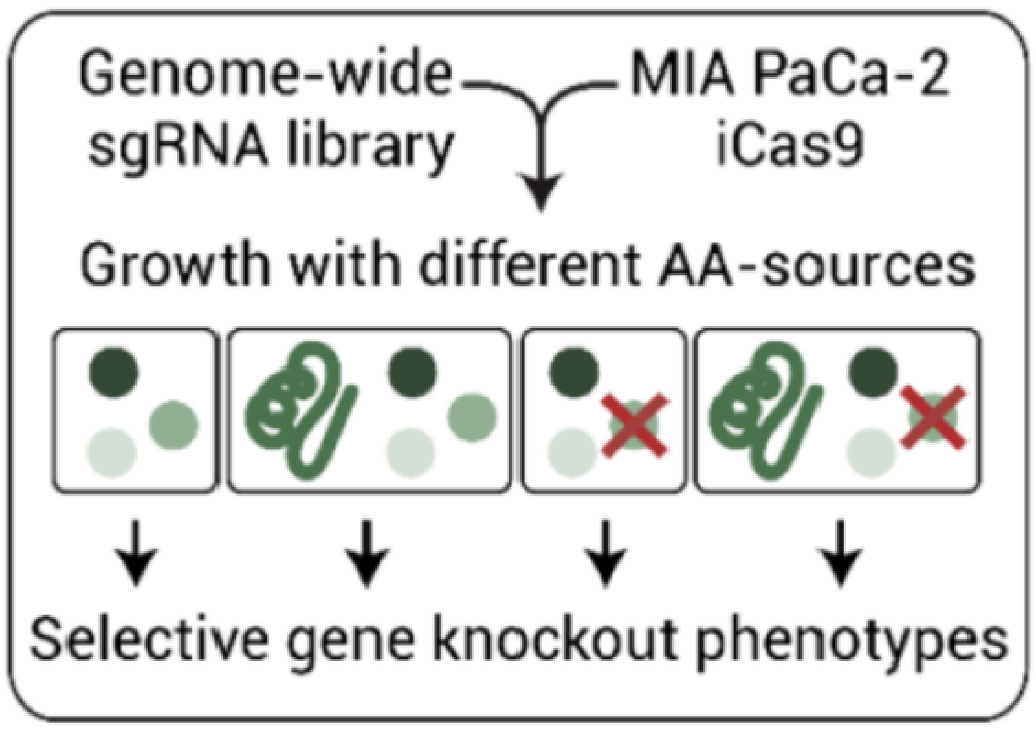
Ren Tian-ling's research group developed an intelligent wearable artificial throat for mixed-modality speech recognition and interaction-Tsinghua University

AUTHOR: SINDY
EDITOR: KATHERINE

CANCER DISAPPEARED! A NOVEL CANCER TREATMENT CAN STARVE CANCER CELLS

Keywords: macropinocytosis, CRISPR, LYSET





WHAT IS MACROPINOCYTOSIS?

Mammalian cells are surrounded by various nutrients, including amino acids and extracellular proteins. Under conditions of abundant nutrition, cells tend to take up free amino acids to meet their physiological needs. However, most amino acids in the blood circulation and extracellular space exist in the form of proteins. In order to obtain these essential substances, cells can actively absorb environmental proteins and transport them to lysosomes—the cellular organelles that require enzymes for digestion. The primary function of these lysosomes is to degrade proteins into their constituent amino acids. In this way, lysosomes can generate endogenous sources of nutrients in a cell-starved state, thereby maintaining normal cellular functions.

In cancer cells, this process is often significantly exploited, especially because cancer cells are typically found in nutrient-deprived microenvironments. Consequently, most of their energy and proteins are acquired through a mechanism known as autophagy. Autophagy, in the context of cancer cells, refers to the cell membrane contracting and enclosing a large amount of extracellular nutrients in response to stimuli such as nutrient factors. These nutrients are then transported to lysosomes (critical degradation compartments within the cell) for breakdown. Lysosomes break down proteins into amino acids, generating an intracellular nutrient source to maintain cellular functions under starvation conditions (refer to the diagram).

FINDING THE "FEEDER" FOR CANCER CELLS

Lysosomes are the primary degradation centers within cells, and dysfunction in their function can lead to rare and common diseases. Certain viruses, including the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), hijack lysosomes to enter cells, initiating a destructive infection cycle. A German research team led by Richard et al. discovered a small protein called LYSET, and the latest research indicates that the LYSET protein is crucial for allowing cancer cells to undergo metabolic transformation. This study also provides a new target for cancer treatment.

The normal functioning of lysosomes is crucial for LYSET. In cells lacking LYSET, the transport of enzymes to lysosomes is severely disrupted, leading to the accumulation of undigested substances in lysosomes. Additionally, the research team found that LYSET selectively acts when cells consume extracellular proteins. Cancer cells often rely on extracellular proteins to provide amino acids. LYSET helps anchor N-acetylglucosamine-1-phosphotransferase to the Golgi membrane for the transport of lysosomal signals to mannose-6-phosphate-tagged enzymes. Without LYSET, the degradative enzymes in lysosomes are depleted, losing the ability to digest extracellular proteins. In other words, cancer cells die because they cannot digest their food.

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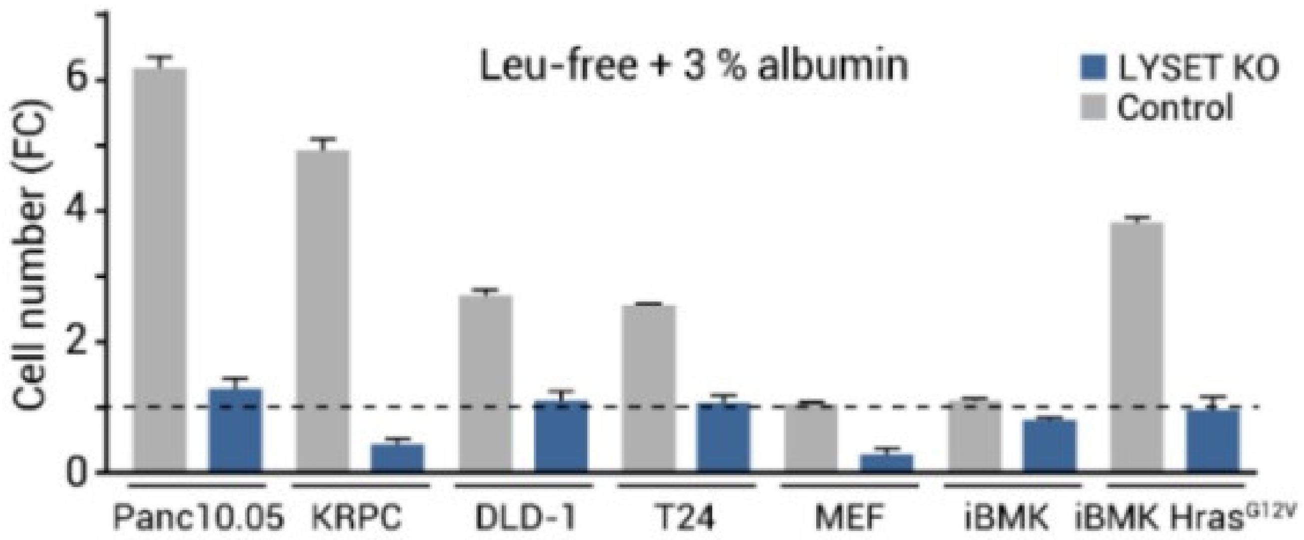
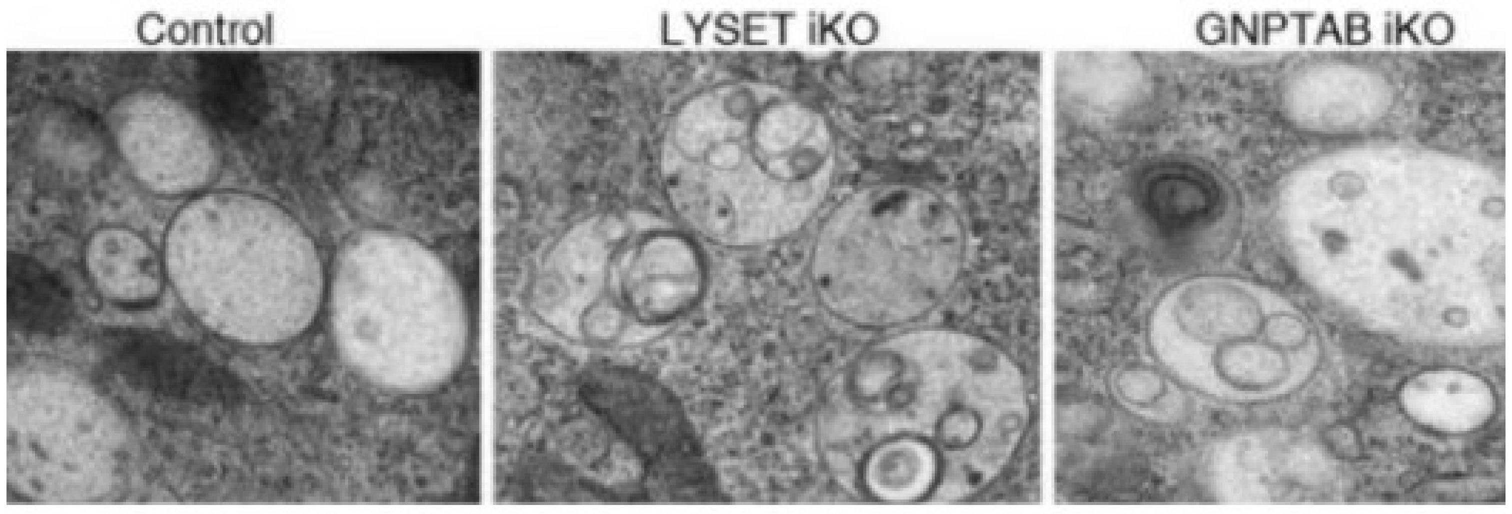
CRISPR SCREENING IDENTIFIES LYSET AND KNOCKOUT

"CRISPR stands for 'Clustered Regularly Interspaced Short Palindromic Repeats,' and it is the basis for the CRISPR-Cas9 genome editing technology."

Using pancreatic cancer cells as an example, the researchers conducted experiments showing that, under conditions of nutrient abundance, LYSET is a non-essential gene for cell viability and growth when knocked out using CRISPR. However, in a culture medium lacking leucine but containing 3% albumin, the absence of LYSET strongly inhibited the proliferation and vitality of all cancer cell lines, mouse embryonic fibroblasts, and kidney cells. This suggests that LYSET is an essential gene when extracellular proteins are essential nutrients, amino acids are depleted in vitro, and during tumor growth in vivo (see the figure below, where the blue represents the experimental group and gray represents the control group).

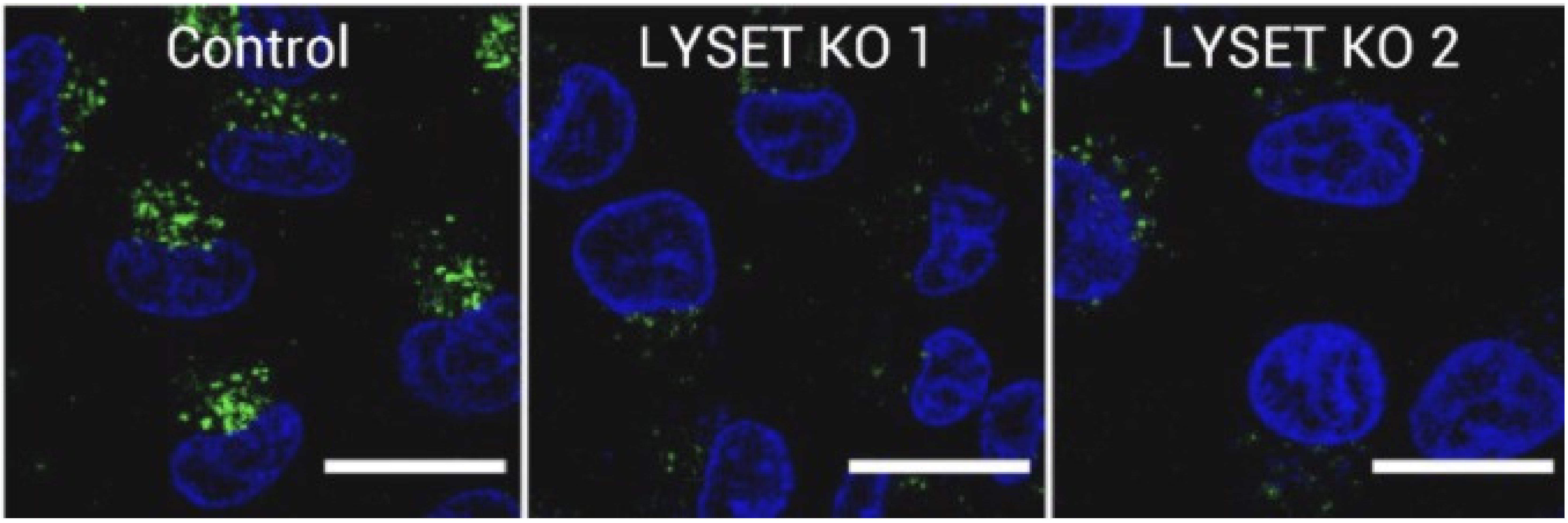
Further experiments on LYSET function indicate that LYSET is a core component of the mannose-6-phosphate (M6P) pathway in the lysosomal enzyme transport process. This pathway is essential for lysosomal enzyme transport and, consequently, for lysosomal nutrient generation. Lysosomes, acting as the cell's stomach, digest proteins within them. However, in the absence of LYSET, cancer cells' lysosomes lack enzymes and can no longer digest proteins (see the figure below).





LYSET IS AN ESSENTIAL FACTOR REQUIRED FOR LYSOSOMAL DEGRADATION OF CARGOS

To further investigate the role of LYSET, researchers conducted experiments using fluorescently labeled bovine serum albumin. Cells with knocked-out LYSET and a control group were placed in culture, and the results showed that the experimental group cells were unable to absorb the fluorescent color, indicating a reduction in green fluorescent labeling (see the figure below).



PROSPECT OF THIS NEW TREATMENT

LYSET is associated with various human conditions: Cells lacking LYSET lack a functional mannose-6-phosphate pathway, providing a mechanistic explanation for the connection between LYSET gene mutations and genetic syndromes, such as lysosomal storage diseases II and III. Additionally, LYSET enables cancer cells to use extracellular proteins as a nutrient source in harsh tumor environments, providing flexibility and resilience to metabolic challenges. Therefore, inhibiting LYSET and the lysosomal enzyme transport pathway may be a promising strategy to suppress key metabolic adaptations in cancer.

AUTHOR： PENNY
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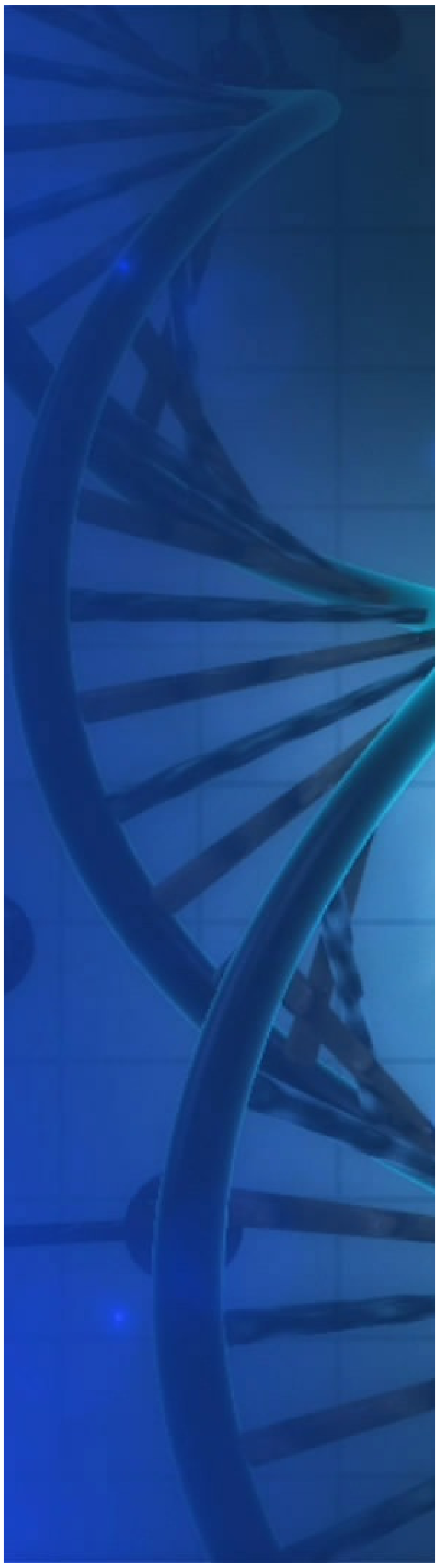
WORLD'S FIRST! CRISPR GENE EDITING THERAPY ENTERS THE MARKET FOR THE FIRST TIME. WRITING DEPARTMENT PENNY PANG NOVEMBER



ABSTRACT

CRISPR gene editing is a revolutionary biotechnology that provides an accurate and efficient method for modifying the genes of organisms. Currently, this technology has been widely used in laboratory research and has made some progress in preclinical studies for treating gene-related diseases. However, due to concerns about safety and efficacy, CRISPR gene editing therapy has yet to enter the market. The UK regulatory authority recently became the first to approve a CRISPR-Cas9 gene editing therapy, named Casgevy, marking a historic milestone. This therapy is designed to treat sickle cell anemia and β-thalassemia, signaling a new peak in the field of biotechnology. This article will focus on introducing the principles, safety, and prospects of the Casgevy therapy.

Keywords: Casgevy gene editing therapy, CRISPR/Cas system, sickle cell anemia, β-thalassemia.

Sickle Cell Disease (SCD) is an autosomal dominant genetic hemoglobin (Hb) disorder. Due to the substitution of valine for glutamic acid at the sixth position of the β-globin chain, hemoglobin S (HbS) undergoes an abnormality, resulting in red blood cells taking on a sickle shape, hence the name. Within the affected individual, sickle-shaped cells aggregate to form long and twisted chains of cell polymers. These polymerized cells cannot freely move within the blood vessels. As they pass through some smaller arteries and veins, they aggregate into more clusters, adhering to the vessel walls. At this point, pain, organ damage, and even strokes can occur throughout the body.

β-Thalassemia is a form of anemia caused by genetic defects. Mutations in the globin gene affect the ratio of globin peptide chain production, leading to a decrease in hemoglobin levels in the blood. This disruption affects red blood cells in the bone marrow and circulating red blood cells, ultimately causing anemia. The condition is commonly observed in infants, with symptoms including weakness, pale or jaundiced skin, facial bone deformities, delayed growth, abdominal swelling, and, in severe cases, can lead to death.

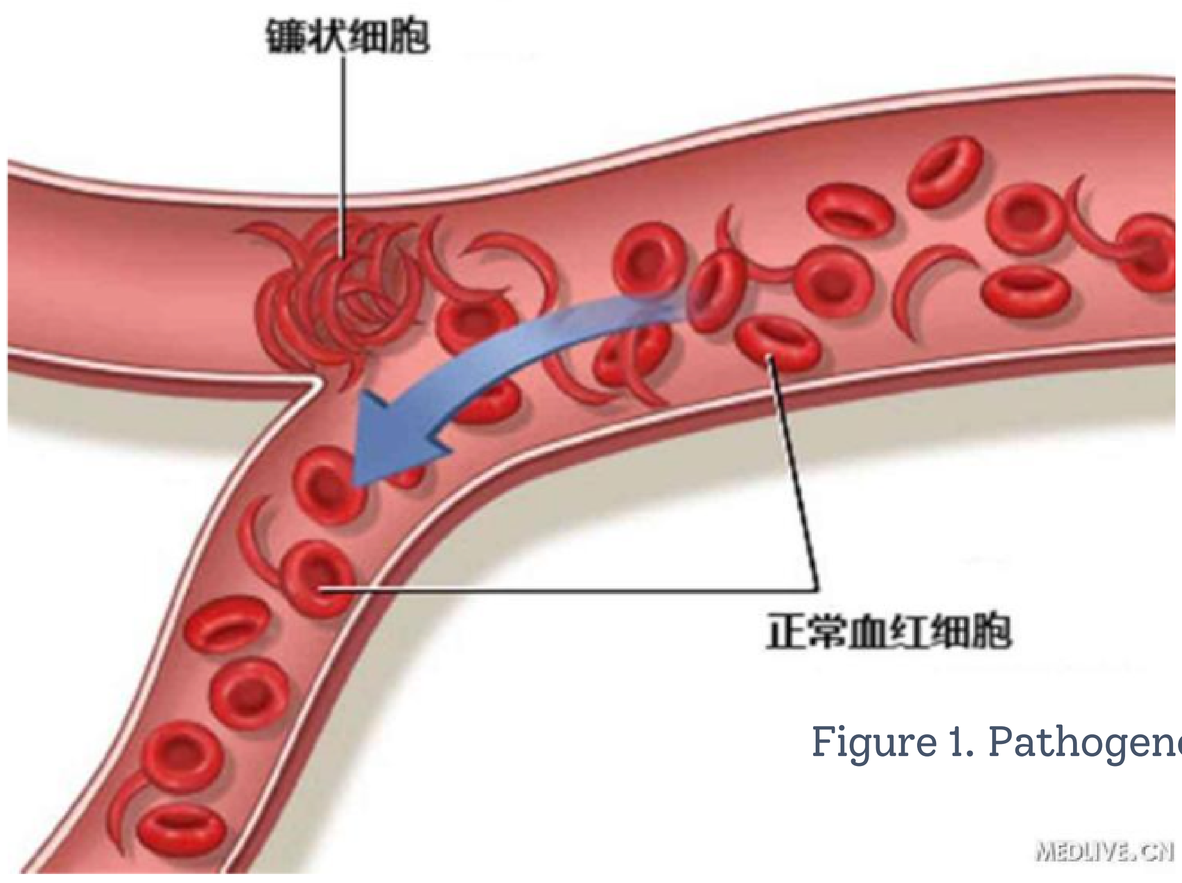
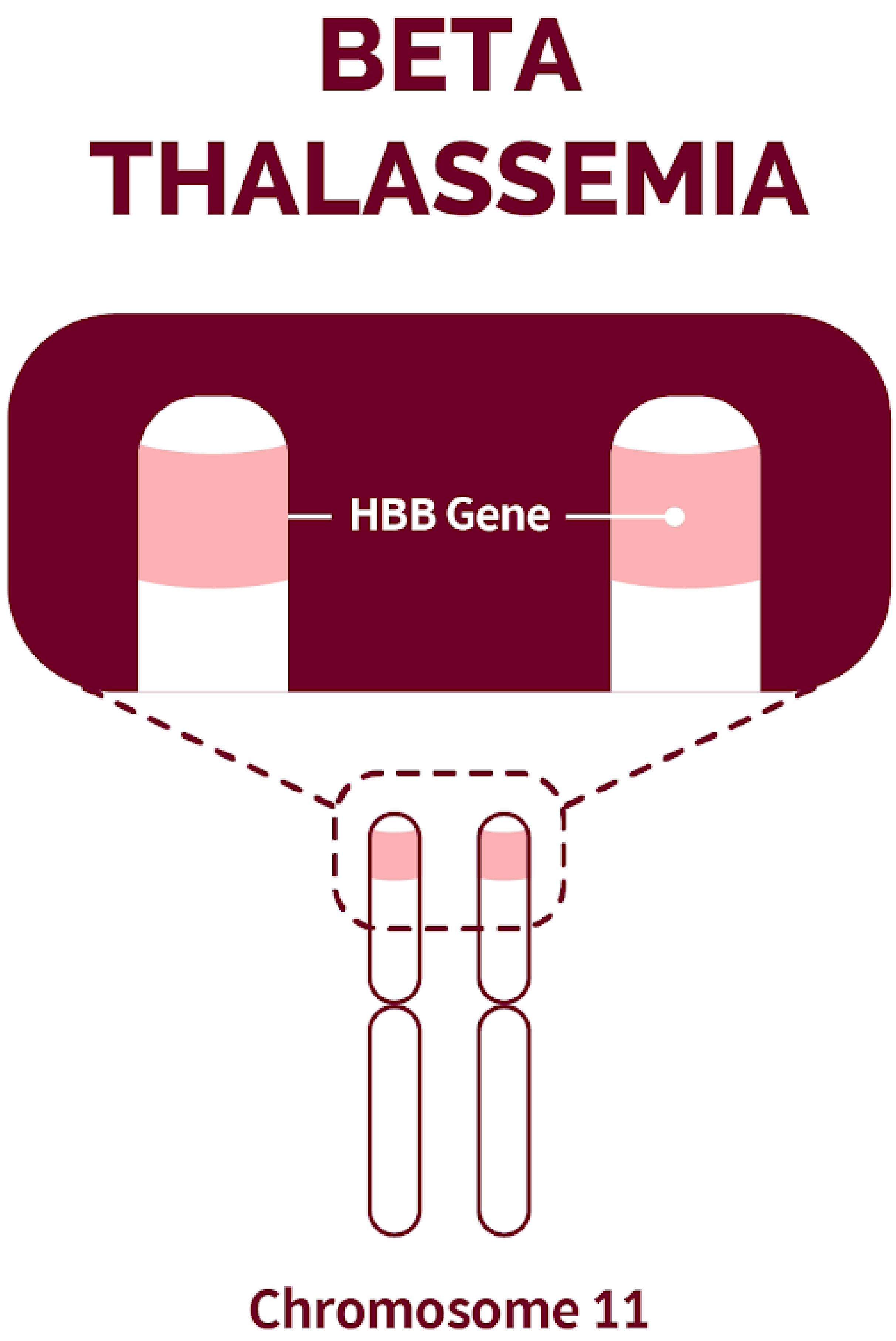


Figure 1. Pathogenesis of Sickle Cell Disease

As both of these anemias are caused by genetic errors, there are currently no known universally successful treatment methods. Julian Beach, the director of the Medicines and Healthcare Products Regulatory Agency (MHRA), stated in a release, "Sickle cell disease and β-thalassemia are both painful, lifelong conditions that can be fatal in certain circumstances. To date, bone marrow transplantation (which must come from a closely matched donor and carries rejection risks) is the only treatment option." Therefore, there is an urgent need to develop a genetic-level therapy that can fundamentally change the current treatment landscape. On November 16th, a gene-editing therapy called Casgevy was born and approved to enter the market. It was developed by the Swiss company CRISPR Therapeutics, founded by Nobel laureate Emmanuelle Charpentier, in collaboration with the Boston-based biotechnology company Vertex Pharmaceuticals. This therapy will be used to treat sickle cell disease and β-thalassemia.



Researchers extract hematopoietic stem cells from a patient's bone marrow and use CRISPR-Cas9 to edit the hemoglobin genes encoded in these cells. Once Cas9 reaches the target gene BCL11A required for Casgevy, it cuts the DNA double strand. BCL11A typically prevents the fetus from producing a specific type of hemoglobin. By disrupting this gene with Casgevy, fetal hemoglobin production begins, and this hemoglobin does not exhibit abnormalities seen in adults with sickle cell disease or beta-thalassemia.

Before transporting the gene-edited cells back into the body, individuals undergo a treatment (preconditioning) to prepare the bone marrow to receive the modified cells. Once infused, the stem cells produce red blood cells containing fetal hemoglobin, alleviating symptoms by increasing tissue oxygenation. According to a press release from MHRA, "Patients may need to be hospitalized for at least a month to allow the gene-edited cells to start producing red blood cells with stable hemoglobin forms in the bone marrow."

Regarding trials for treating sickle cell disease with this therapy, researchers conducted sufficient follow-up on 29 out of 45 participants, finding that at least 28 individuals experienced complete relief from debilitating pain attacks for at least a year after Casgevy treatment, demonstrating the therapy's effectiveness.

As for the therapy's safety, further observation and improvements are needed. Trial participants experienced side effects, including nausea, fatigue, fever, and an increased risk of infection, but no significant safety issues were identified. MHRA and the manufacturer are monitoring the safety of this technology and will release further results. Another concern surrounding this approach is that CRISPR-Cas9 can sometimes lead to unexpected gene modifications and produce unknown side effects, a problem that urgently needs addressing.

Figure 2. A researcher at the Max-Delbrueck Molecular Medicine Center observes the CRISPR/Cas9 process through a stereomicroscope while working with a culture dish.

Future Perspectives

Given the involvement of stem cell editing, this therapy may currently be accessible only to affluent countries with advanced healthcare systems. In the future, there is hope for the development of cost-effective and more efficient gene therapies to make them more universally available. The entry of CRISPR-Cas9 gene-editing technology into the market presents opportunities and challenges. While it effectively addresses diseases, attention must be given to potential side effects, especially false gene modifications by the CRISPR-Cas9 system, which can have unknown or irreversible impacts on the treated cells.

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AUTHOR: CHLOE

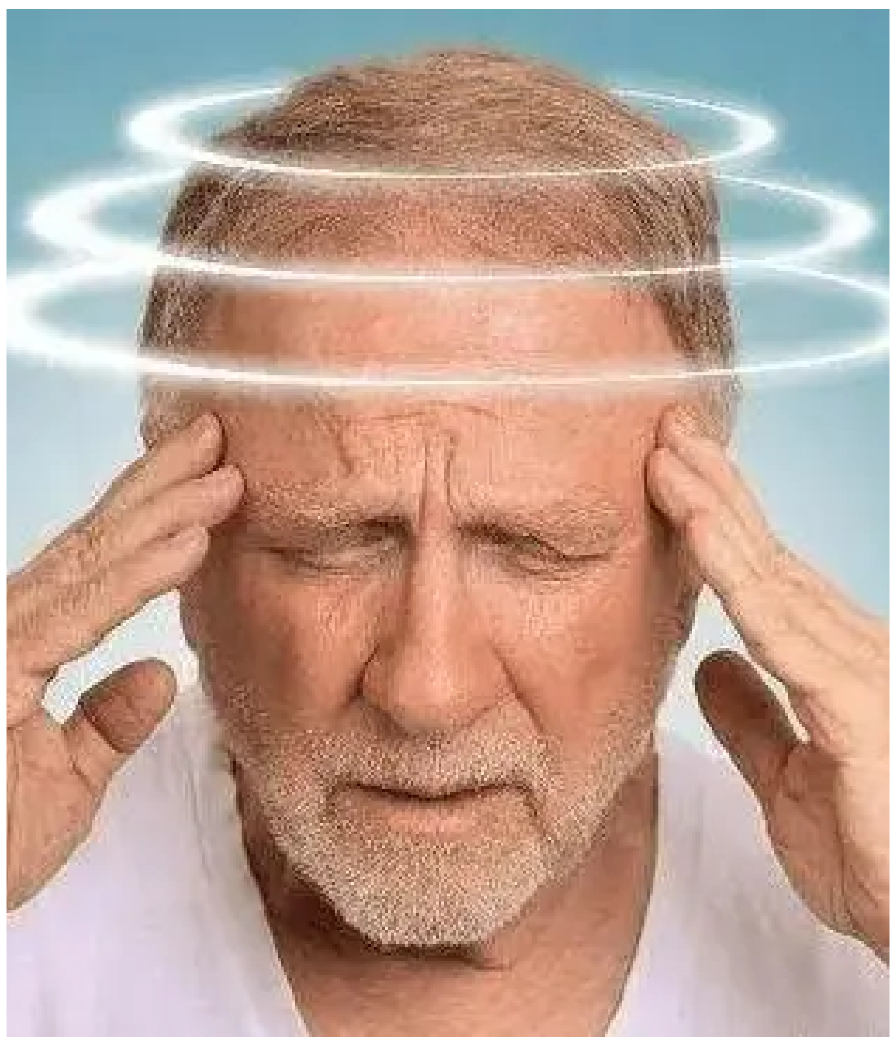
SPINOCEREBELLAR ATAXIA

Keywords: Spinocerebellar Ataxia(SCA), symptoms, cause, treatment

INTRODUCTION

Ataxia is defined as the lack of control over specific physical motions such as “gait stability, eye movement, and speech” (Bhandari). Spinocerebellar Ataxia (SCA) is a type of rare disease that is a hereditary disease that primarily affects the cerebellum (function to “coordinate and plan movement and maintain balance”) and the worst part is that it gets worse over time (“Rare”).

However, it isn’t just affecting the cerebellum, it focuses on attacking different parts of central neural systems too, including “pontine nuclei, spinal cord, peripheral nerves, cortex, basal ganglia, etc” (Bhandari). By 2023, there are more than 40 types of SCA have been found. People distinguish them using SCA followed by the number, which “indicates the order in which experts discovered the associated mutations” (“Spinocerebellar”). Half of the cases were SCA1, 2, 3, and 6, and the most typical case is SCA3 (Bhandari).



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Symptoms and Cause of symptom

People with Spinocerebellar Ataxia will have problems with movements and balancing including but not limited to "involuntary eye movements, poor hand-eye coordination, problems with balance and coordination, slurred speech, and uncoordinated walking" ("Spinocerebellar"). This is because the nucleotides "C, A, and G which code for the amino acid" of people with this disease will repeat multiple times ("Rare"). "The abnormal proteins seem to aggregate within the neurons of the cerebellum and the spinal cord, causing them to die" ("Rare"). To better understand what the death of neurons has on us, we first need to know what neurons did. "Neurons send their axons carrying inputs from the spinal cord, the brain and the internal ear through the brain stem into the cerebellum" ("Rare"). When it gets there, the cerebellum makes use of this data to arrange and regulate movement while preserving equilibrium ("Rare"). People with Spinocerebellar Ataxia may also have problems "processing and remembering information" ("Spinocerebellar"). This is due to the fact that the disabled or the death of neurons would cause people to become less capable of remembering and doing daily duties ("Brain").

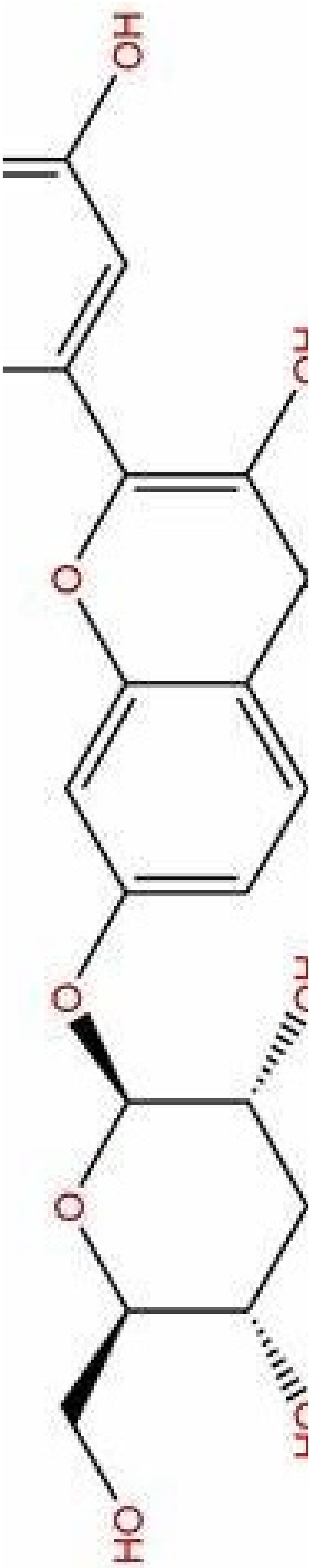
Treatments

FDA, the US Food and Drug Administration hasn't been approved for any "symptomatic or neuroprotective treatments" (Ghanekar). As with many diseases, treatment for SCA focuses on treating its symptoms, "with most clinical trials involving oral medications" (Ghanekar). Riluzole, for example, is an oral medicine for patients with symptoms like amyotrophic lateral sclerosis (ALS) (Ghanekar). Another example is valproic acid, which is an "anticonvulsant and histone deacetylase (HDAC) inhibitor used to treat both seizures and bipolar disorder" (Ghanekar). "Emerging disease modifying therapies are being developed" (Ghanekar).

Examples include the well known technique for gene editing-CRISPR, which have been found to successfully delete the multiple repeat of CAG from a SCA3 individual (Ghanekar). Other disease modifying therapies include "AAV-mediated gene therapy and ASOs to address SCA at its source"(Ghanekar)

AUTHOR: ZHIYUAN

EW HOPE! NATURAL PLANT ACHIEVEMENTS DEMONSTRATE STRONG ENTIAL IN THE TREATMENT OF LUNG CANCER



Keywords: Lung cancer, NSCLC, plant, treatment

INTRODUCTION

Lung cancer is one of the most common malignant tumors worldwide, especially non-small cell lung cancer (NSCLC) which dominates. Significant progress has been made in the treatment of EGFR mutations, but with the emergence of drug resistance, scientists are searching for new solutions. A recent study published in Cell Reports by Professor Qian Xu's team from Nanjing Medical University revealed that a natural plant compound, quercetin, exhibits excellent growth inhibition in the treatment of NSCLC carrying EGFR T790M mutation.

BACKGROUND: LUNG CANCER AND EGFR MUTATIONS

Lung cancer is one of the most deadly cancers, and NSCLC accounts for the majority of lung cancer cases. EGFR mutations are the main driving factor of NSCLC, and EGFR mutations account for up to 85% of non-small cell lung cancer. Although EGFR tyrosine kinase inhibitors (TKIs) have achieved significant therapeutic effects, the emergence of drug resistance limits their long-term efficacy. Among them, the EGFR T790M mutation is one of the main reasons for drug resistance.

THE DISCOVERY AND MECHANISM OF ACTION OF QUERCETIN

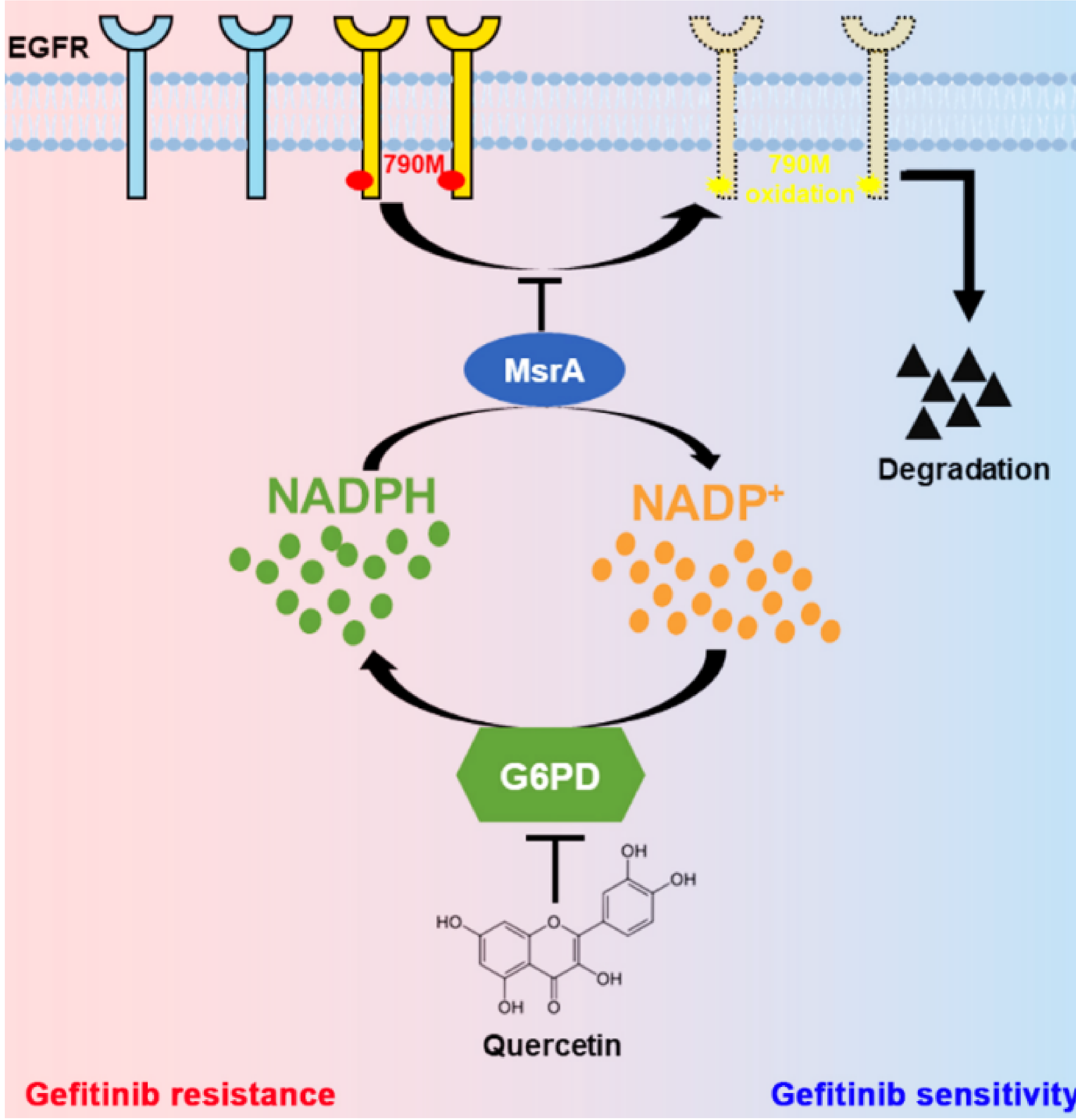
Quercetin is a natural plant compound widely believed to have positive effects in the prevention and treatment of various diseases. Professor Qian Xu's team's research found that quercetin has a strong growth inhibitory effect on NSCLC carrying EGFR T790M mutation. Specifically, quercetin inhibits the activity of glucose-6-phosphate dehydrogenase (G6PD) by targeting, leading to a decrease in NADPH levels and preventing MsrA from providing sufficient reducing power to reduce the oxidized M790 on EGFR T790M, resulting in the degradation of EGFR. More importantly, quercetin also showed a synergistic effect with Gefitinib, enhancing the therapeutic effect on NSCLC.

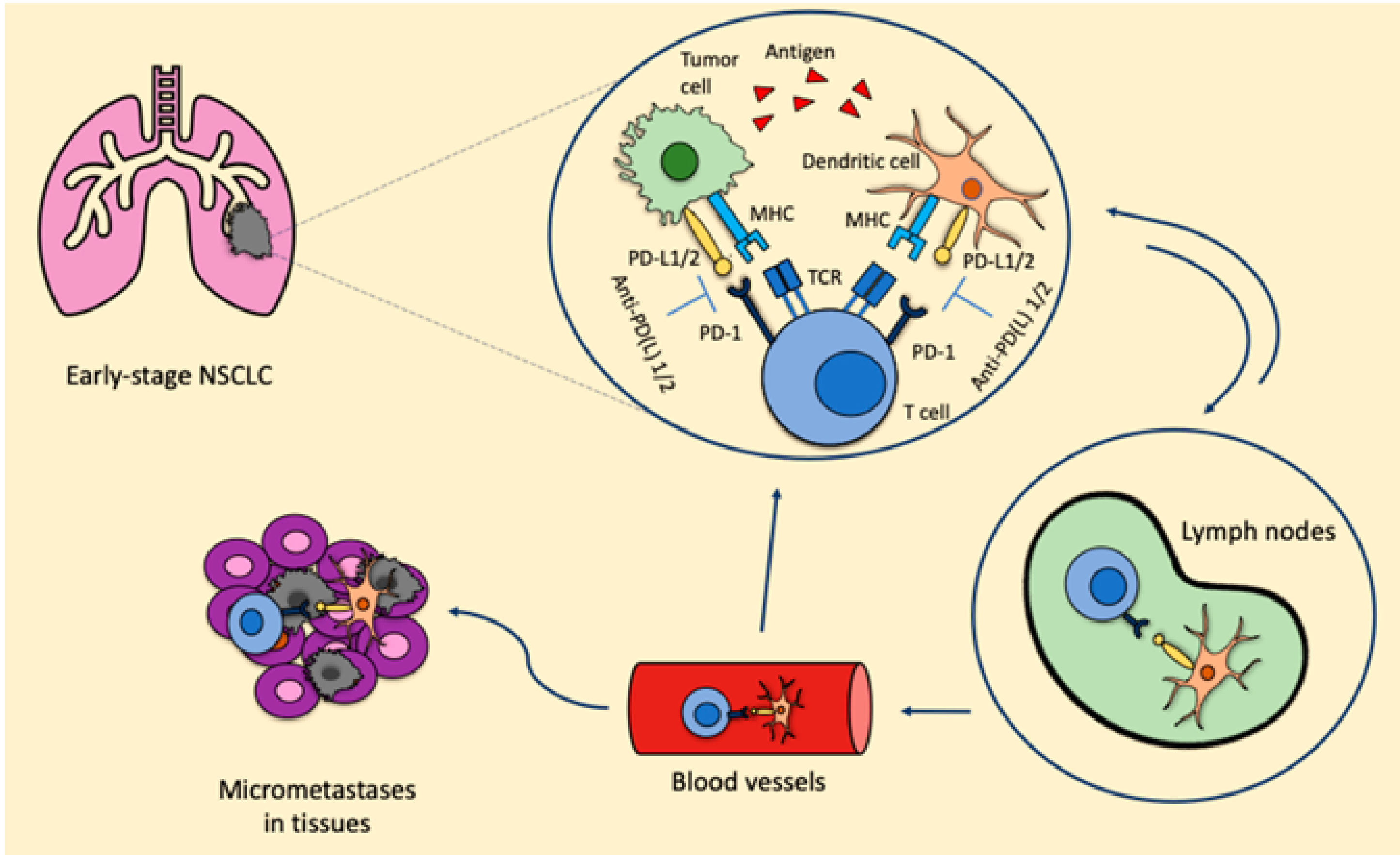
The role of quercetin in tumor metabolism

Research has found that G6PD is highly expressed in lung cancer tissue and is associated with poor prognosis. Analysis of NSCLC clinical samples showed that patients carrying EGFR T790M mutations had higher levels of G6PD protein in tumor tissue, and high levels of G6PD protein indicated that EGFR T790M mutations appeared earlier during TKIs treatment. This discovery emphasizes the important role of G6PD in the development of lung cancer and provides a theoretical basis for the application of quercetin.

CONCLUSION: The Power of Natural Plant Compounds

The discovery of quercetin not only expands our understanding of the role of natural plant compounds in cancer treatment but also provides a new therapeutic option for lung cancer patients. Its growth inhibition properties and synergistic effects with conventional drugs offer researchers new directions for investigation. This breakthrough brings a new dawn for lung cancer patients and solidifies the foundation for the future application of natural plant compounds in cancer treatment.



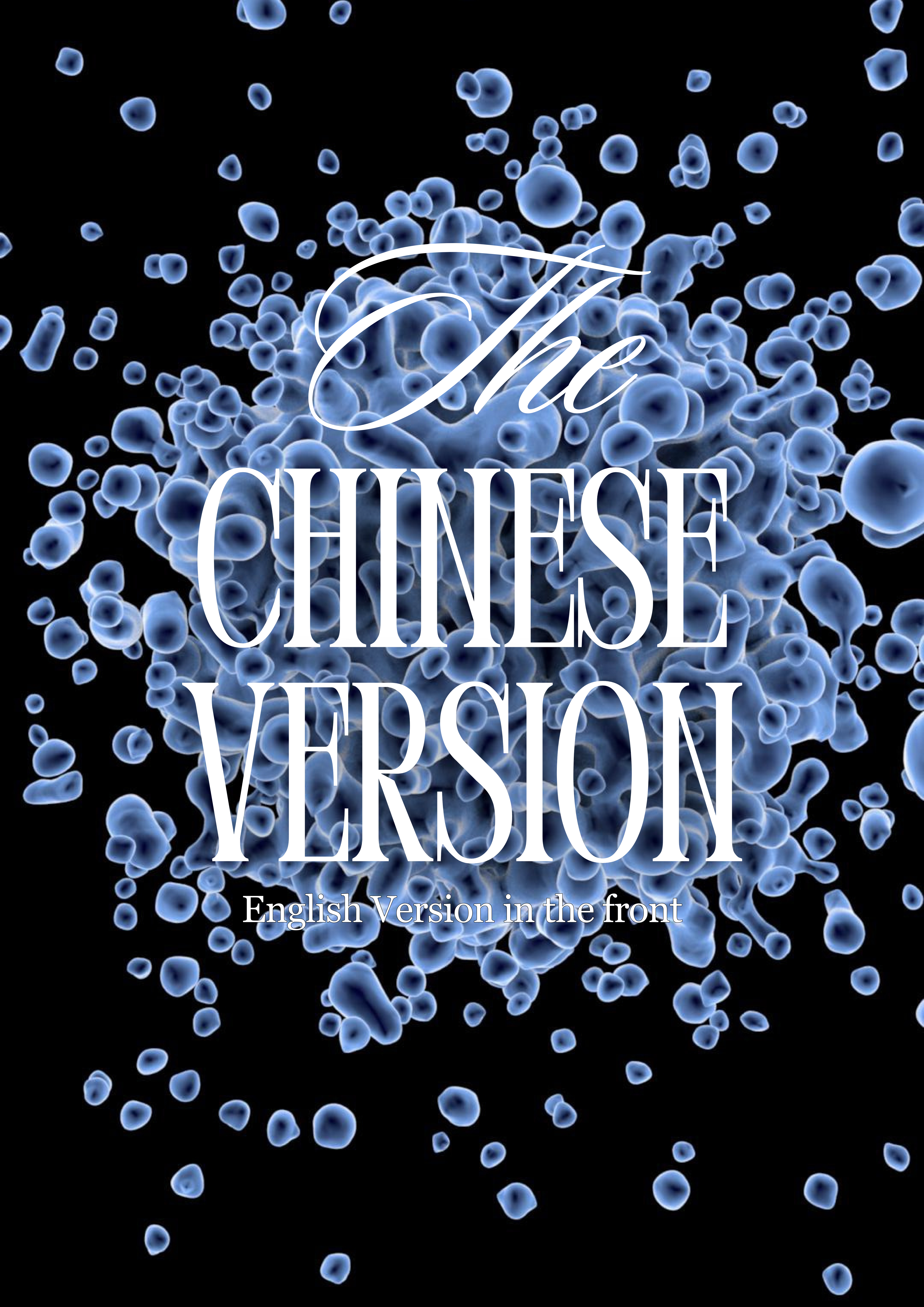


The role of quercetin in tumor metabolism

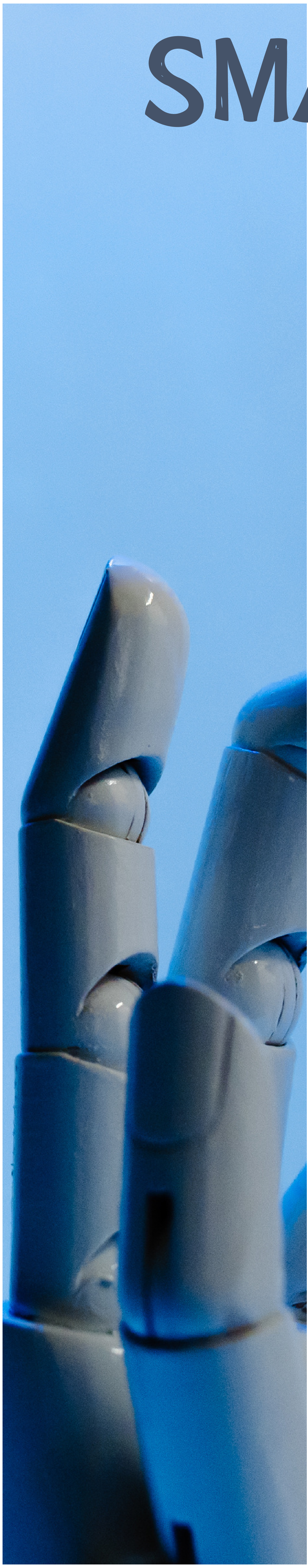
Outlook: The therapeutic potential of quercetin
This study provides a clear understanding of the molecular targets and mechanisms of action of quercetin in the treatment of EGFR T790M mutant NSCLC. Quercetin may become a new therapy to overcome resistance caused by EGFR T790M mutation during EGFR TKIs treatment. In addition, quercetin also demonstrated a synergistic effect when used in combination with Gefitinib, providing new ideas for the design of future treatment plans. This study by Nanjing Medical University has injected new hope into the field of lung cancer treatment, and the discovery of quercetin may become an important component of NSCLC treatment in the future.

The CHINESE VERSION

English Version in the front



AUTHOR: RACHELLE WU

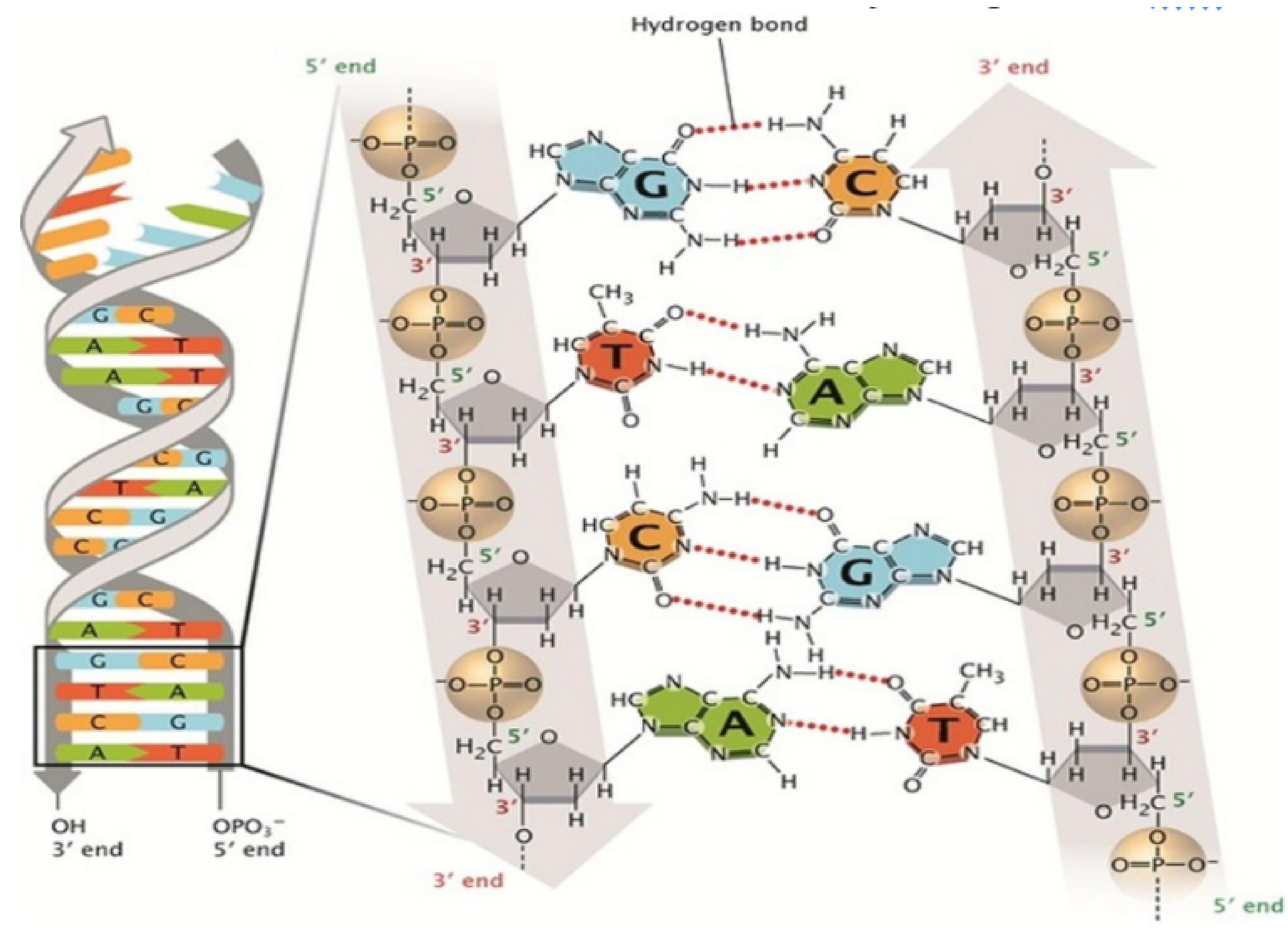


SMARCB1缺失型未分化癌

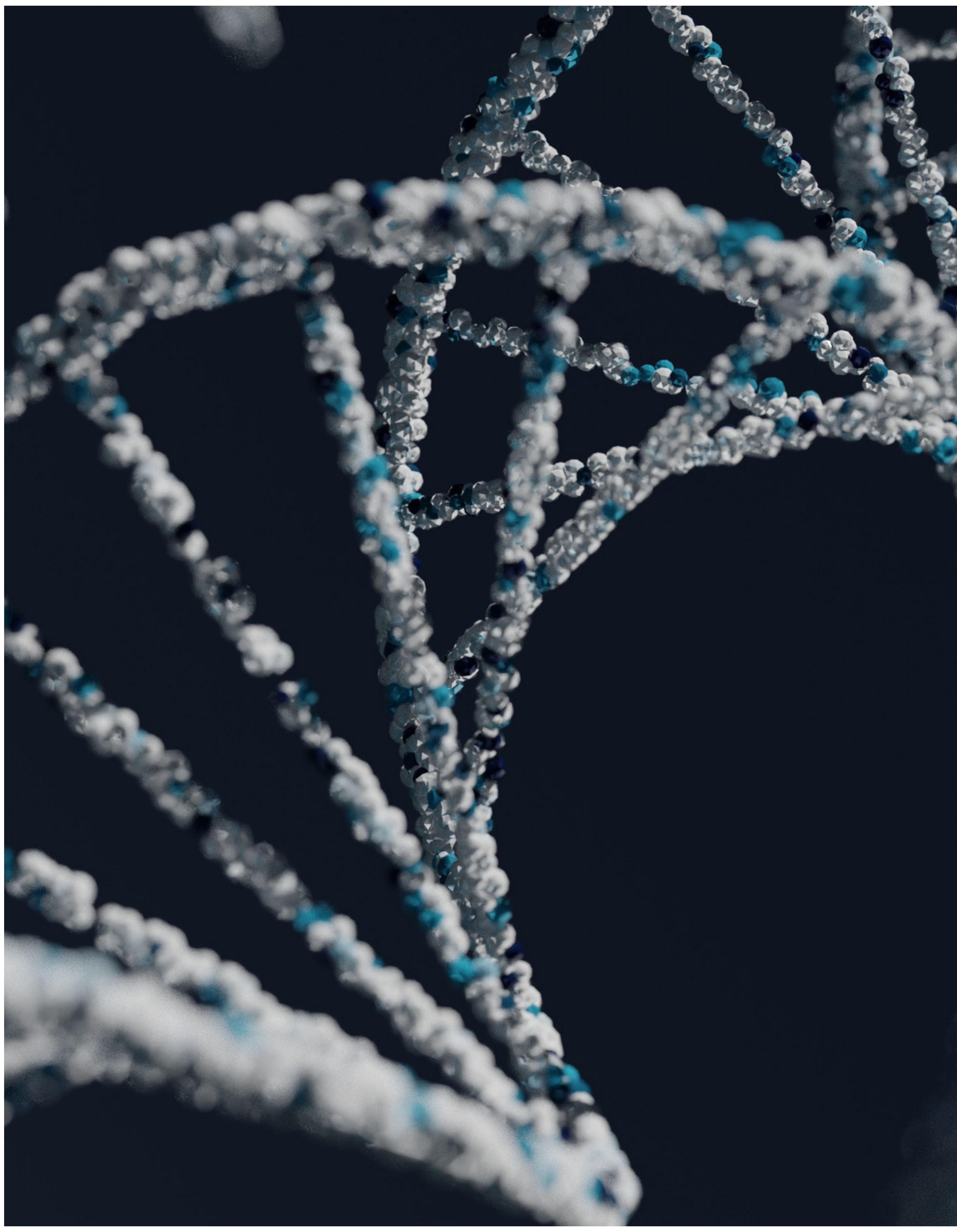
前段时间的博士生患癌事件受到了大家广泛的关注，其中一位学生罹患胰腺癌未分化癌，诊断是“符合胰腺SMARCB1/INI1缺失型未分化癌“。胰腺未分化癌是胰腺癌中一种少见亚型，仅占胰腺恶性外分泌肿瘤的2%，病人的预后普遍不好。是一种治疗难度大，效果不明显的恶性肿瘤。许多人不仅有疑问，癌症中的未分化癌是什么意思呢？SMARCB1/INI1这一串字母又代表了什么？

首先，肿瘤的分型，分级和分期是目前评价肿瘤生物学行为和诊断的最重要的三项指标。其中分级和分期主要用于恶性肿瘤生物学行为和预后的评估。我们讨论的“分化程度”就属于分级。分级主要确定癌细胞与正常细胞的差异程度，共有五个级别来描述这些差异程度：Gx（分级不明），G1（低级别高分化），G2（中级别中分化），G3（高级别低分化）和G4（高级别未分化）。分化程度越高，级别越低证明癌细胞与周围正常细胞越相似，生长越缓慢，越难以扩散到身体的其他部位。相反，分化程度越低，级别越高的癌细胞更具危险性。[2]

低分化癌细胞和周围正常细胞的差异巨大，无法发挥细胞的作用。我们都知道细胞核中的DNA携带了细胞的遗传信息。在DNA双螺旋结构中（见图2），有很多碱基。如果所有碱基都在正确的位置，细胞之间就不会有区别。低分化癌细胞就是碱基排列出现错误（插入，扩增，缺失）的细胞，也就是基因突变的细胞。因此这类基因突变的细胞就会和正常细胞呈现不同的形态。可以想象，存在基因突变的未分化细胞不确定性更强，不知道会朝什么方向发展，也几乎没有功能。[3]



无论如何，对不同肿瘤来说，肿瘤细胞的分化程度和病人的预后并不一定都有直接关系。从治疗的角度上来说，某些分化程度低的细胞对于化疗和放疗更敏感，换言之，这些分化程度越低的肿瘤越容易通过化放疗来治疗。因此，并非高分化肿瘤的预后都好于低分化肿瘤。[3]



开头提到的“符合胰腺SMARCB1/INI1缺失型未分化癌“的这一诊断结论中的SMARCB1全称是SAI/SNF相关（SAI/SNF-related）、相关矩阵（matrix associated）、依赖于肌动蛋白的染色质调控（actin-dependent regulae of chromatin）。染色质亚家族B成员1（SMARCB1）的SWI/SNF相关基质相关肌动蛋白依赖性调节因子，也称为整合酶相互作用物1（INI1），是染色质重塑蛋白复合物的关键组分。[5] SWI/SNF复合体是生物体内非常重要的调控基因转录的染色质修饰蛋白，负责松开致密的染色体，暴露DNA以便于转录。细胞需要通过转录来生成人体所需的蛋白质。人类如果缺失这种复合体，在胚胎时期就会死亡。[6] 因此可见SMARCB1的重要性，并且SMARCB1被认为是真正的肿瘤抑制因子，在抑制肿瘤的生成和复制起到十分重要的作用。图3展示了SMARCB1基因是如何在转录中发挥作用的。

SMARCB1/INI1 基因于 1980 年代后期首次在酵母中被发现.[5] 到1994年，这种基因的人类同系物在成纤维细胞中分离出来。尽管人们很早就发现了这种基因缺陷可能导致癌症，但是由于病例很少等等原因尚未研究出治愈它的有效方法。SMARCB1缺陷所致的肿瘤主要是肉瘤[5]。这些侵袭性肿瘤的预后通常较差。此外，难治性和复发性进展性疾病也很常见。[5]

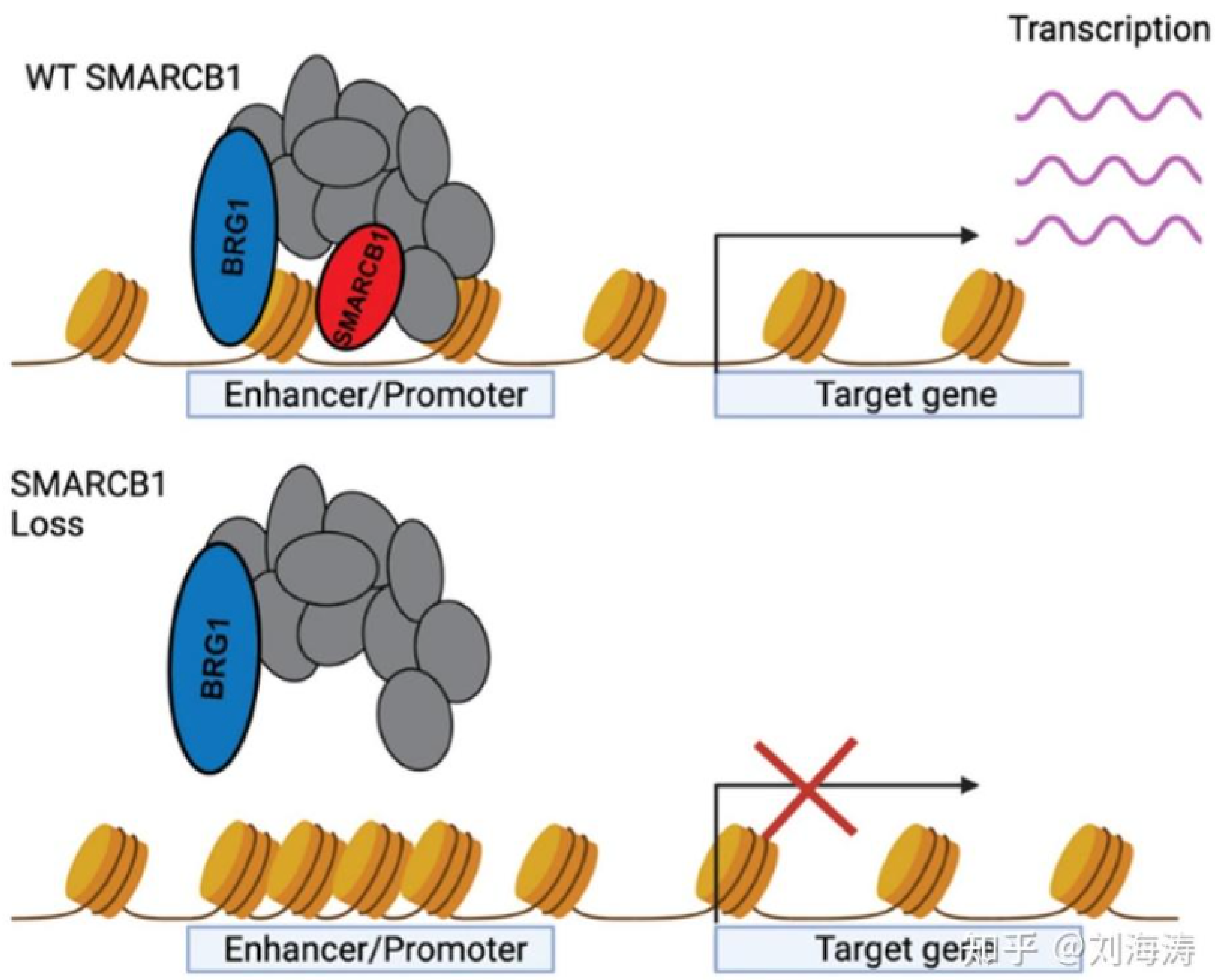


图3

过去，人们常使用阿霉素和异环磷酰胺作为晚期疾病一线治疗的主要药物。现在治疗软组织肉瘤最常用的方案名为AIM，包括阿霉素（多柔比星）加异环磷酰胺和美司钠[5]。这些方案都或多或少有可能导致难治性和进展性疾病（癌细胞有耐药性等等难以医治的疾病）[5]目前生物学家们正在针对SMARCB1缺陷型肿瘤研究更多的药物与疗法，期待更多更加有效的疗法诞生，为身在绝境中的患者带来一线生机。

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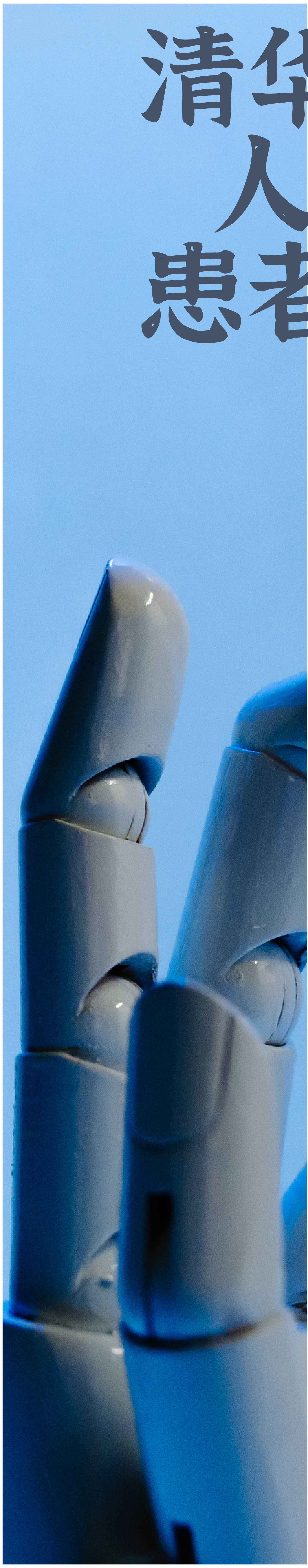
AUTHOR：OLIVIA



清华团队开发智能人工喉，帮助失语患者恢复正常声音

关键词

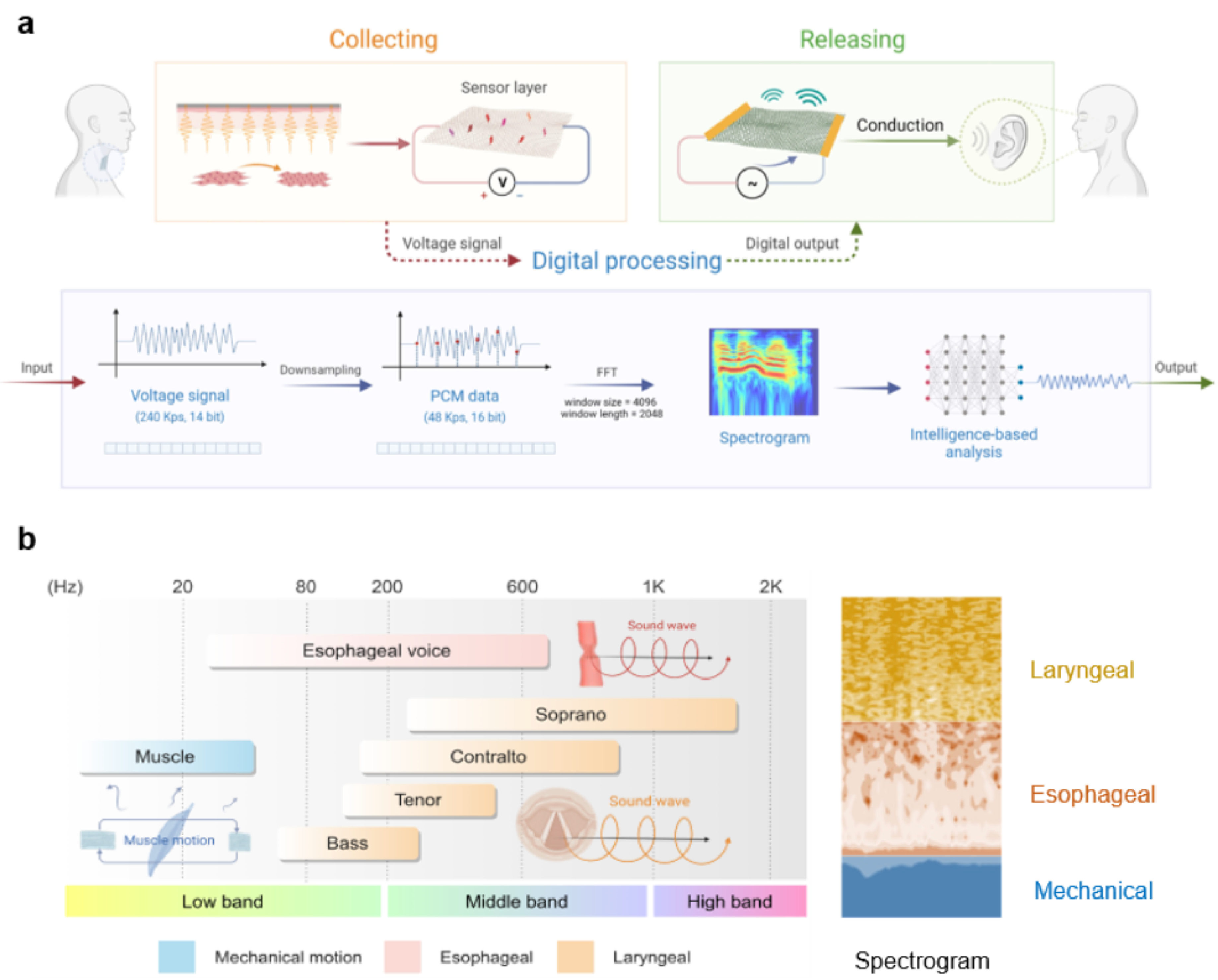
人工咽喉(AT), 渐冻症，石墨烯，石墨烯智能人工喉（WAGT）

应用范围

失语的病因包括任何损伤言语中枢的疾病，例如脑血管病、脑外伤、阿尔兹海默病等神经系统变性病。其他包括肺性脑病、非酮症高渗性昏迷、低血糖症、一氧化碳中毒等等。这些患者都不能自主发声，需外界的辅助。

应用示例

于最近，原京东副总裁、渐冻症患者蔡磊试用了此智能可穿戴人工喉，成为全球首个使用可穿戴人工喉的渐冻症患者。
这工具能够采集蔡磊喉部发声的信号，将其转换并还原出蔡磊病前几乎一模一样的声音。



介绍

石墨烯是由碳原子组成的一层原子厚度的二维晶体。它有极高的电子迁移率、高热导率和低热容率。因此对肌肉运动、食管振动和高频声波信息有很高的灵敏度。它能够分辨人类低吟、尖叫、咳嗽、吞咽、点头等动作。

在2017年，研究团队首次提出了一种基于石墨烯的收发同体的集成声学器件：利用压阻效应来接收信号，并基于热声效应发射声音，从而实现了声音收发同体。

在器件制备工艺上，研究人员采用独特的激光直写技术，能够直接将成本极低的聚酰亚胺薄膜转化为图形化的多孔石墨烯材料。

团队在最新的成果上研发出体积更小，更便捷的集成“人工喉”。这种膜片通过导线与一个仅2平方厘米大小的微控制器相连，后者可以放在口袋里，配有一个纽扣大小的电池，简单又便捷。

当把石墨烯薄膜放在患者喉咙上时，薄膜就能检测喉咙处微弱的震动，且能把这种震动对应成各种声音。

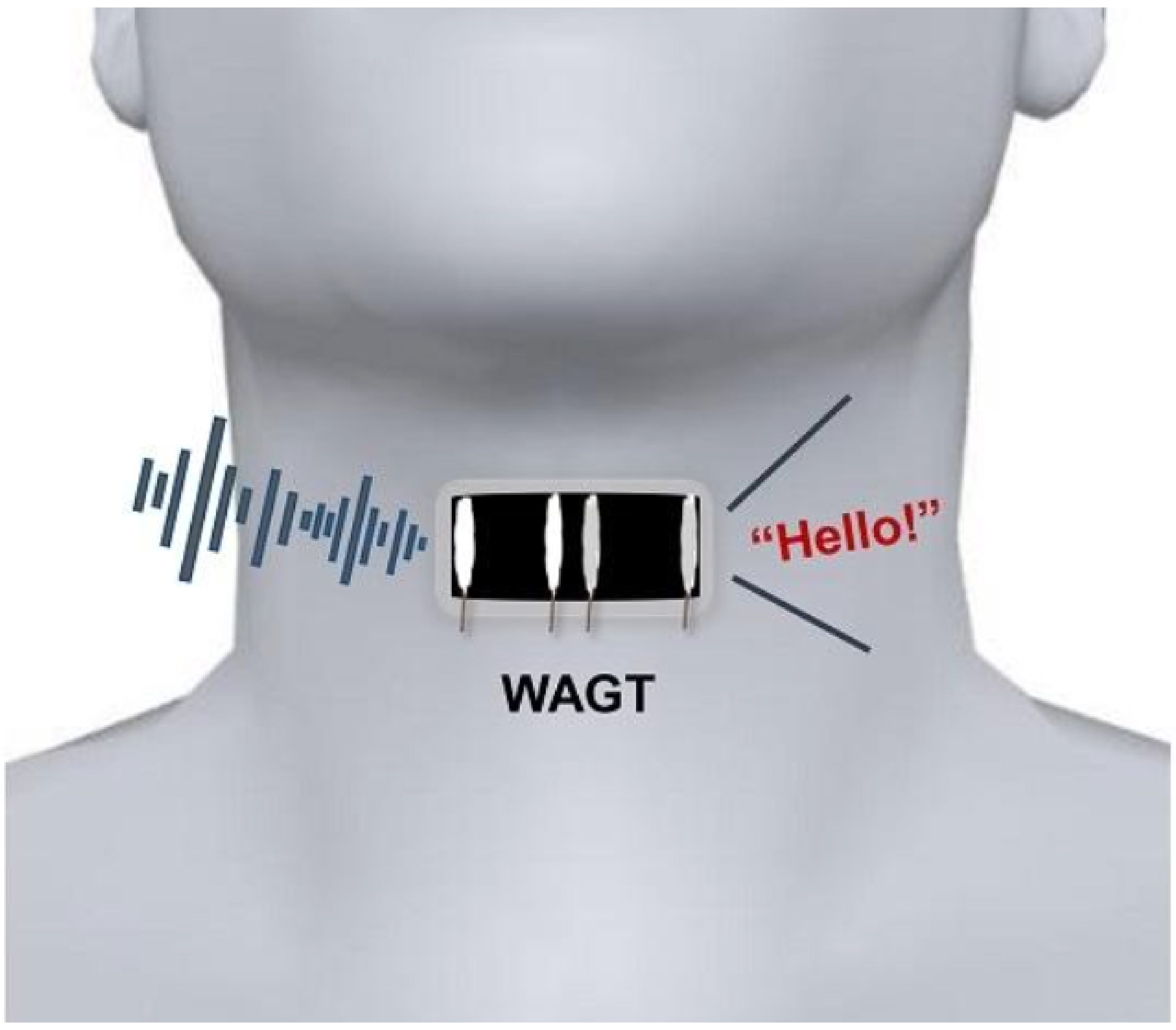
关于其中原理，此研究团队表示：“聋哑人士虽然不能说话，但是喉咙可以震动，把这个（石墨烯材质的黑色薄片）放在喉咙外部，我们就可以检测喉咙的震动。震动检测出来以后，第二步就是识别不同的震动，再把它转换成一种聋哑人士的‘语言编码’。”

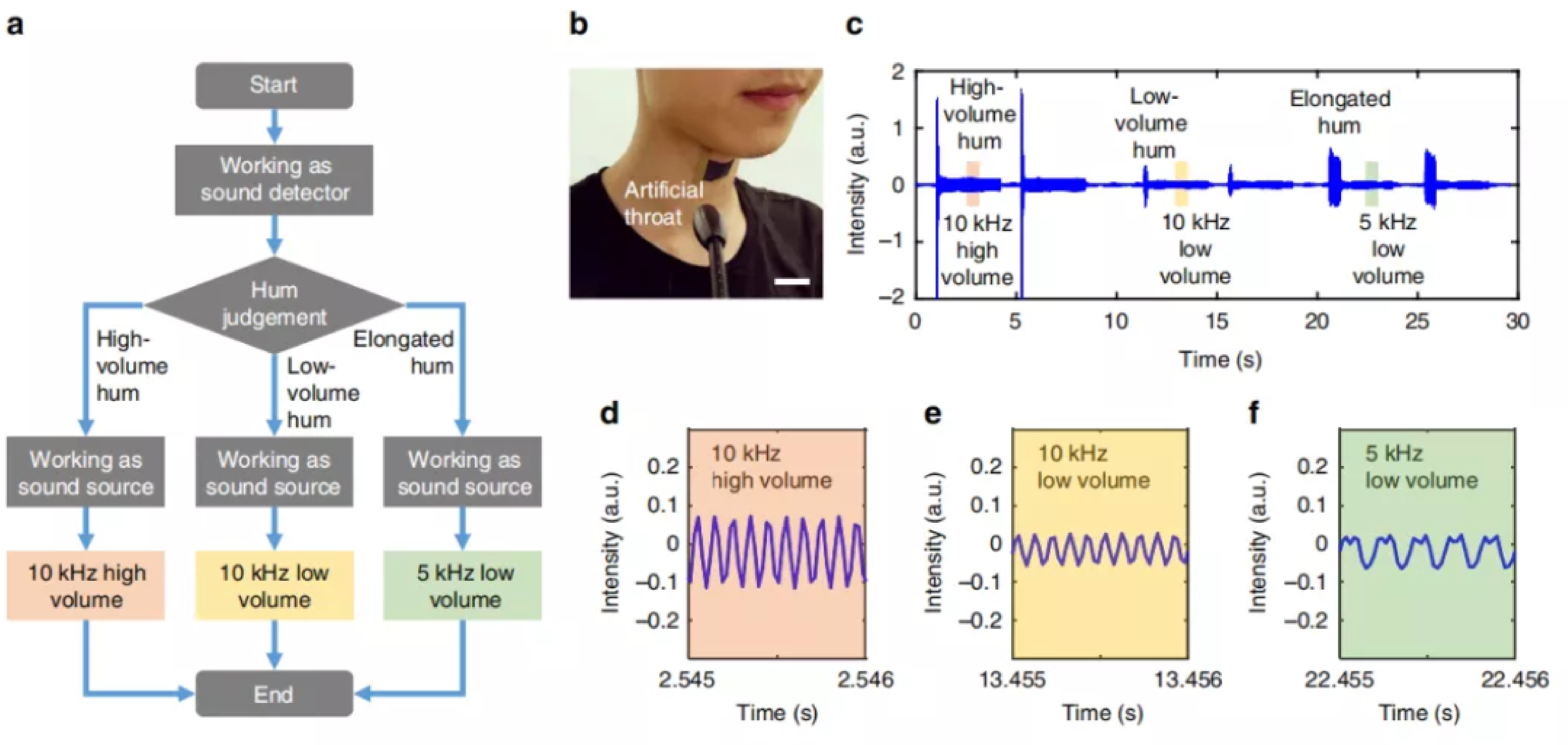
结果

实验结果表明,人工喉能够检测出基本语音元素的平均准确率为99.05 %。一名喉切除术患者使用此工具模糊说出的日常词汇，准确率超过90%。

综上所述，尽管该人工喉还有很大的优化和拓展空间，例如提高声音的质量和音量，增加语音的多样性和表情等，但人工喉无论从制造工艺、稳定性、还是集成发声都可以成为下一代语音识别和交互系统的一个有潜力的辅助工具。

让人工喉造福更多的声音障碍者和语音交互的用户吧！





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Mixed-modality speech recognition and interaction using a wearable artificial throat | Nature Machine Intelligence

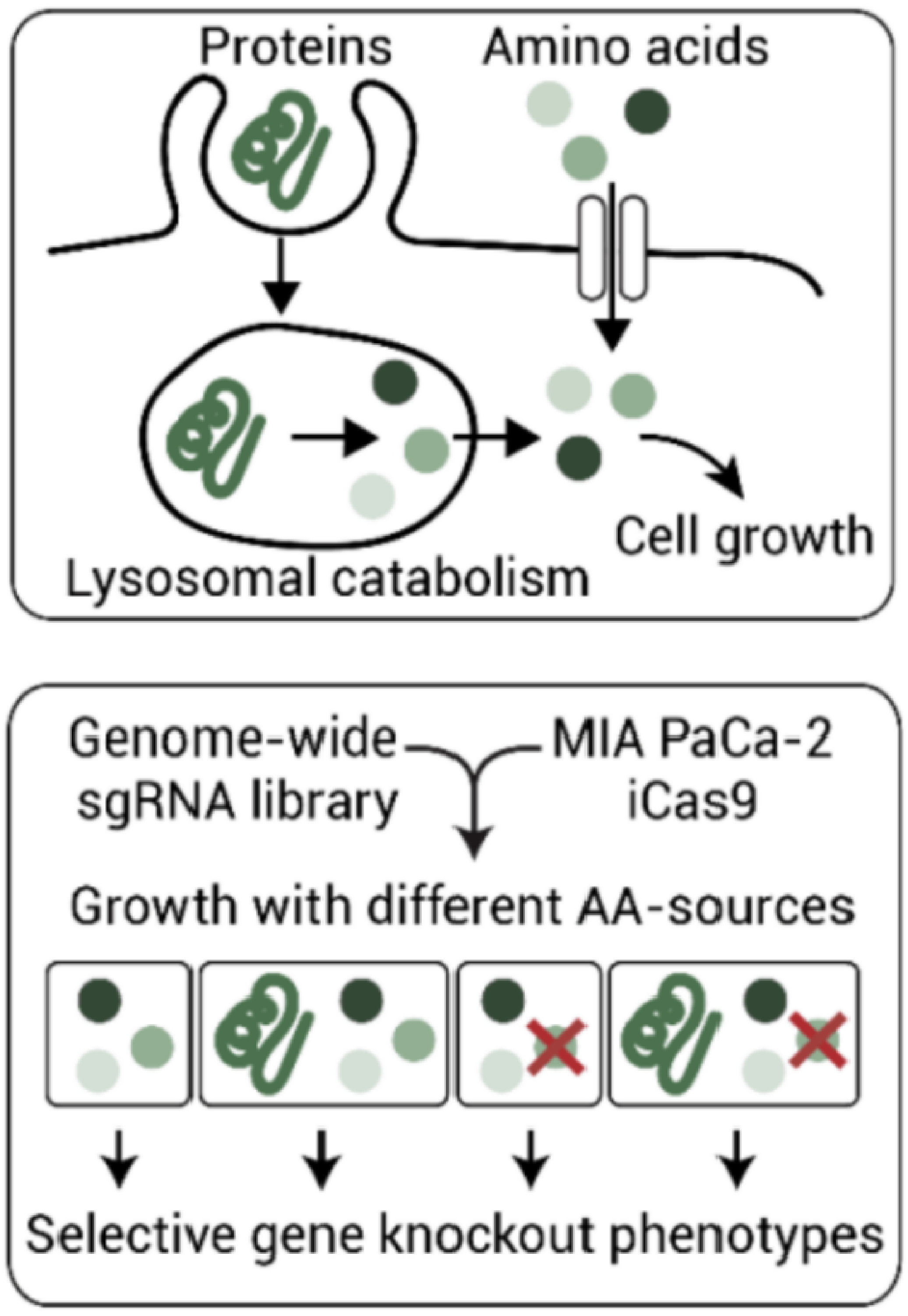
An intelligent artificial throat with sound-sensing ability based on laser-induced graphene | Nature Communications

Ren Tian-ling’s research group developed an intelligent wearable artificial throat for mixed-modality speech recognition and interaction-Tsinghua University

AUTHOR: SINDY
EDITOR: KATHERINE

癌症消失！新型癌症治疗方案居然可以饿死癌细胞

Keywords: 巨胞饮作用，CRISPR，LYSET 小蛋白



巨胞饮作用是什么

哺乳动物细胞周围环绕着多种不同的营养成分，其中包括氨基酸和 细胞外蛋白质。在充足的营养条件下，细胞更倾向于摄取游离氨基 酸，以满足其生理需求。然而，血液循环和细胞外间隙中的大多数 氨基酸都以蛋白质的形式存在。为了获取这些必需物质，细胞能够 主动吸收环境中的蛋白质，并将其运送至溶酶体——他们需要用到 一种含有消化酶的细胞器。这个细胞器的主要功能是将蛋白质降解 为其组成的氨基酸。通过这种方式，溶酶体在细胞饥饿状态下能够 生成内源性的营养来源，从而维持细胞的正常功能。

在癌症细胞中，这一过程通常被大大利用，特别是由于癌细胞通常 处于缺乏营养的微环境中，因此它们的大部分能量和蛋白质都是通 过一种被称为巨胞饮作用的机制获得的。所谓巨胞饮，指细胞在被 营养因子等刺激后，细胞膜皱缩并包裹大量外营养物质，再运送到 溶酶体（细胞中至关重要的的降解区室）中降解。溶酶体将蛋白质 分解成氨基酸，通过产生细胞内营养源以维持饥饿条件下间细胞功 能（参见图片）。

找到癌细胞的「吃饭家伙」

溶酶体是细胞内主要的降解区，其功能障碍会导致罕见和常见的疾病。某些病毒，包括严重急性呼吸系统综 合征冠状病毒 2（SARS-CoV-2），会劫持溶酶体进入细胞，开始破坏性的感染循环。德国研究团队理查 兹等人发现了一种名为 LYSET 的小蛋白，这项最新研究表明 LYSET 蛋白质是允许癌细胞进行代谢转换的 关键。这项研究也为癌症治疗提供了一个新靶点。
LYSET 对溶酶体功能的正常发挥至关重要。在缺乏 LYSET 的细胞中，酶向溶酶体的运输受到严重破坏， 导致未消化物质在溶酶体中堆积。另外该研究团队还发现 LYSET 在细胞以细胞外蛋白质为食时起选择性作 用。癌细胞通常依赖细胞外蛋白质提供氨基酸。LYSET 有助于将 N-乙酰葡糖胺-1-磷酸转移酶锚定在高尔 基体膜上，以便用溶酶体转运信号甘露糖-6-磷酸标记酶。如果没有 LYSET，溶酶体中的分解酶就会被耗 尽，从而失去消化细胞外蛋白质的能力，换句话来说，癌细胞会因为无法消化食物而死掉。

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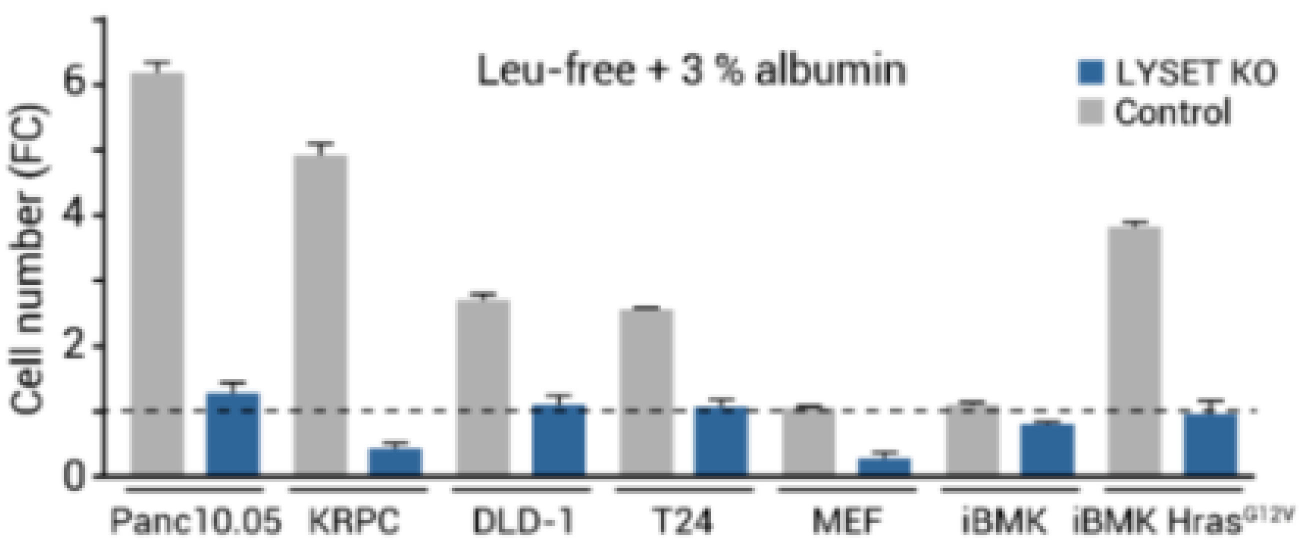
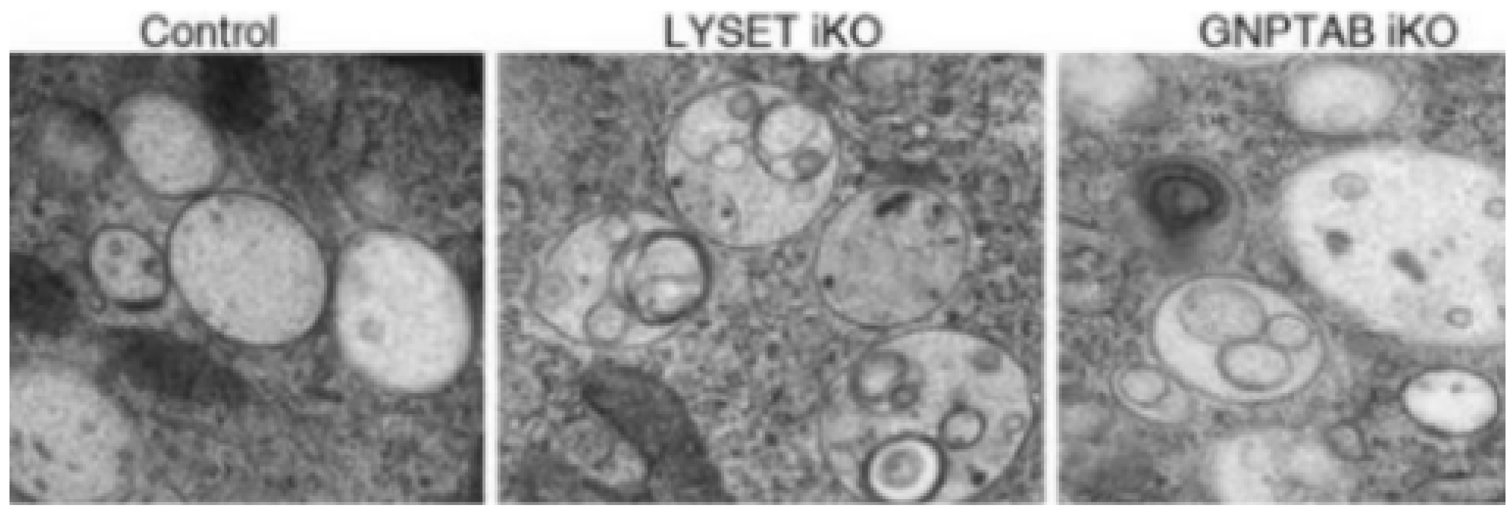
CRISPR 筛选识别敲除 LYSET

「CRISPR 是 "Clustered Regularly Interspaced Short Palindromic Repeats "的缩写，它是 CRISPR-Cas9 基因组编辑技术的基础。」

研究者以一种胰腺癌细胞为例，实验显示，CRISPR 敲除 LYSET 后，在营养丰富的条件下，LYSET 对于细胞活力和生长是非必需基因；但在添加 3% 白蛋白的缺乏亮氨酸的培养基中，LYSET 的缺失强烈抑制了所有癌细胞系、小鼠胚胎成纤维细胞和肾细胞的增殖和活力。这表明，在细胞外蛋白是必需营养素时、在体外氨基酸耗尽条件下，以及在体内肿瘤生长期间，LYSET 是必需基因 （参见下图 蓝色为实验组，灰色为对照组）。

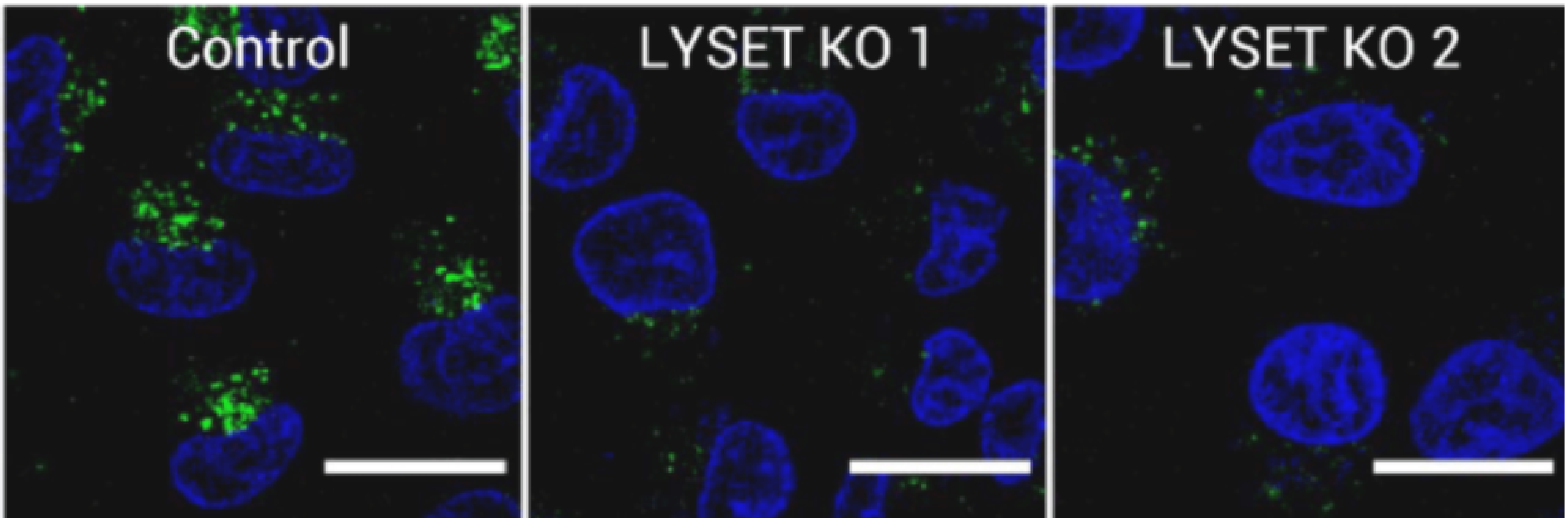
对 LYSET 功能的进一步实验表明，LYSET 是溶酶体酶运输过程中 甘露糖-6-磷酸（M6P）途径的核心成分，该途径是溶酶体酶转运所必需的，因此也是溶酶体营养素生成所必需的。溶酶体是一种小细胞器，作为细胞的胃，蛋白质在溶酶体中被消化；但在 LYSET 缺失的情况下，癌细胞的溶酶体中缺乏酶，因此不再能消化蛋白质 （参见下图）。





LYSET 是溶酶体降解 CARGOS 所必需的必要因子

为进一步研究 LYSET 作用，研究者又将用荧光标记牛血清蛋白，将敲除 LYSET 细胞及对照组放入培养，结果发现荧光色也无法被实验组细胞吸收 （参见下图 绿色荧光标记减少）。

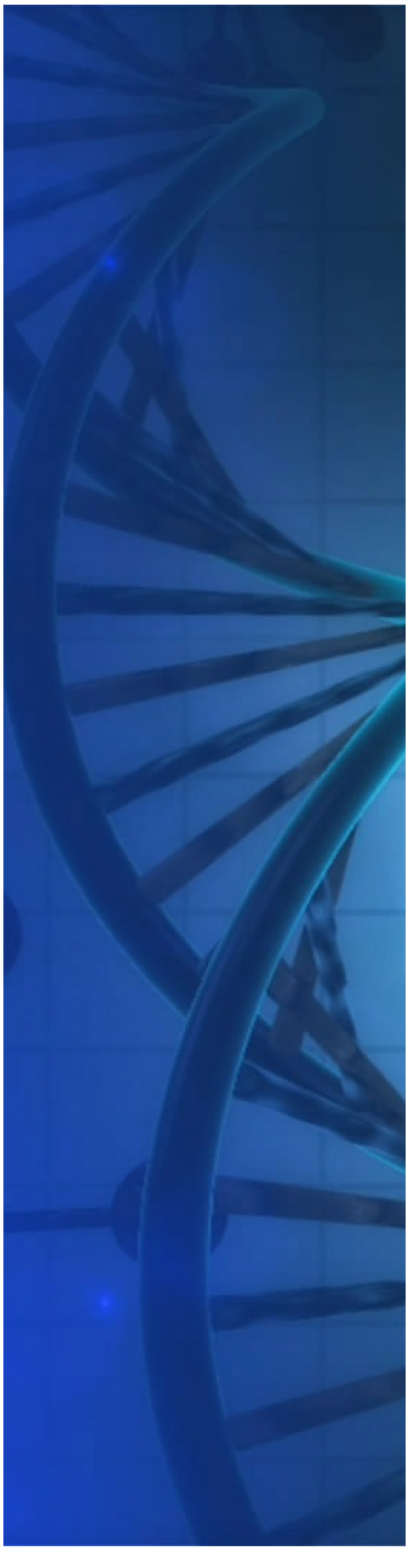


未来攻击癌症主要代谢瓶颈的分子切入点

LYSET 与多种人类病症有关： 缺乏 LYSET 的细胞缺乏功能性的 6-磷酸甘露糖通路，这为 LYSET 基因突变与遗传性综合症（例如溶酶体贮积症 II 和 III）的联系提供了机制上的解释。此外，LYSET 还能使癌细胞在恶劣的肿瘤环境中利用细胞外蛋白质作为营养源，从而获得新陈代谢的灵活性和恢复力。因此，抑制 LYSET 和溶酶体酶运输途径可能是抑制癌症关键代谢适应性的一种有前途的策略。

AUTHOR： PENNY

世界首例!CRISPR基因编辑疗法首次投入市场



摘要

CRISPR基因编辑是一项革命性的生物技术，它提供了一种准确、高效地修改生物体基因的方法。目前，该技术已被广泛用于实验室研究，并在治疗基因相关疾病的临床前研究中取得了一些进展。但出于对安全性和有效性的考虑，CRISPR基因编辑疗法一直未能投入市场。而近期，英国药品监管机构率先批准了一种CRISPR-Cas9基因编辑疗法——Casgevy，创下世界首例，该疗法可治疗镰刀型细胞贫血病和β地中海贫血，这标志着生物技术领域迎来新的高峰。本文将着重介绍Casgevy疗法的原理，安全性及未来展望。

关键词: Casgevy基因编辑疗法,CRISPR/Cas系统,镰刀型细胞贫血病,β地中海贫血症。

镰刀型细胞贫血症（SCD）是一种常染色体显性遗传血红蛋白（Hb）病。由于β-肽链第6位的谷氨酸被缬氨酸替代，使血红蛋白S（hemoglobin S，HbS）异常，以致红细胞呈镰刀状而得名。患病者体内的镰状细胞会聚合在一起形成长且扭曲的链状细胞聚合物，这些细胞聚合物不能在血管内自由的移动，在通过一些较小的动脉和静脉时，就会聚集成更多的团块从而黏附在血管壁上，此时，全身各个部位的疼痛、器官损伤甚至卒中就发生了。

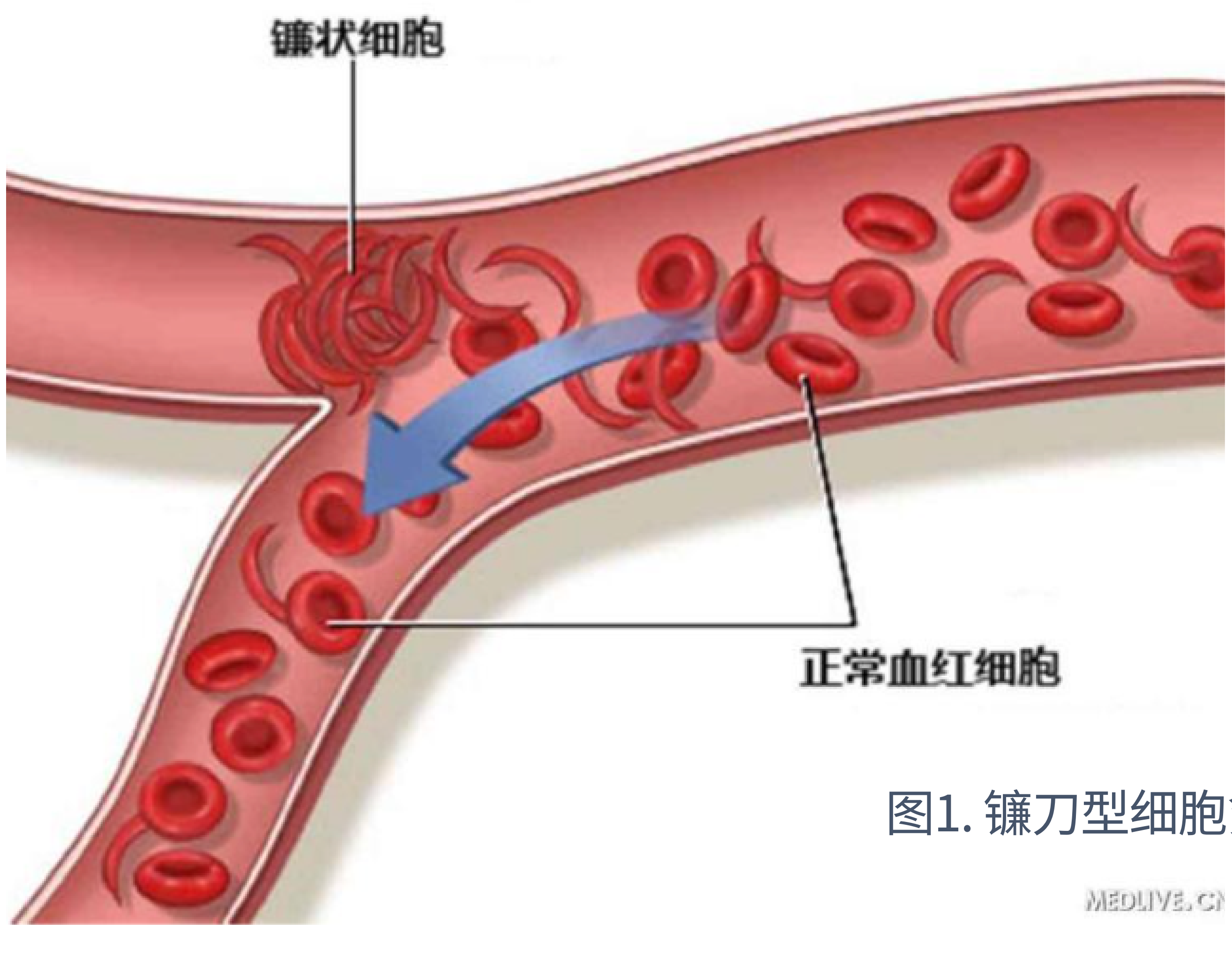


图1. 镰刀型细胞贫血症发病原理

β地中海贫血是由遗传基因缺陷导致的贫血症。患者体内珠蛋白基因突变影响了珠蛋白肽链生成的比例，降低了血液中血红蛋白的水平，并破坏了骨髓中的红细胞及血液循环中的红细胞，最终引发贫血。该病多见于婴儿，症状包括虚弱，皮肤苍白或泛黄，面部骨畸形，发育迟缓，腹部肿胀等，严重可致死亡。

由于这两种贫血症都是基因错误导致的，目前尚无已知的普遍成功的治疗方法。来自药品和保健品监管局（MHRA）的主任Julian Beach在一份声明：“镰状细胞病和β地中海贫血都是痛苦的、终生的疾病，在某些情况下可能是致命的。迄今为止，骨髓移植 (必须来自紧密匹配的供体并具有排斥风险) 是唯一的治疗选择”。因此，亟待开发出一种基因水平上的疗法，彻底改变治疗现状。11月16日，一种叫做Casgevy的基因编辑疗法诞生并获批进入市场，它是由诺贝尔奖获得者Emmanuelle Charpentier创立的瑞士公司CRISPR Therapeutics和总部位于波士顿的大型生物技术公司Vertex Pharmaceuticals开发，该疗法将用于治疗镰状细胞病和β地中海贫血。

研究者通过从患病者的骨髓中取出造血干细胞，并使用CRISPR-Cas9编辑这些细胞中编码的血红蛋白基因。一旦 Cas9 到达Casgevy 所需的目标基因 BCL11A，它就会切断DNA双链。BCL11A 通常会阻止胎儿产生一种血红蛋白。通过使用Casgevy破坏这一基因，胎儿血红蛋白开始产生，而这种血红蛋白不会像镰状细胞病或β-地中海贫血症成人患者的血红蛋白一样出现异常。

在将基因编辑细胞运输回体内之前，人们必须接受一种治疗（预处理），使骨髓准备好接受经过修饰的细胞。一旦输入，干细胞就会产生含有胎儿血红蛋白的红细胞。这可以通过增加组织的供氧量来缓解症状。"MHRA在一份新闻稿中指出："患者可能需要至少留院观察满一个月，使基因编辑细胞在骨髓中开始制造具有稳定血红蛋白形式的红细胞。

关于使用该疗法治疗镰状细胞病的试验，研究者对45名参与者中的29名进行了足够长的随访，发现在使用Casgevy治疗后至少一年内其中28人的衰弱性疼痛发作症状已完全缓解，证明了该疗法的有效性。

关于该疗法的安全性，目前还需进一步观察并做出改进。参与试验的受试者出现了副作用，包括恶心、疲劳、发烧和感染风险增加，但没有发现明显的安全问题。MHRA和制造商正在监测该技术的安全性，并将发布进一步的结果。围绕这种方法的另一个担忧是，CRISPR-Cas9有时会进行意想不到的基因修饰，并产生未知的副作用，这个问题急需解决。

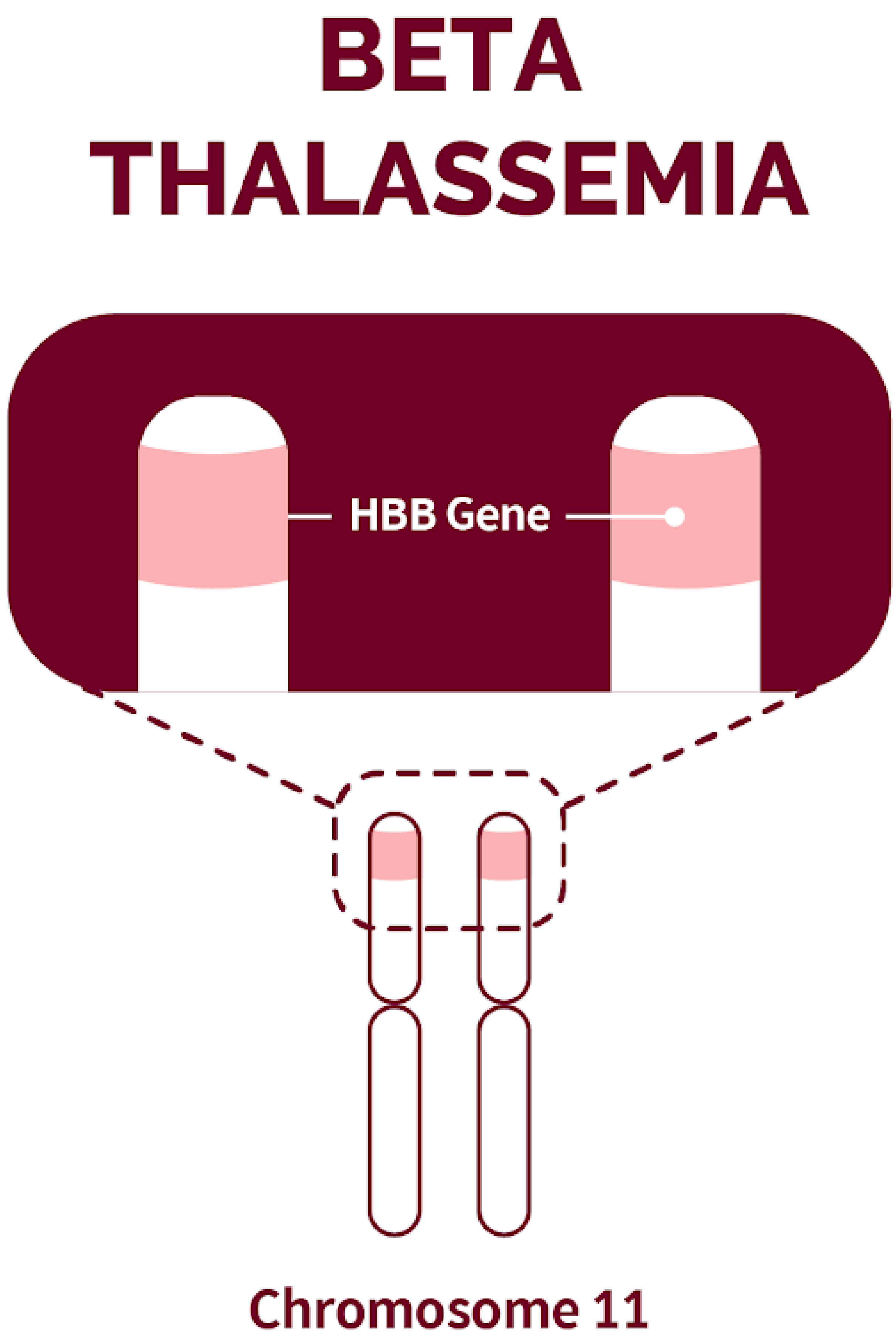


图2. 一名研究人员在Max-Delbrueck分子医学中心通过立体显微镜观察CRISPR / Cas9过程时处理培养皿。

未来展望

由于涉及到干细胞编辑，目前，这种疗法或许只能为拥有发达医疗保健系统的富裕国家所有，在未来，希望可以开发出成本较低效果更好的基因疗法，使其在全球范围内普及。CRISPR-Cas9基因编辑技术疗法初入市场，这是机遇，更是挑战，在有效解决疾病的同时，更应重视可能存在的副作用。尤其需要重视CRISPR-Cas9系统虚假的基因修饰，这会对治疗的细胞产生未知甚至不可逆转的影响。

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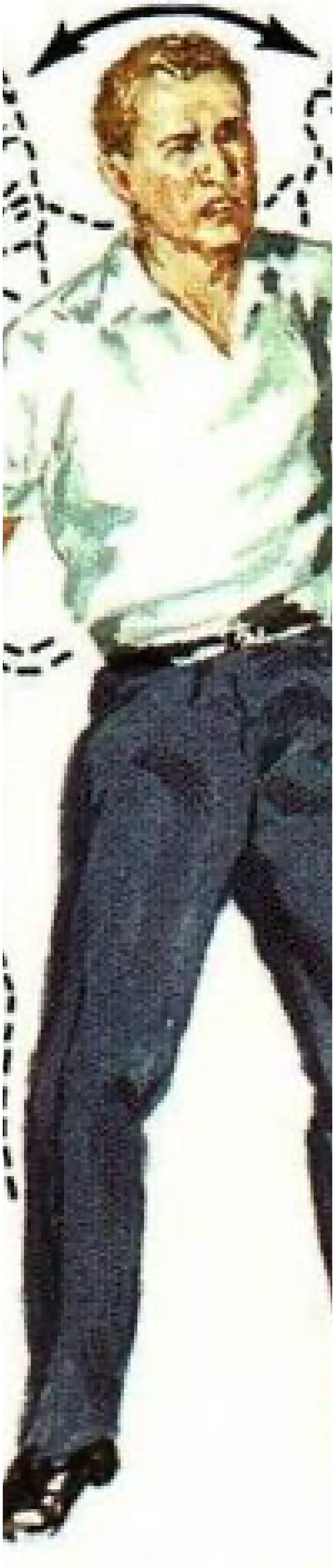
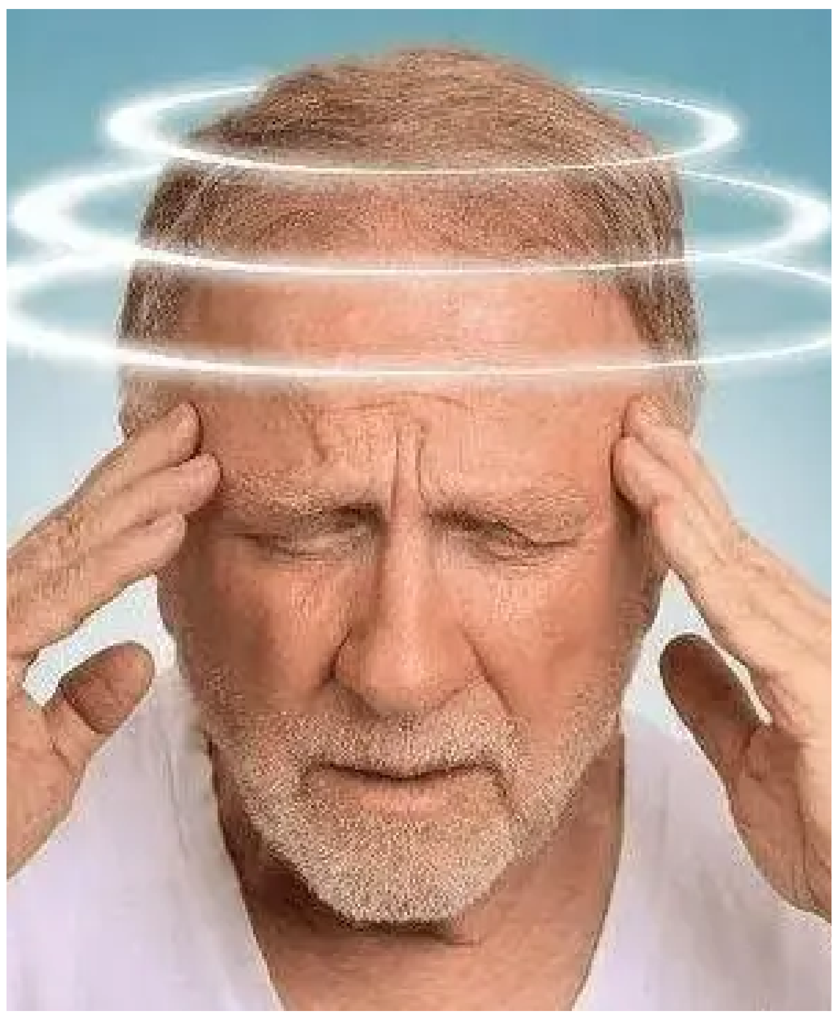


脊额小脑性共济失调

关键词:脊额小脑性共济失调(SCA),症状,原因,治疗

简介

共济失调被定义为缺乏对特定身体运动的控制，如“步态稳定性、眼球运动和语言”(班达里)。脊髓小脑共济失调（SCA）是一种罕见的遗传性疾病，主要影响小脑（“协调和计划运动并保持平衡”的功能），最糟糕的是随着时间的推移，它会变得更糟（“罕见”）。



然而，它不仅仅影响小脑，它还集中攻击中板神经系统的不同部分，包括“脑桥核、卷髓、周围神经、皮层、其底神经节”（班达里）。到2023年，已经发现了40多种类型的SCA。人们用SCA后面的数字来区分它们，这“表明了专家发现相关突变的顺序”(“脊髓小脑”）。半数病例为SCA1、2、3和6，最典型的病例为SCA3(Bhandari)。

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症状和原因

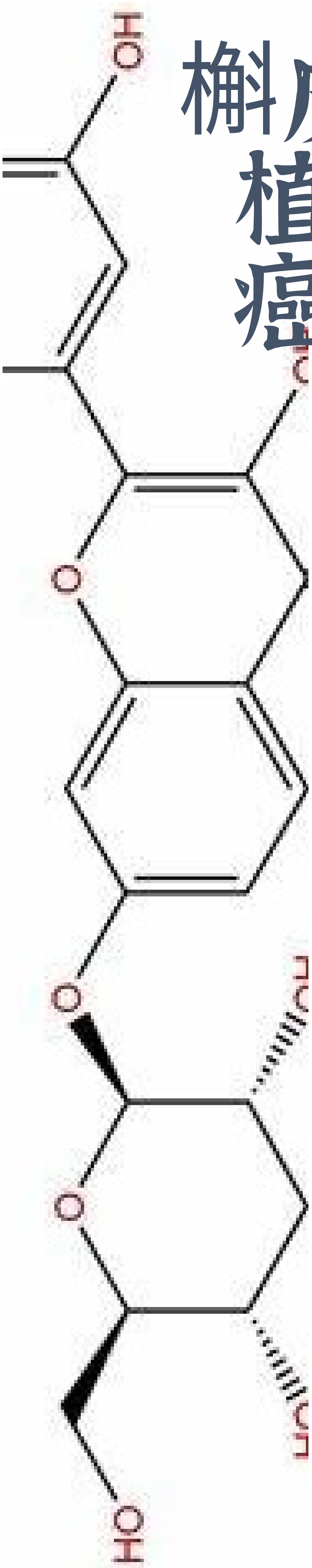
患有脊髓小脑性共济失调的人会出现运动和平衡问题，包括但不限于“不自主眼球运动、手眼协调能力差、平衡和协调问题、口齿不清和行走不协调”（“脊髓小脑性”）。这是因为患有这种疾病的人的核苷酸“编码氨基酸的C、A和G”会重复多次(“罕见”)异常蛋白质似乎在小脑和脊髓神经元内聚集，导致它们死亡”(“罕见”)。为了更好地理解神经元死亡对我们的影响。我们首先需要知道神经元做了什么。“神经元通过脑干将携带来自脊髓、大脑和内耳的输入的轴突发送到小脑”“R are）。当它到达那里时，小脑利用这些数据来安排和调节运动，同时保持平衡（“罕见”）。患有脊酷小脑共济失调的人也可能有“处理和记忆信息”（“脊髓小脑”）的问题。这是因为神经元的残疾或死亡会导致人们的记忆和日常工作（“大脑”）能力下降。

治疗以及应对方法

FDA，美国食品和药物管理局尚未批准任何“综建或神经保拍治片”(Ghanekar)。与许多疾病一样，SCA的治疗侧重于治疗其症状，“大多数临床试验涉及口服药物”(Ghanekar）。例如，利鲁唑是一种口服药物，用于治疗肌萎缩侧索硬化(ALS)(Ghanekar)等症状的患者。另一个例子是丙戊酸，它是一种“抗惊厥和组蛋白去乙酰化酶(HDAC)抑制剂，用于治疗癫痫发作和躁郁症”(Ghanekar）“正在开发新的疾病改善疗法”（Ghanekar）。例子包括已发现的众所周知的基因编辑技术CRISPR从SCA3个体(Ghanekar)中成功删除CAG的多重重复。其他疾病修饰疗法包括“AAV介导的基因疗法和ASOS，从源头上解决SCA”(Ghanekar）

巴括口放约物的临床试验(Ghanekar)。例如，利鲁唑是一种口服约物，用于患有肌萎缩性侧索硬化症(ALS)等症状的患者(Ghanekar)。另一个例子是丙戊酸，它是一种“抗惊厥药和组蛋白去乙酰化酶(HDAC)抑制剂，用于治疗癫痫发作和双相情感障碍”(Ghanekar)。“正在开发新的疾病修饰疗法”(Ghanekar)。例子包括已经被发现的1/2众所周知的基因编辑技术——crispr成功地从SCA3个体中删除CAG的多个重复序列(Ghanekar)。其他疾病修饰疗法包括“laav介导的基因疗法和ASOs从源头解决SCA”(Ghanekar)。

AUTHOR: ZHIYUAN



槲皮素:新希望!天然植物成果展示在肺癌治疗中强大潜力

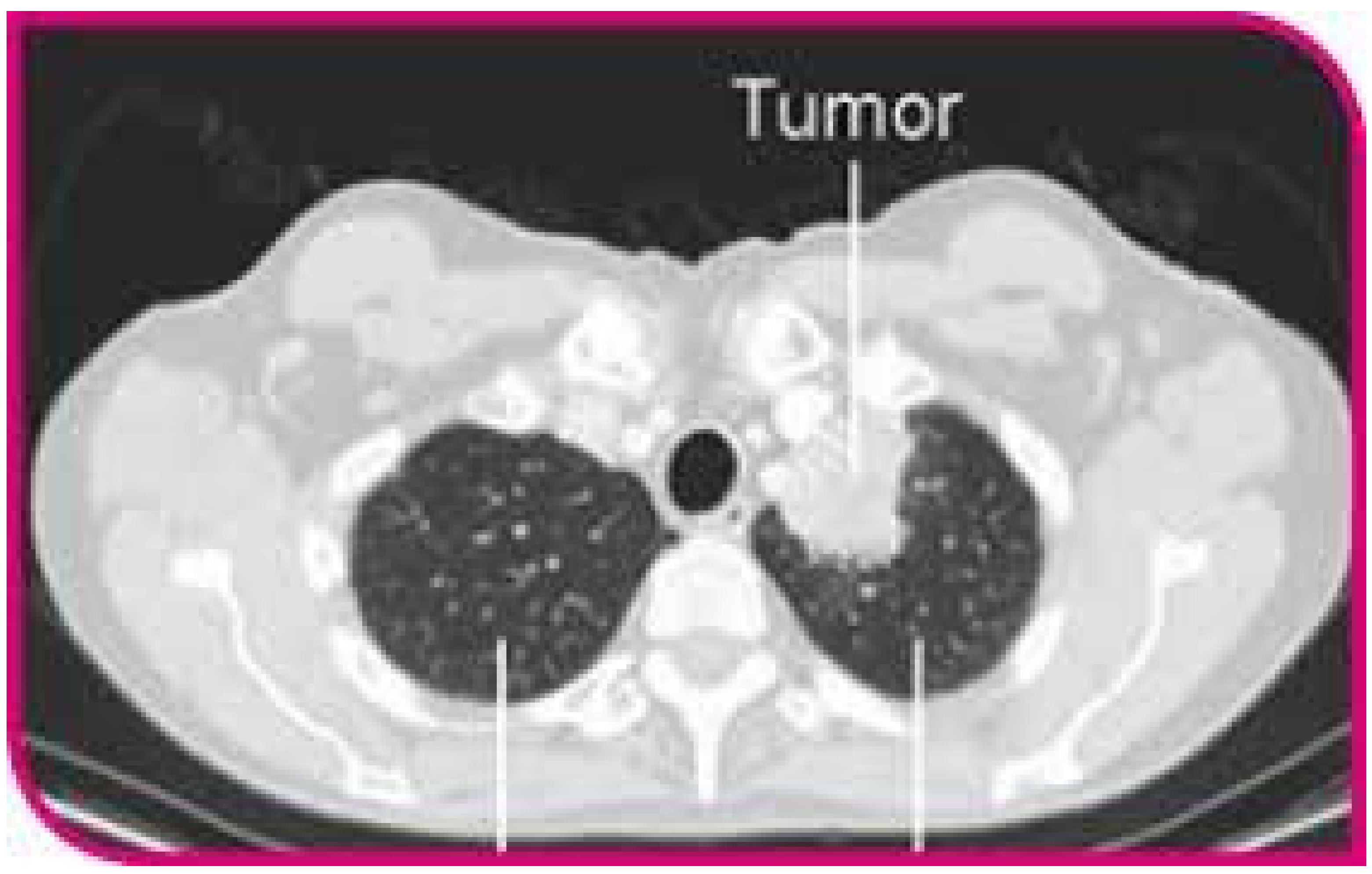
关键词:肺癌,非小细胞肺癌,植物,治疗

简介

肺癌是全球最常见的恶性肿瘤之一，尤其是非小细胞肺癌（NSCLC）占据主导地位。EGFR突变的治疗取得了显著进展，但随着药物抗性的出现，科学家正在寻找新的解决方案。南京医科大学钱旭教授团队最近在《Cell Reports》发表的一项研究揭示了一种天然植物化合物——槲皮素，在治疗携带EGFR T790M突变的NSCLC中表现出卓越的生长抑制作用。

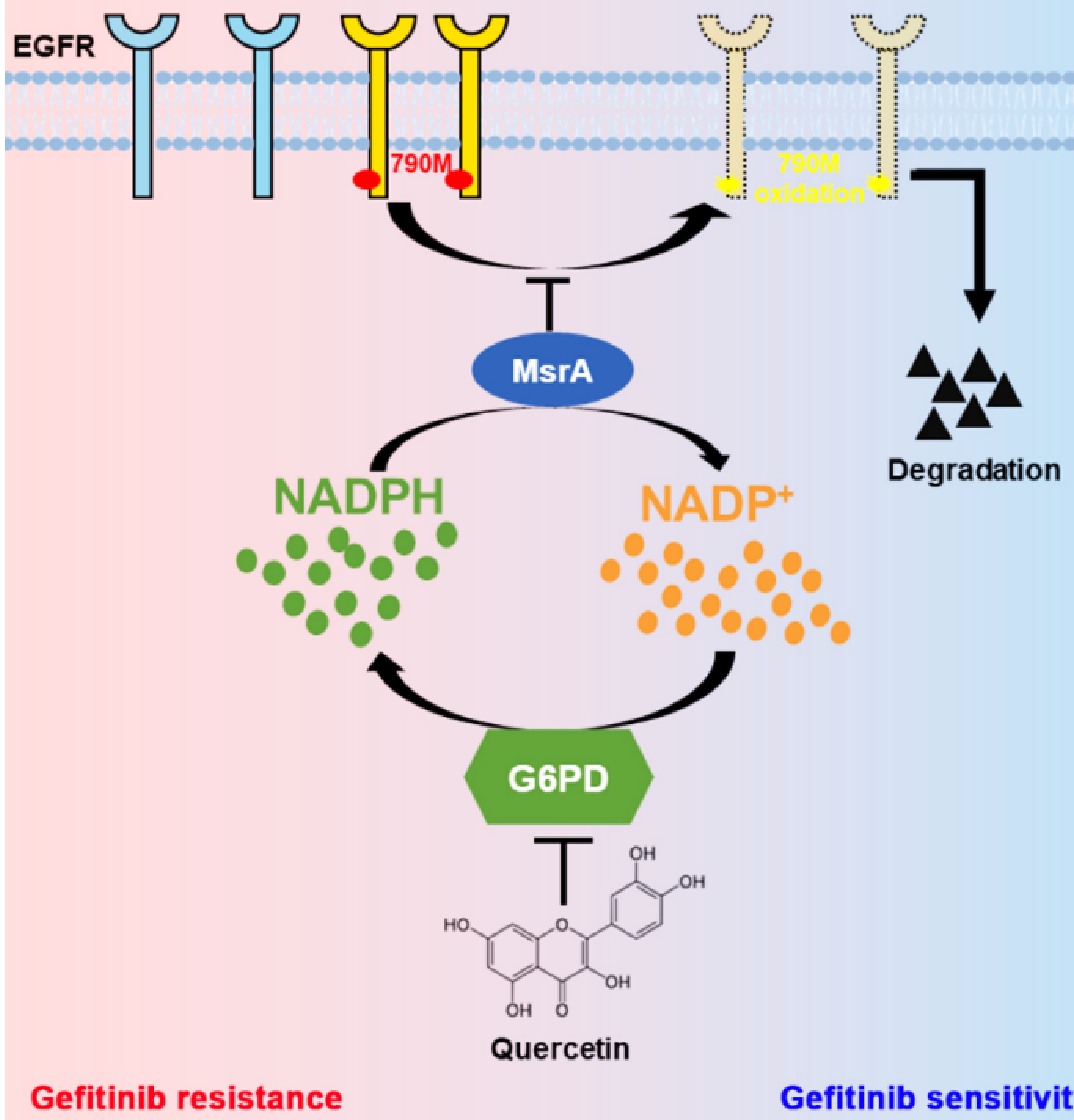
背景:肺癌与EGFR突变

肺癌是最致命的癌症之一，NSCLC占据肺癌病例的大多数。EGFR突变是NSCLC的主要驱动因素，EGFR突变在非小细胞肺癌中占比高达85%。虽然EGFR酪氨酸激酶抑制剂（TKIs）在治疗中取得了显著疗效，但药物抗性的出现限制了其长期效果。其中，EGFR T790M突变是导致抗药性的主要原因之一。



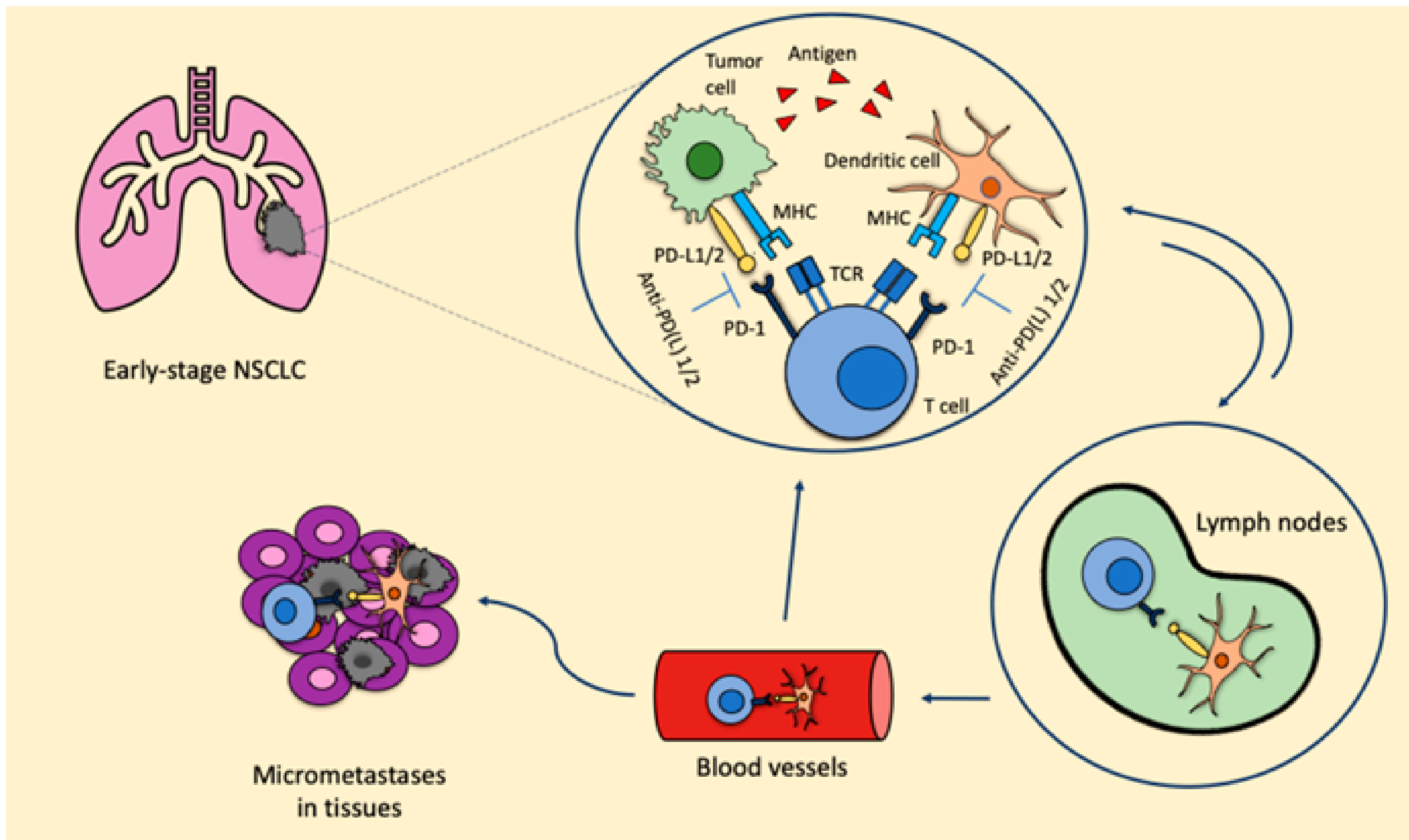
槲皮素的发现和作用机制

槲皮素是一种被广泛认为在预防和治疗多种疾病中具有积极作用的天然植物化合物。钱旭教授团队的研究发现，槲皮素对携带EGFR T790M突变的NSCLC具有强大的生长抑制作用。具体来说，槲皮素通过针对抑制葡萄糖-6-磷酸脱氢酶（G6PD）的活性，导致NADPH水平下降，使MsrA无法提供足够的还原力去还原EGFR T790M上的氧化M790，最终导致EGFR的降解。更重要的是，槲皮素与吉非替尼联合使用还表现出协同效应，增强了对NSCLC的治疗效果。



槲皮素在肿瘤代谢中的作用

研究发现，G6PD在肺癌组织中高度表达，并与不良预后相关。对携带EGFR T790M突变的NSCLC临床样本的分析显示，患者肿瘤组织中的G6PD蛋白水平较高，高水平的G6PD蛋白预示着在TKIs治疗期间EGFR T790M突变出现更早。这一发现强调了G6PD在肺癌发展中的重要作用，并为槲皮素的应用提供了理论依据。



展望:槲皮素的治疗潜力

研究发现，G6PD在肺癌组织中高度表达，并与不良预后相关。对携带EGFR T790M突变的NSCLC临床样本的分析显示，患者肿瘤组织中的G6PD蛋白水平较高，高水平的G6PD蛋白预示着在TKIs治疗期间EGFR T790M突变出现更早。这一发现强调了G6PD在肺癌发展中的重要作用，并为槲皮素的应用提供了理论依据。

结论:天然植物化合物的力量

槲皮素的发现不仅拓展了我们对天然植物化合物在癌症治疗中作用的认识，同时也为肺癌患者提供了新的治疗选择。其生长抑制作用和与传统药物的协同效应为研究人员提供了新的研究方向。这一突破为肺癌患者带来了新的曙光，并为未来天然植物化合物在癌症治疗中的应用奠定了更为坚实的基础。