

# Application and Future Development of Metal Stable Isotopes in Tumor Therapy

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**Abstract.** As tumor treatment technology continues to innovate, the medical community is urgently seeking diagnostic and therapeutic methods that are both safe and sensitive. Metal stable isotopes, with their unique properties of non-radioactivity, traceability, and close relationship with human metal metabolism, are becoming a potential new star in precision medicine. Unlike traditional imaging or blood markers, they reflect the cellular environment and pathological state through subtle changes in isotope distribution and have unprecedented depth of diagnostic and therapeutic information. This article focuses on the research status of key metal stable isotopes such as Fe, Cu, Zn, and Ca and their actual and potential applications in tumor diagnosis and treatment, covering their metabolic mechanisms, tissue distribution characteristics, and tumor correlation. By integrating multidisciplinary research results, their clinical value in early screening, treatment evaluation, and disease monitoring is analyzed. The article also points out that this field still faces challenges such as unclear basic mechanisms, insufficient clinical data, and slow technical standardization..

**Keywords:** Metal stable isotopes, tumor therapy, medicine.

## 1. Introduction

Cancer treatment remains an important challenge in today's medical field. Although some cases have been successfully cured, most cancers are still difficult to cure. Common treatments, such as radiotherapy and chemotherapy, can have certain effects and prolong the life of patients, but they often bring some side effects. Many patients may feel unbearable pain and choose to give up treatment. However, in recent years, scientists are actively studying new strategies to improve cancer diagnosis and treatment. Among them, metal-stable isotopes have attracted widespread attention due to their unique chemical and biological properties.

In the human body, the body regulates metal homeostasis through absorption, transportation, and storage to ensure the normal operation of life activities [1]. This is crucial for maintaining normal physiological processes. Related studies have shown that the occurrence of diseases is closely related to the disorder of metal homeostasis. In terms of cancer, data show that the concentrations of copper (Cu) and zinc (Zn) in the blood of cancer patients change significantly. The metal elements to be mentioned in this article (such as iron Fe, copper Cu, zinc Zn, calcium Ca, etc.) are important elements in human life activities. They can catalyze and regulate complex reactions that occur during activities and play an important role in human metabolism. When used in medical applications, metal-stable isotopes can provide more targeted, effective, and less harmful treatments for cancer patients, and have attracted much attention from the medical community.

In the latest research progress, metal-stable isotopes have provided great help in the treatment of tumors. Unlike widely used radioactive isotopes (such as Cu-64 and Fe-59), metal-stable isotopes do not decay over time, are mostly used for long-term studies in vivo, are non-toxic, and are more suitable for multiple tests. Recent studies are also dedicated to exploring the relationship between diseases and metal-stable isotopes and have made breakthrough developments in the treatment of tumors and cancer.

This article reviews the application of metal-stable isotopes in cancer treatment. The relevant research on metal-stable isotopes is crucial to cancer treatment. This paper will clearly indicate the significant

role metal stable isotopes acted as, the meaning in medical field and looking forward to the future developments.

## 2. Classification and Characteristics of Stable Metal Isotopes

Stable metal isotopes are nuclei that do not experience radioactive decay and do not change spontaneously as well. They can be used in long-term tracking of metal metabolism processes in organisms. In the aspect of tumor treatment, stable metal isotopes can be used as a marker to track the path and destination of a specific substance in a vital process. They can usually be used to track physical processes, chemical reactions, metabolic pathways, or cell localization, and can be distinguished by mass spectrometry or infrared spectroscopy according to the latest research.

Stable metal isotopes can be sorted in different categories through their metallic properties. There are four metal which are of the most typical in the research of stable metal isotopes, Cu, Zn, and Ca:

(a) **Iron (Fe)**: Stable isotopes include Fe-54, Fe-56, Fe-57, and Fe-58, which can be used to study anemia, iron overload, and iron metabolism in tumors. Among these isotopes, Fe-57 is also used to study iron uptake in tumors.

(b) **Copper (Cu)**: Stable isotopes include Cu-63 and Cu-65. These stable metal isotopes play an important role in regulating oxidative stress and mitochondrial function. The isotope Cu-65 is studied for its role in copper metabolism. However, in this paper.

(c) **Zinc (Zn)**: Stable isotopes include Zn-64, Zn-66, Zn-67, Zn-68, and Zn-70, which are often used to study the correlation between zinc transporters and cell proliferation. Zn-66 and Zn-68 show changes in distribution in cancer tissues. Metal ions related to zinc are involved in many metabolic processes of tumor cells, so stable isotopes of zinc are also of great value in tumor research.

(d) **Calcium (Ca)**: Stable isotopes include Ca-40, Ca-42, Ca-43, Ca-44, Ca-46, and Ca-48, which are valuable in studying calcium signaling pathways and their relationship with tumor growth. Ca isotopes have made important contributions to bone diseases and have played an important role in targeted therapy.

In addition, compared with common non-metallic isotopes (such as iodine-131), metal-stable isotopes can often be combined with specific chelators or antibodies, making it easier to target tumor sites. For example, Cu-64 can be combined with a chelator called DOTA to form copper Cu 64-DOTA-ECL1i, and then connected to antibodies against tumor antigens, which can improve the ability to locate tumors, help predict chemotherapy resistance in certain cancers, and identify early metastatic diseases. In contrast, although iodine-131 can also treat differentiated thyroid cancer, its targeting ability is weak and has limited effects on other types of cancer.

In general, metal-stable isotopes are becoming an important direction in tumor treatment research due to their unique characteristics and good targeting ability. Although they are not radioactive, they retain chemical properties similar to radioactive isotopes, so compared with radioactive isotopes, they are less harmful to patients and are a highlight of modern medical research.

## 3. Main Strategies of Metal Stable Isotopes in Medical Tumor Treatment

Stable metal isotopes have improved cancer diagnosis, monitoring and treatment through their unique properties. Due to their non-radioactive, low toxicity and ability to safely track metabolic processes, they are less harmful to the human body and play a vital role in promoting cancer treatment. Related application research has also received increasing attention. Next, this article will focus on the mechanisms, principles and applications of four metal elements, iron (Fe), copper (Cu), zinc (Zn) and calcium (Ca), in tumor treatment.

### **3.1. Mechanisms, Principles and Applications of Iron (Fe) in Medical Tumor Treatment**

Iron is a transition metal and an essential element in the human body that participates in a variety of metabolic processes. It plays a key role in human life activities, especially in oxygen transport and cellular respiration. The role of iron in cancer treatment has received increasing attention because it involves the metabolism and proliferation of tumor cells. This section will discuss the mechanisms, principles and applications of iron and its isotopes (taking Fe-57 as an example) in cancer treatment.

#### **3.1.1. Mechanisms and principles of Fe**

Iron is used in the human body to form heme proteins such as hemoglobin and myoglobin and is responsible for transporting oxygen to the blood and muscles. In tumors, iron plays a key role in cell metabolism, such as DNA synthesis and energy production. Cancer cells often exhibit the alterations of ion homeostasis, as they take up more iron to support their rapid growth and division. This metabolic feature makes iron an attractive target for cancer therapy. To inhibit tumor growth, the concept of "ferroptosis" has been raised and researched have been conducted accordingly.

#### **3.1.2. Application of Fe in medical tumor therapy**

The stable isotope of iron, Fe-57, currently being focused researched, is often used to track iron metabolism in tumors as this article mentioned above. Fe-57 can be absorbed by cells and monitored and tracked via mass spectrometry or imaging techniques, thereby providing valuable information about the utilization of iron in cancer cells. By studying the path of iron in tumors, researchers can identify potential drug delivery or radiotherapy targets.

Furthermore, iron-based therapies have been further developed in both clinical and preclinical settings. For example, iron chelators can limit the utilization of iron by tumor cells by binding to excess iron in the body to inhibit tumor growth. A typical example is deferoxamine, an iron chelator which has shown great potential in inhibiting the growth of certain cancers, such as glioblastoma and liver cancer. Besides, iron-loaded nanoparticles and iron complexes are being studied for targeted drug delivery. These nanoparticles can deliver chemotherapy drugs directly to the tumor site, minimizing systemic toxicity. The role of iron in radiotherapy has also been explored, with iron-based compounds used to increase the sensitivity of tumor cells to radiation, in order to enhance the effect of radiotherapy.

### **3.2. Mechanisms, Principles and Applications of Copper (Cu) in Medical Tumor Treatment**

Copper is another transition metal that is also involved in various physiological processes, including angiogenesis, iron metabolism and cellular respiration. The function of copper in cancer has been well established because it is essential for tumor growth and metastasis. This section will discuss in depth the mechanisms, principles and applications of copper and its isotopes (such as Cu-63 and Cu-65) in cancer treatment.

#### **3.2.1. Mechanisms and principles of Cu**

Copper participates in the formation of enzymes that regulate angiogenesis. Angiogenesis is the process by which tumors forming new blood vessels to supply oxygen and nutrients. Angiogenesis is a key event in cancer progression, and the role of copper in this process makes it an important factor in tumor survival and growth. Moreover, copper is essential for the normal function of multiple enzymes involved in oxidative stress and DNA repair, processes that are often dysregulated in cancer cells. Similar to the properties of iron, the concept of "copper death" has also been proposed by scientists due to the utilization of copper in tumor cells and corresponding research methods have been generated.

#### **3.2.2. Application of Cu in Medical Tumor Treatment**

Copper-based compounds, such as copper chelators and copper-loaded nanoparticles, have received high attention as potential anticancer drugs. Copper chelators have proved to inhibit tumor growth and metastasis in various cancer types such as breast cancer and lung cancer by reducing the

bioavailability of copper. For example, the copper chelator ATN-224 has demonstrated promising results in reducing tumor growth and improving patient survival rates in clinical trials. The newly developed nanoparticle NP@ESCu has also been confirmed to induce copper death and can be combined with  $\alpha$ PD-L1 to enhance the therapeutic ability of cancer [2].

What's more, its role in enhancing radiotherapy effect is noteworthy. Take Cu-64 as an example, radioisotopes of copper have gained increasing attention in recent years in the application in diagnostic imaging and therapy. Cu-64 is a positron-emitting radioisotope, is commonly used in positron emission tomography (PET) technology to visualize copper metabolism in tumors. This enables non-invasive imaging of tumors and provides valuable information about tumor location, size, and progression. Additionally, Cu-64 can be combined with a chelator called DOTA to become a peptide radiotracer copper Cu 64-DOTA-ECL1i based on the A20FMDV2 sequence [3]. Studies have shown that it is promising for targeted detection of integrin  $\alpha_v\beta_{(6)}$ , a cell surface receptor associated with many aggressive cancers, and allows long-term studies of Cu-64 tracer, highlighting its strong detection capabilities.

### **3.3. Mechanism, Principle and Application of Zinc (Zn) in Medical Tumor Treatment**

Zinc is an essential trace element for the human body and plays an important role in various biological processes, including immune function, protein synthesis and cell division. Its role in cancer has become a research focus due to the participation in regulating the growth and apoptosis of tumor cells. This section will explore the mechanism, principle and application of zinc and its isotopes (such as Zn-64 and Zn-68) in cancer treatment.

#### **3.3.1. Mechanism and principle of Zn**

Zinc is involved in more than 300 cellular physiological processes and is critical for the activity of the activity of enzymes that regulate cellular processes, including DNA synthesis, protein folding and antioxidant defense [4]. At the same time, zinc is necessary for the immune system, and both zinc deficiency and excess can affect the immune response. Related studies have confirmed that the content of zinc ions in tumor cells is often lower than that in normal cells. Therefore, the value of zinc in the human body is also extremely high, and related research is also very necessary.

#### **3.3.2. Application of Zn in medical tumor treatment**

As mentioned above, metal isotopes play a revolutionary role in targeted therapy. Here, targeted therapy refers to the precise application of drugs or radiotherapy to cancer cells. Targeted molecules can recognize and bind to specific molecules on the surface of cancer cells, thereby minimizing damage to normal human cells. Using Zn isotope tracing technology, it is possible to track the absorption, distribution, transport and excretion of zinc in the body, and then understand the metabolic process of zinc, which is an extremely important step.

Moreover, zinc nanoparticles also show potential in targeted drug delivery. Studies have shown that zinc gluconate in oral supplements binds to plasma proteins to form zinc oxide (ZnO) nanoparticles [5]. Researchers have demonstrated that ZnO nanoparticles can actively cross the blood vessel wall to achieve efficient intratumoral accumulation and found that they can be used as a chemotherapy drug delivery platform. They selectively accumulate in papillary Caki-2 renal cancer tumors and promote the recruitment of dendritic cells and cytotoxic CD8+ T cells to tumor tissues. Renal cancer tumor targeting is mediated by the preferential binding of zinc ions to the metallothionein-1X (MT-1X) protein, which is continuously overexpressed in Caki-2 renal cancer cells. This binding event further upregulates the expression of MT-1X in the cell, thereby inducing additional nanoparticle binding and retention. The results suggest that supplement-derived ZnO nanoparticles can serve as a versatile drug delivery and cancer immunotherapy platform. The ability of zinc to modulate immune responses is also being explored, especially in immunotherapy, where it may help enhance the efficacy of immune checkpoint inhibitors.

### **3.4. Mechanisms, Principles, and Applications of Calcium (Ca) in Medical Tumor Therapy**

Calcium is very important for living organisms. It is a key element in biological processes such as nerve conduction, maintenance of the main components of bones and teeth, signal transduction, muscle contraction, and enzyme activation. Not only that, bones and teeth are also mainly composed of calcium compounds, so the role of calcium in the human body cannot be underestimated. Since calcium signaling pathways are often disrupted in cancer cells, they have also received a lot of attention. This section will discuss the mechanisms, principles, and applications of calcium isotopes (such as Ca-42 and Ca-44) in cancer treatment.

#### **3.4.1. Mechanisms and principles of Ca**

Calcium plays a key role in cell signaling, especially in regulating cell proliferation, differentiation, and apoptosis. In cancer, calcium signaling is often disrupted, leading to uncontrolled cell proliferation and resistance to apoptosis. Here, calcium is a promising target for cancer treatment because it is involved in tumor cell metastasis, angiogenesis, and immune regulation.

#### **3.4.2. Application of Ca in medical tumor treatment**

Calcium (Ca) stable isotopes have been shown to be of great value in bone metabolism research. Studies have shown that Ca isotope composition is closely related to a variety of bone-related diseases, especially providing new analytical methods for the assessment of bone disease induced by bone marrow cancer. In 2007, SKULAN et al. reported that in the urine of patients with bone degeneration, the lighter Ca-42 isotope is more likely to be enriched than Ca-44[6]. This is because during bone formation, Ca-42 is preferentially absorbed into bone tissue, while during bone degeneration, the isotope is more easily released from bone tissue into the blood and soft tissue, and finally excreted through urine, resulting in changes in the Ca isotope ratio in urine. This discovery provides a new direction for the non-invasive diagnosis of bone-related tumor diseases, especially for real-time monitoring of disease progression.

In aerospace medicine, the ratio of Ca isotopes is also used to assess the bone health of astronauts. Long-term weightlessness can lead to calcium loss and the risk of osteoporosis. Compared with traditional bone density scans, Ca isotope analysis can reflect bone changes earlier and more sensitively, showing unique advantages in aerospace medicine.

With the development of analytical technology, metal-stable isotopes are gradually cross-integrating with molecular biology, cell biology, etc., promoting technological innovation in the field of tumor diagnosis and treatment, and heralding broad development prospects in future tumor treatment.

### **4. Application of Metal Stable Isotopes in Targeted Therapy and Novel Treatment Options**

Metal-stable isotopes are gradually being integrated into the innovative path of cancer treatment, especially in targeted therapy and novel treatment strategies. As mentioned above, these isotopes can not only improve the selectivity of drug therapy and reduce damage to healthy tissues but also participate in the precise delivery of drugs as functional carriers.

Taking Ca-44 as an example, its labeled calcium phosphate nanoparticles have been widely studied in bone cancer-related targeted drug delivery systems due to their excellent biocompatibility and natural similarity to bone structure. This isotope-labeled nanomaterial is expected to improve the local accumulation efficiency of drugs in tumors while reducing systemic toxicity.

In addition, metal-stable isotopes can also be used as efficient tracers for dynamic monitoring during treatment. By using mass spectrometry technology to detect isotope distribution in the body before and after treatment, clinicians can evaluate the treatment effect in real time, adjust strategies in time, and achieve more personalized precision treatment.

In the field of immunotherapy, the application of stable isotopes is also gradually expanding. For example, some studies have proposed using Zn-66-labeled T cells to track their migration paths in

vivo and their interactions with tumors. This technology can not only reveal the behavioral mechanisms of immune cells in the tumor microenvironment but also provide important data support for the optimization of new immunotherapy strategies.

## 5. Existing Challenges and Future Development of Metal Stable Isotopes

Although metal-stable isotopes have significant advantages in the medical field, isotope analysis technology is constantly improving, and extensive research has been carried out on this basis, showing many potentials, but their widespread clinical application still faces a series of challenges. First, the stable isotope systems that have been deeply studied are relatively limited, mainly focusing on Fe, Cu, Zn and Ca. There are still a large number of potential metal elements that have not been fully explored, which limits the diversified development of this field.

Secondly, there is still a lack of systematic understanding of the biological behavior of stable isotopes under different physiological and pathological conditions. Each isotope may show different distribution patterns and biological effects in specific tissue types, tumor subtypes and different metabolic states. Future research urgently needs larger-scale, more diverse clinical samples and interdisciplinary collaboration to build a more comprehensive standardized data system and improve the accuracy of isotope technology in personalized medicine.

Looking to the future, the research on metal-stable isotopes will increasingly rely on nanotechnology, molecular targeting technology and artificial intelligence. By integrating multidisciplinary cutting-edge technologies, such as labeling nanocarriers with stable isotopes for targeted delivery, or using AI-assisted mass spectrometry data analysis and disease prediction, researchers are expected to open up a new paradigm for tumor diagnosis and treatment and promote precision medicine into a new era.

## 6. Conclusion

Metal-stable isotope technology is gradually revealing its unique potential in the field of tumor therapy and diagnosis. Through analyzing the isotopic composition of metal elements such as Fe, Cu, Zn and Ca, the researchers can see the microscopic changes caused by the abnormal metabolism of tumor cells, thus providing a new scientific basis for early disease identification, progression monitoring and efficacy evaluation. This technology not only expands the understanding of the mechanisms of tumorigenesis but also provides strong support for the establishment of more personalized and dynamic medical intervention programs.

Although current applications still face challenges such as incomplete mechanism elucidation, missing standard systems and insufficient accumulation of clinical data, metal stable isotopes have shown wide potential in basic research and preliminary clinical practice. In the future, the development of this technology will increasingly rely on the deep integration of interdisciplinary disciplines, especially breakthroughs in the fields of nanomaterials, molecular targeting carriers and artificial intelligence-assisted analysis. By further optimizing detection methods, expanding the scope of research and strengthening clinical transformation, metal stable isotopes are expected to become a key force to promote precision medicine and individualized cancer treatment.

Thus, the metal stable isotope is not only an innovative tool in basic scientific research but also is expected to open a new round of diagnosis and treatment paradigm innovation in the medical field. Continuous exploration and innovation will promote it from the laboratory to the clinical front, and become an indispensable part of the future anti-cancer technology.

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