



The 150 most important questions in cancer research and clinical oncology series: questions 102–104★

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Abstract – To accelerate our endeavors to overcome cancer, *Visualized Cancer Medicine* continues the previously launched program of publishing the 150 most important questions in cancer research and clinical oncology. In this article, three more questions are presented as follows: Question 102: Can non-glucose-based tumor imaging techniques facilitate tumor detection and metabolic classification? Question 103: how can we develop medicines to inhibit the cancer-specific metabolic functions of metabolic enzymes in tumors expressing wild-type IDH, without interfering with their canonical catalytic activities? Question 104: Can dietary-based cancer therapy be proven effective in treating cancer?

Key words: Imaging, PET/CT, Targeted therapy, Cancer metabolism, Isocitrate dehydrogenase, Pyruvate, Choline.

To accelerate our efforts in overcoming cancer, the *Chinese Journal of Cancer* and *Cancer Communications* initiated a program in 2016 to publish the 150 most important questions in cancer research and clinical oncology, with 101 key questions already published [1–14]. Beginning in 2024, *Visualized Cancer Medicine* continues this program by inviting revisions of previously published key questions and by publishing newly selected and peer-reviewed key questions [15]. In this article, three additional key questions are selected and peer-reviewed. Please send your thoughtful questions to Dr. Liang Tang via email: tangliang@mail.sciencep.com.

Question 102: Can non-glucose-based tumor imaging techniques facilitate tumor detection and metabolic classification?

¹⁸F-FDG PET/CT (Fluorodeoxyglucose Positron Emission Tomography-Computed Tomography), is a widely used imaging technique in oncology for detecting and staging various types of cancer. However, there are some types of cancer for which ¹⁸F-FDG PET/CT may not be as effective or is not routinely used for diagnosis. These include:

1. Brain tumors: ¹⁸F-FDG PET/CT is less effective in detecting primary brain tumors due to the high metabolic activity of the normal brain tissue, which can mask tumor activity.

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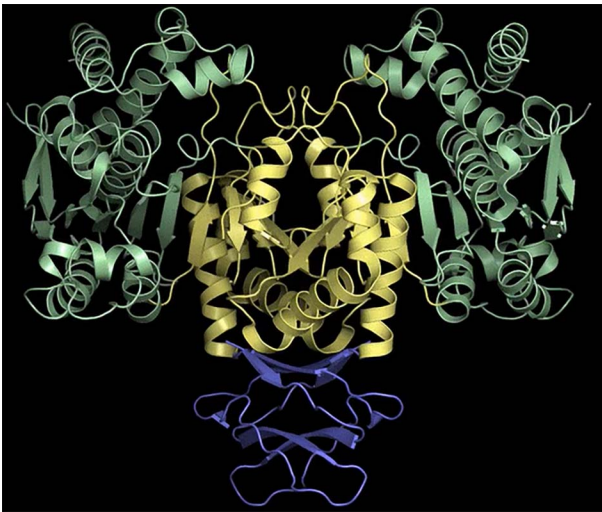
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2. Renal cell carcinoma (RCC): RCC typically does not show significant FDG uptake, making ¹⁸F-FDG PET/CT less sensitive for detecting these tumors.
3. Well-differentiated tumors: Some well-differentiated tumors, such as low-grade prostate cancer or thyroid cancer, may have low FDG uptake and may not be effectively visualized with ¹⁸F-FDG PET/CT.
4. Non-FDG-avid tumors: Some types of cancer, such as mucinous tumors or certain types of sarcomas, may have low FDG uptake and are considered non-FDG-avid, limiting the utility of ¹⁸F-FDG PET/CT for their diagnosis.

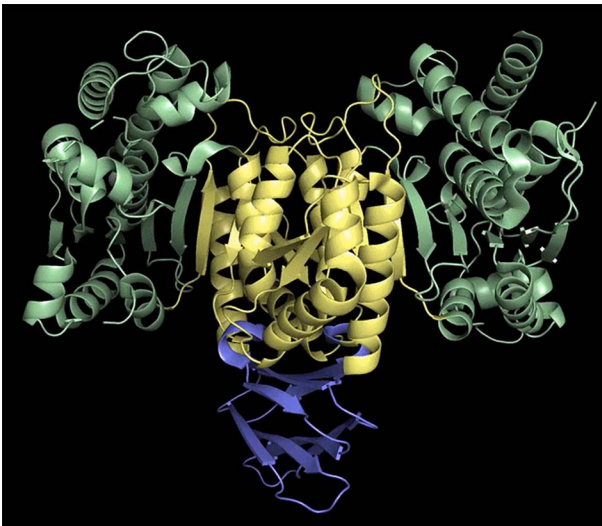
Advancements in understanding cancer metabolism highlight the potential use of metabolites, such as pyruvate and choline, to complement ¹⁸F-FDG PET/CT. The development of clinically validated and innovative non-glucose-based tumor imaging techniques aimed at enhancing tumor detection and metabolic classification will provide additional tools for cancer care.

Question 103: How can we develop medicines that block the cancer-specific metabolic functions of non-mutated metabolic enzymes without affecting their canonical catalytic activities?

Many metabolic enzymes have been targeted for disease treatment. However, intervening in the canonical catalytic activities of these enzymes, e.g., isocitrate dehydrogenase



Video 1. Three-dimensional model of isocitrate dehydrogenase 1 (IDH1) monomer. The IDH1 monomer is composed of three domains: a large domain (gray green, residues 1–103 and 286–414), a small domain (sandy yellow, residues 104–136 and 186–285), and a clasp domain (dusky blue, residues 137–185). <https://vcmedpsciences.org/10.1051/vcm/2024005#V1>.



Video 2. Three-dimensional model of isocitrate dehydrogenase 2 (IDH2) monomer. Similar to the structure of IDH1, IDH2 monomer possesses three domains: the large domain (gray green, residues 42–143 and 325–452), the small domain (sandy yellow, residues 144–176 and 225–324), and the clasp domain (dusky blue, residues 177–224). <https://vcmedpsciences.org/10.1051/vcm/2024005#V2>.

(IDH, [Videos 1](#) and [2](#)), unavoidably disrupts their regular functions, which are essential for physiological activities in organs and body systems. IDH1/2 mutations confer a noncanonical function for the production of 2-hydroxyglutarate rather than α -ketoglutarate. This has led to the successful development of drugs for the clinical treatment of acute myelogenous leukemia (AML). While metabolic enzymes are rarely mutated in cancer, research has demonstrated that they can possess moonlighting

functions crucial for tumor progression. These enzymes, including pyruvate kinase M2 (PKM2), phosphoglycerate kinase 1 (PGK1), hexokinase 2 (HK2), phosphoenolpyruvate carboxykinase 1 (PCK1), fructose biphosphatase 1 (FBP1), and many others can function as protein kinases, protein phosphatases, or signaling molecules, playing vital roles in diverse cellular activities in tumor cells. Thus, a key question is how to develop medicines that can block the cancer-specific metabolic function of non-mutated metabolic enzymes without affecting their canonical catalytic activities?

Question 104: Can dietary-based cancer therapy be proven effective in treating cancer?

Precision food therapy has been proposed, with examples such as the keto diet being employed in clinical trials. However, there is debate about the conceptual basis for these trials. Therefore, the question arises: Can future advances in understanding cancer metabolism lead to the identification of key elements in nutrients and foods that could be utilized in dietary-based cancer therapy?

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