“New Metabolic Approaches to Cancer Treatment” (Ahmed Elsakka, MD) [#120]

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“Developing an effective way to translate this medical information from the bench side to the bedside is what matters, because science without application is not a science for me.” – Ahmed Elsakka, MD

“Cancer cells love to have lots of iron. However, iron has dual properties: it can facilitate tumor growth, or it can cause cell death (ferroptosis), due to the accumulation of iron and failure of the antioxidant defensive mechanism of cancer cells.” – Ahmed Elsakka, MD

“Methionine is an essential amino acid involved in protein synthesis and methylation processes, which are critical for cancer cell growth. In a clinical study, 5-fluorouracil alone failed to shrink tumors, but when combined with methionine restriction, a significant tumor-shrinking effect was observed. This suggests that methionine restriction can sensitize cancer cells to chemotherapy.” – Ahmed Elsakka, MD

Meeting Summary

Advanced cancer patients and caregivers are continually searching for optimal treatment options. It’s often challenging because treatment options are continuously advancing and some forms of cancer have become drug-resistant. One area of great potential is metabolic approaches to controlling cancer – working to inhibit the systems that drive cancer growth and disrupting cancer cells’ energy production – a method that makes cells more vulnerable when paired with other cancer treatments.

What are the new metabolic therapies at the cutting edge of cancer care that cancer patients and caregivers need to know about?

Dr. Ahmed Elsakka, Director of Research at the Metabolic Terrain Institute of Health, is uniquely qualified to discuss clinical metabolism, cancer metabolism, and clinical applied biochemistry in the prevention, diagnosis, and treatment of cancer and other complex metabolic diseases. He is a metabolic therapy specialist, clinician, and scientist with expertise in various research fields, including neurometabolism, ozone therapy, regenerative medicine, photodynamic therapy, sonodynamic therapy, methionine metabolism, ferroptosis, tissue healing, and metabolic management of cancer. He was the Senior Researcher and Medical Director of the Egyptian Foundation for Research and Community Development. After completing his medical education at the prestigious Faculty of Medicine of Alexandria University, Egypt, and a rigorous residency program in Egypt, Dr. Elsakka pursued advanced studies in neurometabolism at Johns Hopkins University in the United States, focusing on the impact of ketogenic diets in epilepsy and other neurological disorders. His deep exploration into cellular energetics, particularly the role of ketogenic diets in cancer cell metabolism, piqued his interest in cancer research at submolecular levels. Notably, he collaborated with Professor Thomas Seyfried, a global leader in cancer metabolism studies. Together, they co-authored multiple scientific papers. Dr. Elsakka

further obtained a postgraduate diploma in clinical applied biochemistry from Harvard Medical School, a certificate in epigenetics and gene expression from Melbourne University in Australia, and a Masters of clinical nutrition and metabolism from the National Nutritional Institute in Cairo, Egypt. He is associated with prominent organizations, including the Global Society of Metabolic Therapy (as the co-founder), the Global Leadership Panel at Fight Cancer Global, the Egyptian Functional Medicine Association, and the Egyptian Medical Society for Ozone Therapy and Complementary Medicine. Moreover, his expertise extends to drug delivery systems, nanotechnology, and phytochemical extraction, having collaborated with a medication facility in Brazil to conduct workshops and train their company’s teams.

Why might you want to better understand how cancer metabolism can be used to treat your cancer?

Cancer treatments aim to identify unique characteristics of cancer cells—such as genetic mutations, metabolic dependencies, or rapid growth—and target those features to hinder or kill the cancer cells. For example, traditional chemotherapies often attack rapidly dividing cells, while newer therapies target specific molecular pathways or immune responses.

Understanding cancer “metabolism” – how cancer cells use carbohydrates, fats, and proteins from food to get the energy they need to grow and spread – and how it is different from the metabolism of normal cells can lead to additional treatment options. Compared to healthy cells, cancer cells use more glucose, produce less energy when making what they need to multiply and spread, and favor fermentation over breaking down glucose in the presence of oxygen. Unlike surgery, chemotherapy, or radiation, metabolic therapies often work by altering cancer cell metabolism, either slowing growth or inducing cell death through mechanisms like ferroptosis. Over time, this can lead to tumor shrinkage and cell death.

Researchers are looking for ways to block the unique metabolic processes of cancer cells while leaving healthy cells alone by reducing the food supply to the cancer cells and disrupting the messaging systems (“pathways”) used by cancer cells. For example, inhibiting “glycolysis” – the process of breaking down glucose to release energy – may help stop the development of cancer cells. New pathways are being explored through the possible roles of iron and oxygen.

What can you do to address your cancer using a metabolic approach?

Metabolic approaches to treating cancer are in the early stages of research. They are not part of the standard of care, but show much promise. Oncologists are not taught about the metabolic pathways beyond the “Warburg effect” (a “hallmark” of cancer cells – cancer cells preferentially break down sugar using glycolysis to produce energy, rather than using the more efficient approach of normal cells). There are multiple pathways that cancer can use to increase its nutrient uptake. Blocking those pathways can weaken the cancer. Examples of metabolic treatments include “ferroptosis” (a type of cell death triggered by the accumulation of iron within cells), sound, light, methionine (an essential amino acid) restriction, and nanotechnology.

What is the role of iron in cancer and ferroptosis as a new cell death mechanism?

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Cancer cells require high levels of iron for growth and proliferation. However, iron also plays a dual role: while it can facilitate tumor growth, excessive iron accumulation can lead to “ferroptosis”, a form of iron-dependent cell death. This occurs due to the buildup of iron and the subsequent failure of the antioxidant defense mechanisms in cancer cells, leading to lethal “lipid peroxidation” - a chemical process that damages cell membranes by oxidizing fatty compounds that perform a variety of functions in your body.

How can sound and light be applied to control cancer?

In photodynamic therapy (PDT), a photosensitizing drug is administered and accumulates in cancer cells. When exposed to a specific wavelength of light, the photosensitizer is activated, transferring energy to molecular oxygen and generating reactive oxygen species (ROS). This oxidative burst damages cellular components, leading to cancer cell death.

In sonodynamic therapy (SDT), ultrasound waves are used to activate “sonosensitizing” (sound sensitizing) drugs within cancer cells. This activation generates reactive oxygen species (ROS), which induce oxidative stress and cancer cell death. Unlike photodynamic therapy, SDT can penetrate deeper tissues, making it suitable for internal tumors. The energy emits light through a phenomenon called **sonoluminescence** (light that is produced from sound), stimulating the photosensitizer drug as mentioned above, causing the similar photodynamic effect that results in the generation of ROS and killing of the cancer cell.

However, sonodynamic therapy may increase the size of the tumor in some cases. Still, the metabolic uptake of the tumor of sugar which is measured in PET scans will be less in the metabolism, and more in the size that is shown on the scan. This is called “pseudoprogression” – it’s not a true progression.

How can methionine restriction control cancer?

Methionine restriction diets aid cancer control by reducing oxidative stress to inhibit tumor growth. Cancer cells are “addicted” to methionine because their growth is dependent on the substance **glutathione.** Glutathione depletion via methionine-restricted diets can induce endoplasmic reticulum (ER) stress. This, paired with the depletion of antioxidant stores, induces cell death.

What are emerging developments in nanotechnology that can impact cancer care?

Nanotechnology has emerged as a transformative tool in cancer treatment, enabling ultra-specific drug delivery systems that enhance the stability, bioavailability, and targeting of therapeutic agents. Though research is primarily conducted on cell cultures and animal models, research found that the minimum effective dosage of sulfasalazine (anticancer medicine) was reduced, with nanotechnology delivery, from 12 grams to 125 milligrams.

Nanotechnology’s continued development enhances the oral bioavailability of the drug itself. In recent labs, nanotechnology has come in the form of polymer-based particles, inorganic materials (including silica-coated, iron, gold, and silver particles), and lipid-based nanoparticles that are highly effective at passing through membranes and targeting specific cells.

How would you know whether a metabolic approach might be right for you?

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If you are interested in exploring innovative and scientifically grounded approaches to cancer treatment, metabolic therapies may be worth considering. However, evaluating these treatments can be challenging, as they are not yet part of the standard of care and require further clinical validation.

Most patients and caregivers who lean to the natural mindset solve this difficult treatment evaluation challenge by finding and relying on a quality natural healing center and organizing a team, including some combination of (1) a doctor, (2) a nutritionist or naturopath who specializes in oncology, and (3) resources at the integrated oncology department of a nearby academic research cancer center.

You need to be prepared to pay out-of-pocket for these therapies. You might see a doctor in a natural healing center every three months to advise you, which can cost something like $600/hour. A supplement program can cost over $650/month if you are buying only the best quality supplements.

How can I learn more about the metabolic approach to cancer?

- See our discussions with Jane McLelland and Nasha WInters. They are both active in the same area. Dr. Elsakka works with Nasha Winters.
- Contact Dr. Elsakka at drahmed@mtih.org
- Read or view our discussions with Mark Taylor and Gabriele Gavazzi, and Bapcha Murty on complementary therapies and the evidence they have gathered.
- Join the many Facebook pages that focus on health, healing, and natural remedies, such as Jane McLelland’s off-label drugs for cancer, the Patient Led Oncology trial group, Integrative Metabolic approach to health and wellness, Medicine Cabinet-Natural Healing Remedies, Beating Cancer with Diet and Lifestyle, and many more.
- Identify medical facilities or labs that administer metabolic treatments under guidance.

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Meeting Notes

KEYWORDS

Cancer metabolism, metabolic management, ferroptosis, iron dependency, cancer cell death, methionine restriction, nanotechnology, drug delivery, photodynamic therapy, sonodynamic therapy, antioxidant defense, glutathione, reactive oxygen species, low glycemic diet, clinical trials.

SPEAKERS

Ahmed Elsakka (90%), Roger Royse (7%), Brad Power (2%), Ellen Miller (1%), Robb Owen (1%), Raj Aji (0%)

CHAT CONTRIBUTORS

David Plunkett, Ellen Miller, Robb Owen, Raj Aji, Scott Petinga, Brian Kane, Noel Resch

SUMMARY

Dr. Ahmed Elsakka discussed the metabolic management of cancer, emphasizing the complementary role of metabolic pathways and standard therapies. He detailed the ferroptosis protocol, which targets iron-dependent cell death, and its effectiveness in liver and pancreatic cancers. He highlighted the use of artemisinin, sulfasalazine, and nanotechnology to enhance treatment efficacy. He also explained the importance of methionine restriction diets and the role of selenium in managing oxidative stress. He shared case studies showing significant tumor reductions using these methods, stressing the need for precise dosing and monitoring biomarkers, such as urinary MDA, a biomarker of systemic oxidative stress.

OUTLINE

Overview of Metabolic Management of Cancer

- Dr. Elsakka explains the focus of the session: translating metabolic management of cancer from bench to bedside.
- He differentiates between metabolic management and standard of care, emphasizing the complementary nature of the two approaches.
- The metabolic management targets cancer pathways, including energy sources, redox balance, signal transductions, and epigenetic modifications.
- He introduces the topics of ferroptosis application, sound and light in cancer management, cancer methionine restrictions, and nanotechnology in drug delivery systems.

Ferroptosis and Its Mechanisms

- Dr. Elsakka introduces ferroptosis, a new term in cancer research since 2009, and explains its mechanisms.
- Ferroptosis is an iron-dependent form of cell death, different from apoptosis or necrosis, and is dependent on iron and lipid oxidation.

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- Certain cancer types, like liver and pancreatic cancers, respond well to the ferroptosis protocol.
- Dr. Elsakka discusses the role of hepcidin in iron regulation and its impact on cancer cell iron storage.

Iron and Cancer Cell Death

- Dr. Elsakka explains the relationship between cancer and hepcidin, highlighting the importance of iron in cancer cell survival.
- He describes the dual role of iron in cancer: facilitating tumor growth and causing cell death.
- The cancer cell's antioxidant defense mechanisms, including glutathione, are crucial in resisting chemotherapy and radiotherapy.
- Dr. Elsakka discusses the role of methionine in cancer cell metabolism and the potential benefits of a low methionine diet.

Methionine Restriction and Cancer Treatment

- Dr. Elsakka explains the rationale behind methionine restriction, including its role in reducing oxidative stress and tumor growth.
- He discusses the clinical trials and successes of methionine restriction in cancer treatment.
- The combination of methionine restriction with chemotherapy, such as 5-FU, shows promising results.
- He shares a case study of a patient with renal cell carcinoma who showed significant tumor reduction with a low methionine diet.

Application of Light and Sound in Cancer Management

- Dr. Elsakka introduces the use of light and sound in cancer management, including red and infrared lasers, and ultrasound.
- He explains the concept of photobiomodulation and its effects on cancer cell proliferation and regression.
- Photodynamic therapy (PDT) involves the use of a photosensitizer, oxygen, and light to induce cancer cell death.
- He discusses the limitations of PDT, such as tissue hypoxia and light penetration, and potential solutions like sonodynamic therapy.

Sonodynamic Therapy and Its Benefits

- Dr. Elsakka explains the principles of sonodynamic therapy, including the use of ultrasound to stimulate photosensitizers.
- He discusses the advantages of sonodynamic therapy over photodynamic therapy, such as deeper tissue penetration and reduced side effects.
- He shares clinical trial results and case studies demonstrating the effectiveness of sonodynamic therapy in various cancer types.
- He highlights the potential of combining sonodynamic therapy with other treatments like hyperbaric oxygen and acriflavine.

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Nanotechnology in Cancer Treatment

- Dr. Elsakka discusses the role of nanotechnology in drug delivery systems, enhancing the effectiveness of cancer treatments.
- He explains the benefits of nanoparticles in improving drug stability, bioavailability, and targeting specific cancer cells.
- He shares examples of different types of nanoparticles, such as polymeric, inorganic, and lipid-based nanoparticles.
- He discusses the development of new dye photosensitizers for targeted cancer cell detection and resection.

Case Studies and Practical Applications

- Dr. Elsakka shares case studies of patients treated with various metabolic and photodynamic therapies.
- He discusses the success of sonodynamic therapy in treating neural cancers and urinary bladder cancer.
- He emphasizes the importance of monitoring biomarkers like urinary MDA to assess the effectiveness of ferroptosis protocols.
- He highlights the potential of nanotechnology in improving the clinical outcomes of cancer treatments.

Q&A Session and Closing Remarks

- Roger Royse and Dr. Elsakka address questions from the audience about the practical application and effectiveness of the discussed treatments.
- Dr. Elsakka explains the importance of monitoring biomarkers and the potential side effects of high-dose treatments.
- He discusses the need for further research and clinical trials to validate the effectiveness of these treatments.
- Roger Royse thanks Dr. Elsakka for his presentation and encourages the audience to reach out for more information.

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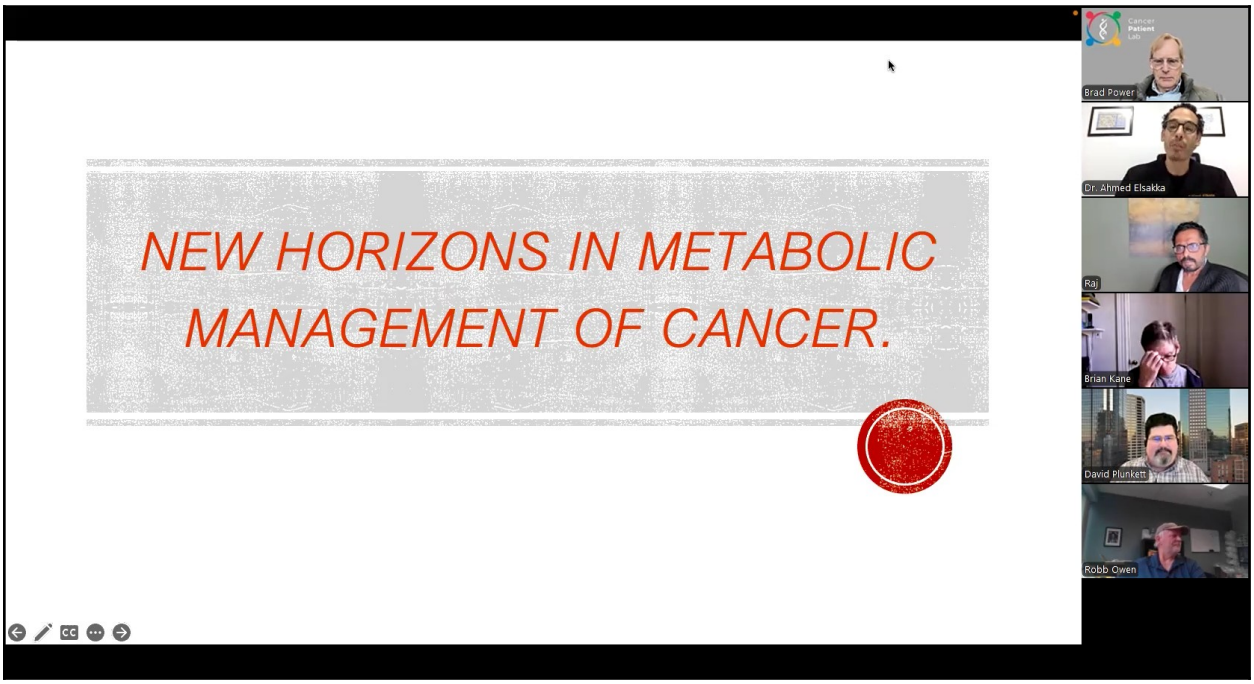
TRANSCRIPT

Brad Power
This is the Cancer Patient Lab.

Today we’re honored to have Dr. Ahmed Elsakka with us. He’s going to be talking to us about his work – how cancer can grow and get fed – and the metabolic approach. He’s a colleague of Dr. Nasha Winters, who's been on our session before, and who recommended him to us.

This is for informational purposes only. This is not medical advice. We try to arm patients and caregivers with information they can take to their medical team. We are a patient-led, volunteer-led nonprofit, and we welcome donations, which you can do through our website, at cancerpatientlab.org, and there's a donate button. With that I’ll turn it over to Dr. Elsakka.

Ahmed Elsakka 1:17
First of all, I need to express how lucky I am to be with amazing people like you guys. I really appreciate that, and thank you for giving me the opportunity to be a part of this wonderful event.



Ahmed Elsakka 2:26
Our topic today is a new horizon in metabolic management of cancer, which means I’m not introducing anything new for you; I think most of you know this information. However, the question is how to implement this information. Developing an effective way to translate this medical information from the bench side to the bed side is what matters, because science without application is not a science for me.

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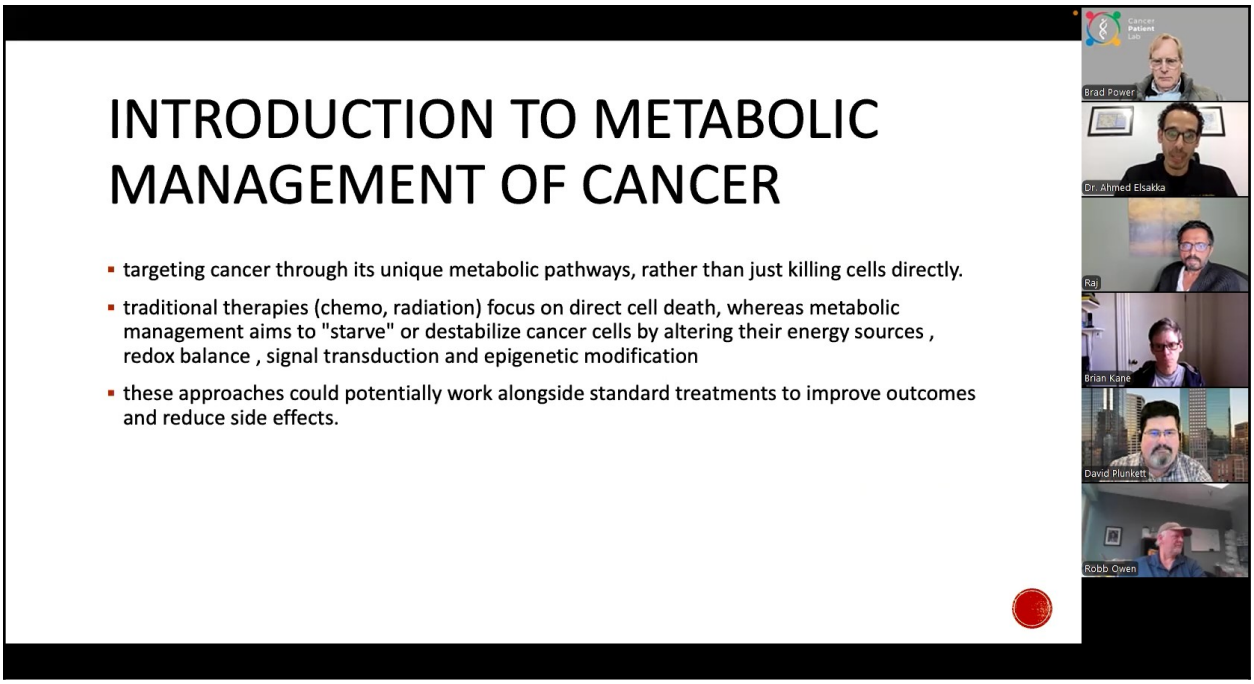

Today I am focusing on exposing my idea about cancer metabolism, and how we can make this happen in a clinical setting. First, let me differentiate between the metabolic management of cancer and the standard of care. In the metabolic management of cancer, we target the cancer pathway: we don’t target the cell directly. We target the metabolic pathway that enables the cancer cell to survive.

Unlike the traditional therapy, which is the chemotherapy and radiotherapy, which is focused on direct cell death, the metabolic management aims to starve or destabilize the cancer cell by changing the energy source, the redox balance, the signal transduction, and even epigenetic modifications. And we need to know that these approaches could potentially work alongside each other (...) and we see the best result when we’re combining the standard of care with the metabolic management. They’re not alternatives: they’re complementary to each other. Today, as you know, we’ll talk about ferroptosis, application of sound and lighting in cancer, methionine restriction, and nanotechnology in drug delivery systems. Let’s start with ferroptosis.

Ferroptosis is a new term that was first scientifically described in 2009. Ferroptosis is an intracellular, iron-dependent form of cell death. It’s completely different from apoptosis or necrosis, because it depends on two novel mechanisms: iron dependency (that cancer cells are iron-rich which predisposes them to lipid damage) and lipid peroxidation (the buildup of peroxides in cell membranes which leads to cell death). So for this cancer cell death mechanism to occur, we need cancer cells that have very high concentrations of iron, or **free labile iron**. And also, this iron can be highly oxidative, to oxidize lipids for peroxidation. So, ferroptosis is actually a very good therapeutic opportunity for certain cancer types like liver and pancreatic cancers, especially the **KRAS mutation**. Many cancers show a response to the ferroptosis protocol. Some chemotherapy itself can trigger ferroptosis, such as erastin, that is being used for hepatocellular carcinoma. Some phytochemicals that are coming from the nutraceutical like

artemisia, peperlongamin, and withaferin A can also trigger cancer cell ferrotopic cell death. So actually, ferroptosis is a very effective mode for treatment for cancer that is usually drug-resistant or resistant to chemotherapy.

To understand the role of iron in the cancer cell, we have to be introduced to **hepcidin** (a small protein hormone that plays a crucial role in regulating iron metabolism in the body). Hepcidin is an iron-regulated peptide (small protein fragment). If we have a low hepcidin condition, despite an increase in iron uptake, we’re not going to be storing very much iron. Instead, we are releasing the iron into circulation. If we have a high hepcidin, we do the opposite. A higher iron uptake. We store the iron inside the cell, not excreting the iron into circulation. So we’re having a lot of iron in storage form inside the cell when we have high hepcidin.

The relationship between the cancer and the hepcidin is in the tumor itself. The tumor leads to macrophage activation and it produces the proinflammatory cytokines which affects the liver – which is the main source of the hepcidin. This will increase the iron in storage form inside the cell, and decrease the plasma free-labile iron. This will cause a functional iron-deficiency anemia, or a cancer-related anemia, which is actually completely different from obsolete iron deficiency anemia, because treatment is different. In **obsolete iron deficiency**, the treatment is iron or blood transfusion; however, in the cancer cell, it’s completely different. There is no problem with the iron – we have a lot of iron inside the cell. Rather, we have a problem with hepcidin. So, if I need to treat the cancer-related anemia, I need to decrease the inflammatory cytokines: I need to inhibit the tumour itself to deplete the function of the deficiency anemia. However, from this slide, we know that iron is very important in cancer as a different mechanism. Cancer depends on the iron signalling pathway. It controls the p53 pathway, which is a tumour suppressor gene, cell cycle progression, oxidative stress control, and the hypoxia-induced factor pathway. Moreover, iron also functions as a crucial coenzyme in DNA replication and repair.

Thus, cancer cells love to have lots of iron. However, iron has dual properties, as we established previously: it can facilitate tumor growth, or it can cause cell death (ferroptosis), due to the accumulation of iron and failure of the antioxidant defensive mechanism of cancer cells. Because iron is good and bad at the same time, cancer cells tend to increase the antioxidant defense mechanism, also tending to pack the iron in a ferrite, as opposed to a free-labile form.

Speaking about the cancer antioxidant defense mechanisms. There are multiple. However, the most important mechanism is an antioxidant system, again, what ferroptosis and the glutamine / cysteine antiport hinge upon. Glutathione, which is the major antioxidant that the cancer uses to resist chemotherapy and radiotherapy and frankly, any oxidative therapy including ferroptosis, high doses of vitamin C, hyperbaric therapy. All of these treatments are oxidized. In treatment, oxidative stress is increased in the tumor. Thus, if the tumor is able to produce an excess of glutathione, it will buffer this treatment at coding resistance. Where are the tumors bringing the glutathione? The glutathione is coming from cysteine (building molecule), and the tumor cell can get cysteine from two mechanisms: the first, and more popular one, 80% of the glutathione is made from the extracellularly imported cysteine that is exchanged with intracellular glutamate.

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So cancer cells bring the glutamate outside the cell, and take the cysteine inside, making the glutathione. Luckily enough, most of the pharmacological treatments used in ferroptosis can efficiently block the cysteine / glutamine antiport and protect the cancers from being able to produce an excess of glutathione.

Ahmed Elsakka 10:34
However, we have another source of cysteine. As we said, cysteine can be produced at the cystine/glutamate antiport as a building block of the glutathione. But cysteine can also be obtained from homocysteine, which is an inner metabolite accumulated inside our body and is washed out within the homocysteine cycle, or methionine cycle. Methionine, which is one of the essential amino acids in diet, can turn into homocysteine and again into cysteine – leading to glutathione production. One reason why the cancer cell is addicted to methionine, is because the amino acid is dependent on glutathione; it needs a lot of glutathione to increase the trans-sulfration pathway, which in turn increases the addiction to methionine. (...)

Ahmed Elsakka 11:36
A lot of research has been done on ferroptosis. It will be on the horizon in cancer management.

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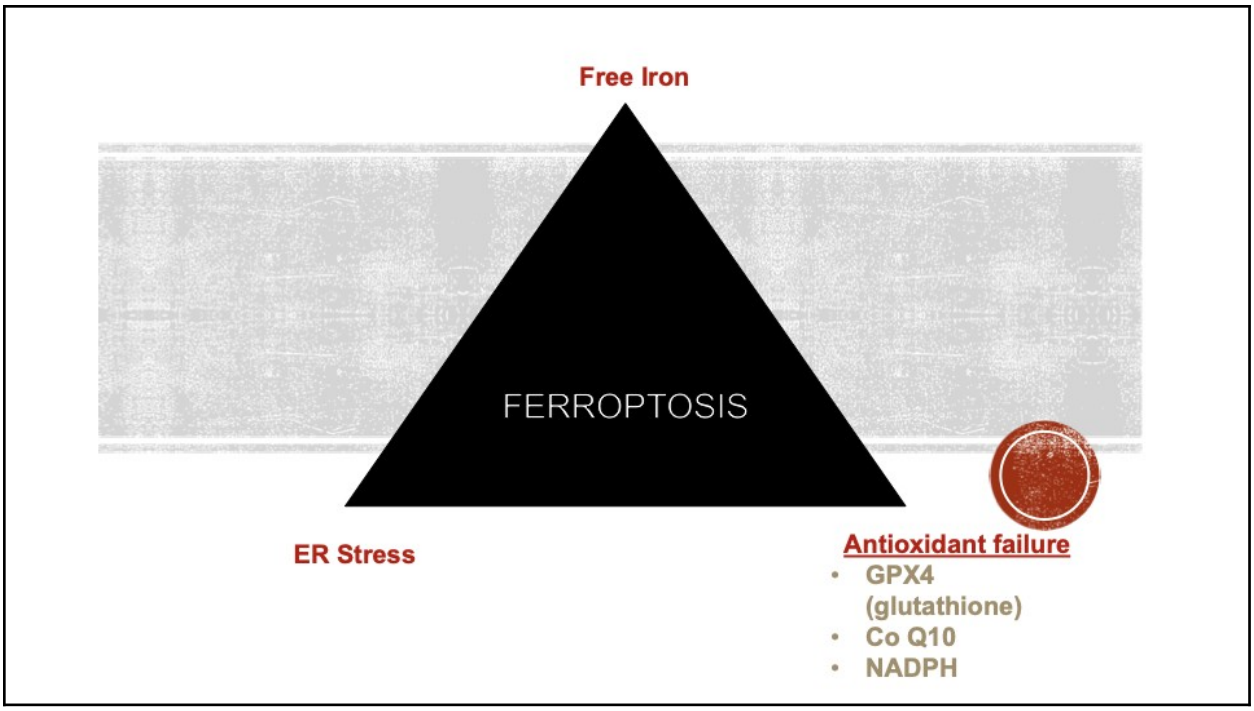

There has been lot of success with ferroptosis treatment of cancer, and to move this success from animal models and cell cultures to humans, we need to understand more about the molecular mechanism of the process itself, in addition to the pharmacokinetics and pharmacodynamics of the drug that is being used in these mechanisms. Ferroptosis causes antioxidant failure, especially glutathione depletion, and can induce endoplasmic reticulum (ER) stress. If we can induce ER stress and antioxidant failure at the same time, we can induce ferroptosis as a cell death. There are some herbs and medications that can actually transport the ferritin iron from a storage form to free iron. [These medications are] called unpacked ferritin, because it unpacks the iron from ferritin form to free-labile iron that is capable of cell death.

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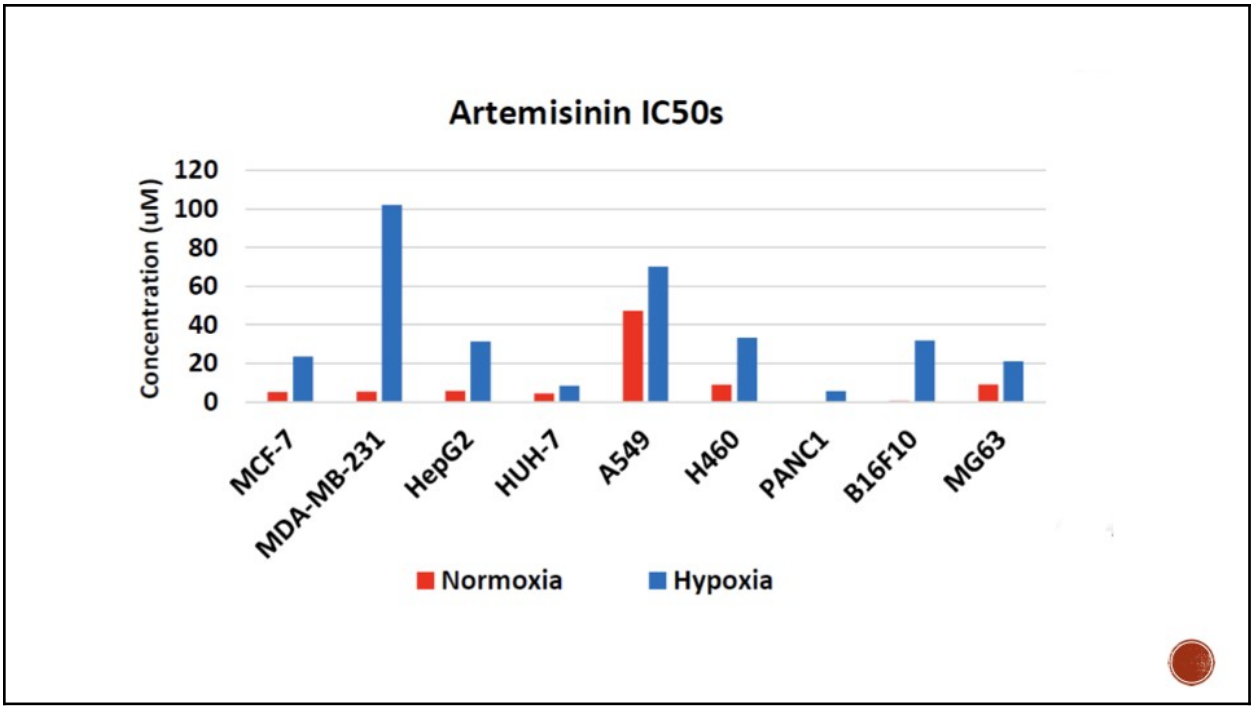
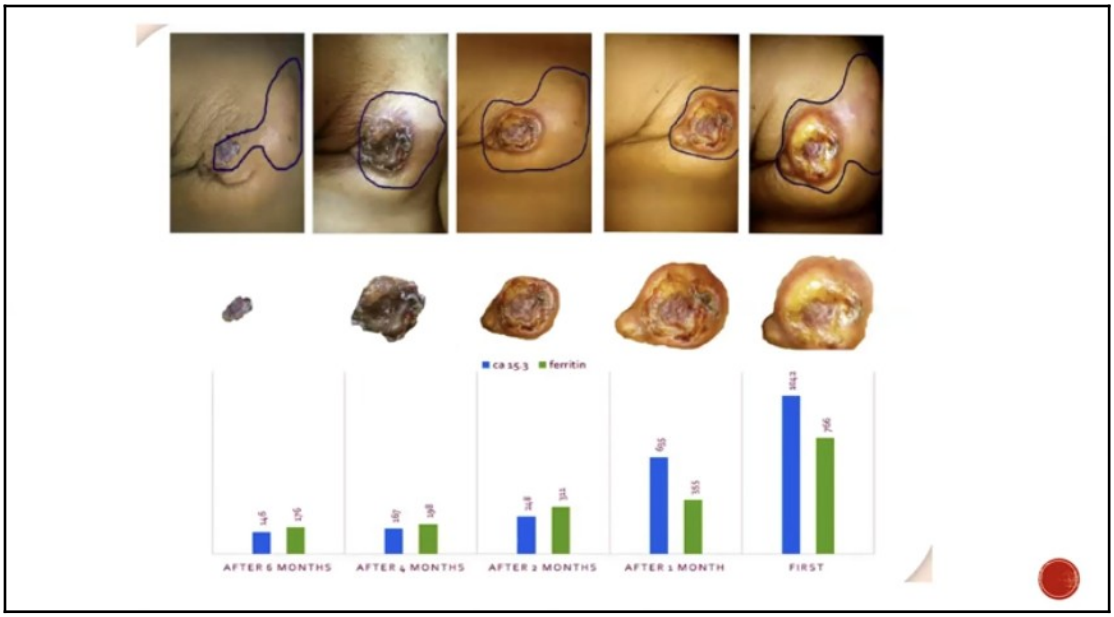


Ahmed Elsakka 12:46
The most famous one of such medicines is artemisinin. Artemisinin is a phytochemical. The active molecules coming from **artemisia**, or wormwood (one of the traditional Chinese medicines), is very effective in driving cell death due its accumulation of iron. By the way, it is FDA-approved in malaria because of the same reason: artemisinin is used (...) to unpack the iron inside the malaria parasite, increasing the oxidative stress inside, causing its death. In my lab, we did a formulation of artemisinin to be used in cell culture trials, and we used six different kinds of cancers: breast cancer (hormonal positive and hormonal negative), hepatic carcinoma, pancreatic carcinoma, and glioma, to name a few. And we found that artemisinin was able to reduce the concentration of the cancer cell with even low doses; however, this is only in normoxia conditions – or normal oxygen levels. In hypoxic conditions, which is present in most cancer cases, we lack the artemisinin effect. Or at least, there is a huge difference between the hypoxia and normoxia when using the artemisinic, which is completely logical because artemisinin is not directly killing the cancer, it’s unpacking the iron which makes the iron more reliable for oxidation. If you don’t have the oxygen, you don’t have oxidation. If you have oxygen, you have oxidation. And that’s why we can increase one more element when treating with ferroptosis: the concentration of free-labile iron in the presence of oxygen.

Ahmed Elsakka 14:31
Sulfasalazine, the other drug that can inhibit the cysteine-glutamine antiport, can deprive the tumor of cysteine and glutathione antioxidant systems. Unfortunately, though, it has a very high dose tolerance curve. As you can see in the bottom image, (...) it doesn’t have any effect on the cancer with the low dose or medium dose. It did [have an effect] on the massive, high dose of more than 1000 microlitres. It’s very effective to kill the cancer, but it also carries a lot of side effects. That's why we use nanotechnology and drug delivery systems to increase the selectivity

and effectiveness of this drug without actually having any kind of toxicity, which is [crucial] in nanoparticle technology.

Ahmed Elsakka 15:29
Long story short, we use multiple phytochemicals like artemisia, from wormwood; withaferin A from ashwagandha, and lactoferrin, one of the components of milk to induce free-labile iron. We use EGCG, coming from green tea, nutritional deprivation (fasting) to create the effect of endoplasmic reticulum stress. And we use sulfasalazine, the most [common] treatment used in sustaining cystine-glutamate antiporter inhibitors. Sometimes, we combine this with homocysteine balance via a low-methionine diet. If we did that, we can have this result:



Ahmed Elsakka 16:14
This is the first patient of mine. It was a palliative case of stage four breast cancer once it had spread to everywhere in the body. And she had a huge recurrence in her breast. She had a very high concentration of ferritin, and a very high concentration of tumor biomarkers: over 1000 and 700 respectively. When we started the ferroptosis protocol, we noticed a decrease of the ferritin, and also a decrease in the tumor markers. Also, the tumor has [visibly] become smaller and smaller.

Ahmed Elsakka 16:55
So, as we just said that with a methionine-restriction diet, (methionine being one of the essential amino acids), your body is unable to make methionine. Basically, if I restrict the intake of methionine, you will not be able to provide the methionine or even the methionine-metabolic pathway. That’s why it’s FDA-approved in the treatment of children, with a very high homocysteine level (...). However, the low-methionine diet which is FDA-approved in children is not a low-glycemic index diet, for it still contains too much carbohydrates. Carbohydrates, even if I’m not intending to restrict intake, allows the tumour to benefit from increased insulin, obesity,

and inflammation. So, we did a small modification to the FDA-approved low methionine diet to be also a low glycemic index diet, restricting carbohydrate intake.

Ahmed Elsakka 17:57
Methionine is not only important for the tumor because of cysteine, which is the precursor of glutathione, but also very important for the tumor because it dissociates into polyamines – important for cell proliferation – and is essential in the process of methylation, which controls DNA and RNA protein repair.

Ahmed Elsakka 18:19
Many clinical trials have been done in restriction of methionine in cancer patients. The most famous of them, they used the methionine restriction diet in clinical Phase II trials with breast cancer and glioma – with or without the chemotherapy. They found that 5-fluorouracil, one of the very old chemotherapy medications, a fluorine-based chemotherapeutic drug, when used alone in low doses or moderate doses did nothing to the tumor. When you combine it with a low-methionine diet, there is a great change.

Ahmed Elsakka 19:10
Breast cancer (...) can cause hyperhomocysteinemia, and if you have high homocysteine or folate deficiency [there is an elevated risk of] carcinogenesis as revealed in this meta analysis. There are also multiple single-nucleotide polymorphisms that are very common among most of the cancer cells, related to methionine or the methionine-metabolism pathway, like homocysteine.

Ahmed Elsakka 19:54
That’s why in 2019, the National Cancer Institute Magazine published this – not for the scientific community but for the public people – saying that altering your diet enhances the [ability of chemotherapy cancer treatments] And the diet they mean here is the low-methionine diet. They found that methionine is needed for cell repair and also to reduce oxidative stress. In a clinical study, 5-fluorouracil alone failed to shrink the tumors. However, coupled with methionine-restriction, we saw the tumor-shrinking effect.

Ahmed Elsakka 20:45
Clinical studies have been done with preoperative colonic carcinoma patients. They gave methionine-restriction patients 5-fluorouracil 14 days before surgery, and they found a complete regression in most of them, even before surgery – which is a **grade 3 response**. (...) I will advise you guys to read this book by Robert Hoffma, one of the godfathers of methionine science, and you will find a lot of research that is being published combining the chemotherapy – or multiple chemotherapies – with zero-methionine diets. And you can see a great reduction in tumor cell counts, when using methionine restriction.

Ahmed Elsakka 21:40

Also, we found that methionine restriction is better than chemotherapy. Methionine restriction alone was better than chemotherapy alone, with the best response combining all of them together.

Ahmed Elsakka 21:52
This is one of my patients that is on a low-methionine diet, and had a renal cell carcinoma. I published this as a poster session in multiple conferences (...). This patient also unfortunately had a congenital agenesis of one of the kidneys: she has only one kidney, and on top of this kidney she developed renal cell carcinoma. She refused the surgery, because she refused to do blood hemodialysis for life. So we brought her methionine restriction and multiple other metabolic treatments because she had hyperhomocysteinemia at the time. And we found a great reduction in the tumors up to a complete necrotic area of the tumors on a PET scan. No chemotherapy, no radiotherapy. However, methionine restriction was not only helping [in tumor inhibition], but also helped the kidney [because it is a plant-based diet]. So when we applied the plant-based methionine restriction diet to the patient, not only the tumor cell improved in response, but also the kidney profile.

Ahmed Elsakka 23:13
The third topic today is the application of light and sound in cancer management. When I mention light, I mean laser, especially the red laser (660nm), the infrared laser (810nm) and blue light (430nm), and ultrasound (low intensity 1-3MHz focused).

Ahmed Elsakka 23:40
This is a visible spectrum of light, and this is the near infrared, starting from the near infrared to the near ultraviolet A and B, called photobiomodulation effect. What is the meaning of photobiomodulation? Before we say that, let me differentiate between laser and LED (light-emitting diodes)

Ahmed Elsakka 24:01
Both of them can do the same work, the same biological actions; however, lasers are more ‘coherent’ carriers of light and hold, most of the time, a single wavelength. The LED has multiple wavelengths, as you can see, and the power of the laser is much higher than the power of the LED. Both of them can do the job, but using the laser is more powerful than using LEDs.

Ahmed Elsakka 24:26
We talk about the photobiomolodulations coming from “photo,” which means light, “bio” which denotes the living cells, and “modulation” to exert influence on. So, the term photobiomodulation describes the biochemical reactions that occur in living cells in response to light, including an influence on their metabolism.

Ahmed Elsakka 24:51
Inside our mitochondria, we contain natural photosensitive substances called chromophores. These chromophores are cytochrome c oxidase mechanisms. If we irradiate the mitochondria with the red light (600 to 610nm) and infrared lights (810nm), we increase the calcium ion flux,

we increase the ATP synthesis, and the reactive oxygen species (ROS). If we increase the ROS to the migrant level, it will act as signal transduction, increasing the cell progressions. If we increase it to a very severe level, it will cause a severely oxidative cell, and will cause cell regression and proliferation.

Ahmed Elsakka 25:37
So, photobiomodulation carries dual biphasic moods: it can inhibit, or it can stimulate the cell graft with a low dose of laser and low laser exposure, [which has] the best stimulation effect to the cell progressions or cell divisions. Or, with the higher dose of the laser, we can reduce the cell progression to the limit that causes a cancer cell death. So, if we use photobiomodulation in sport injury and wound healing, we will use a photobiostimulatory effect with a very low dose. If we use the red light or infrared light as photobiomodulation with cancer, we need a huge dosage that can cause cancer cell regressions. And be careful, if you use a red light or infrared light with a low dose, you can increase the cancer cell proliferation.

Ahmed Elsakka 26:41
(...) With photobiomodulation, there is a natural photosensitive component inside the mitochondria, so you don’t have to do anything unless you expose the area that you want to treat to the light. However, photodynamic therapy is different. It is a very ancient practice — my grandfather in Egypt found this [artefact] in the temples in Egypt where the Pharaoh is giving the patient some kind of plant and placing them under sunlight to treat their sickness, which is the basic idea behind photodynamic therapy.

Ahmed Elsakka 27:27
Photodynamic therapy has been developed since the 1800s until now. And it has become FDA-approved, and the last FDA approval of photodynamic treatment of cancer was in 2022 in prostatic carcinoma. The first approval in 2004 in superficial skin cell cancer.

Ahmed Elsakka 27:50
In photodynamic therapy, I basically give you a drug called a photosensitizer, and then after a period of time, I allow the accumulation of this photosensitizer in the cancer cell, then irradiate the cancer cell with a laser. What’s happening here is the laser, the power source, stimulates the photosensitizer from the ground state to the excited state. And during this stimulation, it releases oxygen atoms, and reactive oxygen species are generated. This kills the cancer cell by causing cellular toxicity – the same way as radiotherapy, but without radiation.

Ahmed Elsakka 28:31
Each one of these three basic elements is nontoxic. The photosensitizer is not toxic alone; the laser is not toxic alone; and the oxygen, of course, is not toxic alone. However, the combination of these nontoxic components will cause a cytotoxicity through generation of free radicals – leading to cancer cell death.

Ahmed Elsakka 28:53

So, this is the area [the intersection] that photodynamic therapy [deals with] – the combination between the photosensitizer, oxygen, and a light source. We need to make sure when we treat patients with photodynamic therapy not to harm normal cells; so we make sure that only inside the cancer cell can this combination occur. [At the same time], we need to make sure that in normal cells, if the oxygen is there, the photosensitizer is not there, or if there is both a photosensitizer and oxygen, there is no light source going there. And I will tell you why in a minute.

Ahmed Elsakka 29:26
We have limitations of photodynamic therapy, and we have a way to solve these limitations. The first limitation is tissue hypoxia, because when there’s no oxygen – no oxidation – the treatment will not have any kind of effect, just like the artemisinin ferroptosis. That’s why when the patient undergoes photodynamic therapy, just before the sessions, they are administered ozone, hyperbaric oxygen therapy, or an hypoxia-inhibitor drug like **acriflavine**. It’s actually approved to be a potent hypoxia inhibitor. So, while the tissue hypoxia is a limitation, we can solve the limitation this way. Limited light penetration is another limitation, because the penetration laser can treat only two to three centimeters below the skin. Most cancer cells are deeply-seated. How can we solve that? Well, we change the energy source: instead of being a light, it will be an ultrasound, and we can have what we call a sonodynamic effect. And ultrasound can treat up to twelve to twenty centimeters below the skin. Also, we can use fiber optics to deliver the light directly inside the tumor, called interstitial or intratumoral photodynamic therapy. Sometimes we use intracavity photodynamic therapy; for example, in some urinary bladder carcinomas, we can introduce the light inside the urinary bladder by a fiber optic. A third problem with photodynamic therapy is that we still risk possible damage to normal tissue. That’s why we need a targeted nanoparticle technology to enable the photosensitizer to target only the cancer cell with minimal effect on the normal cell. And we need to design this photosensitizer in a way so that it only accumulates in cancer cells, so even if the normal cell takes in some of them, it is removed or excreted during the period of accumulation.

Ahmed Elsakka 31:38
The amazing molecule in the acriflavine was examined alone or in combination with photodynamic therapy.

Ahmed Elsakka 31:50
If you see here, this is the violet dyed image of the cancer cell. When we did photodynamic therapy alone, we had a good response. When we gave acriflavine alone, we still had a very good response – better than photodynamic therapy alone because it inhibits hypoxia. But when we combine them both together, we have the most effect on the cancer cell. Despite photodynamic therapy being FDA-approved, there is no approval for the oxidative therapy or the anti hypoxia therapies to be used with photodynamic therapies – I don’t know why.

Ahmed Elsakka 32:33
In sonodynamic therapy, as we just mentioned, we use the focal ultrasound, which will cause a phenomenon called acoustic cavitation. Basically, it forms a cavity, and then this cavity will

increase in size. When it takes more ultrasound energy, the bubble, or the cavity, will increase in size until the limit that the surface tension of the fluids made over the bubble becomes lower than the high energy acquired inside the bubble – it explodes. When it explodes, it releases a massive amount of energy causing thermal damage, or hyperthermia; it emits light through sonoluminescence, which means a light that can be produced from sound. This light can actually stimulate the same photosynthesizers and cause the photodynamic effect (generation of reactive oxygen species). Also, the ultrasound shock waves can cause mechanical damage to the tumor cell itself. The cell death because of the sonoluminescence is the same as photodynamic therapy – it’s **apoptosis**, programmable cell death. However, the cell death from mechanical or thermal damage is **necrosis**, causing swelling and some inflammation. That’s why we found that treating patients with sonodynamictherapy, while sometimes a succesful treatment, may actually increase the size of the tumor [in some cases]. Still, the metabolic uptake of the tumor in PET scans will be less in metabolism, but greater in size – this is called pseudoprogression, it’s not a true progression.

Ahmed Elsakka 34:21
Sonodynamic therapy is very famous right now for treatment of intracranial gliomas like **GBM** and a combination of sonodynamic and photodynamic therapy shows enhanced long-term cures of brain tumour patients.

Ahmed Elsakak 34:42
There are ongoing clinical trials in Phoenix about the recurrent high-grade glioma and [treatment with] sonodynamic therapy. And these are actually thermographic pictures of a musculoskeletal sarcoma treated with sonodynamic therapy to demonstrate the treatment’s immediate effects. As you can see in the picture, the first image on the top left is the tumor before treatment, and it has a very high **vascularity** that it colors. When we treat it with an ultrasound, the redness (on the top right) spikes, and that’s because of the thermal damage of the tumors. After ten minutes (bottom left), it comes to decrease, and then after twenty minutes (bottom left), we observe a vasoconstriction effect, causing the tumors to be less viable, decreasing blood circulation to the tumor.

Ahmed Elsakka 35:45
We mentioned photosensitizers, which is a drug that is being excited, either by light in photodynamic therapy, or by sound in sonodynamic therapy. Multiple photosensitizers can be obtained from a natural source, like curcumin, which carries the same photosensitizing effect, like chlorine, coming from chlorophyll, methylene blue (a red light photosensitizer). Each one of these, however, can be stimulated by only one laser light. Methylene blue is stimulated by red light. Curcumin is stimulated by blue light.

Ahmed Elsakka 36:22
There are multiple generations of photosensitizers. But the third generation is the best, a conjugated liposome that actually accumulates the dye of the photosensitizer only in the tumor tissue, and causes the photosensitizer to only target the cancer cell.

Ahmed Elsakka 36:41
One more thing we can then do is administer a drug-loaded microbubble. We can make a microbubble in the lab and load it with any artificial gas, like oxygen or carbon or even a drug. Then we inject this microbubble into the patients. At the site of the tumor, we will put an ultrasound. The ultrasound will cause the expulsion of this buble, releasing the cargo or the drug or the gas into the tumor tissue when it's under the ultrasound. So just like a trigger, we try to target the drug to be just inside the tumor by using the ultrasound combined with the drug-loaded microbubble.

Ahmed Elsakka 37:26
And there are a lot of chemotherapeutic agents that, using a lipid micro-bubble, have been proved in clinical trials to decrease the dose and increase the concentration of the drug inside the tumor cell.

Ahmed Elsakka 37:39
We can use a microbubble to increase the effect of photo and sonodynamic therapy inside the cancer cell. This microbubble was developed in my lab, containing methylene blue, one type of photosensitizer, and filled with oxygen. And we injected it into the patients, and then multiple patients also underwent sonodynamic therapy. We found – this paper is published on the internet, you can find the source – pseudoprogression was observed as a novel radiological sign of solid tumors that underwent sonodynamic therapy.

Ahmed Elsakka 38:17
And actually, we administer the photosensitizers that we developed in our facility through oral and IV microbubbles, and then the sonodynamic therapy after oxygenation – either by using ozone or a hyperbaric oxygen, or a combination of all of them, including the acriflavine.

Ahmed Elsakka 38:35
You can see here in the results. This is the definition of pseudoprogression. It’s a metabolic regression, despite morphological progressions, which means the tumour size may increase, but there is a huge reduction in tumor activity. There is an immediate effect: after three months, we saw a total regression. You can see here (bottom right) that the tumor in the image was larger than before; however, now there is much less activity. And we treat lung, ovarian, and even urinary bladder carcinomas.

Ahmed Elsakka 39:21
This is one of my cases. I love this case because she was a twelve year old female with paraparesis, and was diagnosed with an dorsal ependymoma – which is not a bad tumor, not a horrible one. However, it cannot be treated with chemotherapy or radiotherapy: the only treatment available is surgical resection. You can see in the left image, the tumor is here and here (marked with lines), and is very big; it occludes the spinal cord, it’s *inside* the spinal cord – it was totally impossible to surgically remove the tumor from the spinal cord. So they could only take a biopsy from the small tumor parts to confirm the diagnosis, but could not recommend treatments. She was referred to me by one of her colleagues to see if I had any options for her.

We started the photodynamic therapy and sonodynamic therapy; luckily enough, during surgery, they removed the posterior arch of her bone in the vertebral column, which was optimal because ultrasound cannot travel through bone – but since it was removed, it directly travelled to the tumor. Then, we introduced needles here (to mark the tumor) (...) and irradiated the tumor with light. After eight sessions, we saw a dramatic change in the size of the tumor. It was the same outcome seen with radiation – *without* radiation. The patient was able to walk again because of this method.

Ahmed Elsakka 41:04
[Another patient had a] grade-three astrocytoma invading the corpus callosum. Part of it was surgically resected, and surgeons were able to remove most of the tumor; however, the part that was touching the corpus callosum was unable to be removed.

Ahmed Elsakka 41;20
[This is an image of the procedure] during surgery. We did a photodynamic-guided resection and an intraoperative photodynamic therapy . And then, this [image] is the immediate MRI after the surgery. We removed most of the tumor, however in the red circle, this is the corpus callosum, and this is the part of the tumor that could not be removed.

Ahmed Elsakka 41:43
After only eight sessions, which is actually like two months of treatment with sonodynamic therapy, there was a perfect response in neural cancers: tumors in the spinal cord or brain.

Ahmed Elsakka 43.43
We used intraoperative photodynamic therapy to the part that could not be resected. Of course, immediately after surgery, we can’t judge the effect of the photodynamic therapy. (...) Through a pair hole that cleft open a sonic window to allow the ultrasound to travel to the tumor parts, we applied the ultrasound for two months. We then found a complete regression of the tumor. Later on, we learned that sonodynamic and photodynamic therapy is very sensitive to neural tissue – particularly for neural cancers like glioma, astrocytoma, and spinal cord tumors. They are very responsive and sensitive to the photodynamic and sonodynamic therapies.

Ahmed Elsakka 45.04
Urinary bladder cancer is a perfect candidate for photodynamic therapy, because we can apply a urinary catheter to inject photosynthesizers, ozone, and oxygenation inside the urinary bladder cancer, and we can introduce the light through a fiber optic going through the urinary catheters. We did this with a man not fit for surgery, and not fit for chemotherapy. Analysing the before and after, as you can see, there is a complete regression and removal of the tumor. Blood scans are not the optimal scans to judge or monitor the urinary bladder carcinoma because the FDG dye itself is excreted into the urinary cavity. So, if you have a low grade tumor, you cannot differentiate this lower grade tumor from normal tissue. However, we can see a huge reduction in FDG uptake from before and after comparisons.

Ahmed Elsakka 46.05

The last part of the topic is nanotechnology. If you can’t see, I’m trying to connect all parts together – ferroptosis, with methionine restrictions, the nanoparticles and a formulation of photosynthesizers of photodynamic therapy. So, nanotechnology and drug delivery systems are very important, because, I think, this is a missed link in the metabolic management of cancer. It’s explained and solved that gap between the bench side and the bed side. We have a lot of drugs, a lot of medications, and a lot of maneuvers that have shown success in animal models and cell culture – however, it doesn’t have any clinical benefits. So, the transition from the bench side to the bed side is because of the [specific] drug delivery system. We need to do a deep dive into the nutraceutical and pharmaceutical aspects of treatment – everything about them: absorption, tissue distribution, minimal yet effective dosage, the mode of action of the drug, the excretions (the bioavailability in the pharmacokinetics and pharmacodynamics of the drug).

Ahmed Elsakka 47.14
Bioavailability means that when we get any drug, it goes into circulation and is then distributed to the tissue, metabolised, and excreted. If you study the bioavailability – which accounts for all of these distributary elements, you can explain why curcumin is very effective in cell culture trials, but not effective in clinical trials. The bioavailability of curcumin is very bad. When applied in animal models, usually by injection, we introduce a drug directly into the blood; when we try in the cell culture trial, we add the drug inside the cell. However, neither of these is the case in human beings: we’re giving them the curcumin orally and it then goes into the blood and is distributed among tissues – we also have to monitor the metabolism and excretion of that.

Ahmed Elsakka 48.12
This is [a cycle of] metabolism, distribution, and excretion – called pharmacokinetics, another study of pharmacodynamics, which includes the drug’s clinical effect, mode of action, and the response effect. The sulfasalazine in ferroptosis treatment was steady up until 1000 grams, which is a very huge dose in cell culture. (...) 12 grams is the minimum effective dose in a sulfasalazine clinical trial to induce ferroptosis cell death – a huge dose, 24 capsules, or 24 tablets. There can be terrible side effects. However, when we use nanotechnology, we reduced 12 grams to 125 milligrams, huge reductions in the minimal effective dose.

Ahmed Elsakka 49.14
How do we do that? Basically, nanotechnology is made to be a specific carrier for oral drugs. It enhances the physicochemical stability of the drug. If the drug is **photosensitive**, you can encapsulate the drug with something that’s not photosensitive so it can be more stable. If the drug is thermosensitive, you can encapsulate it into something that can protect it against thermal instability. It can protect the drug from the enzymatic degradation in the stomach, and enhance the blood residence time (which means the drug will continue for longer durations). Some drugs that have very good absorption and bioavailability like methylene blue still only have a stain circulation of two to four hours – which means that for every four hours, we need to ingest a new dose, which is not practical. However, in liposomal preparation of nanoparticles technology (...) we use liposomes to extend the release of methylene blue up to every 12 hours and sometimes 24 hours, so you can get one dose every 12 hours, and you maintain the same

drug residence time in the plasma. We can target the drug to target the cancer cells specifically, not just any kind of cell – which is perfect in photosensitizers. We can increase the aqueous suitability, or the water distribution of the drug, enhance the lymphatic transport, and reduce the drug efflux. All of this will enhance the oral bioavailability and enhance the drug itself. If we apply pharmacodynamics, and we solve the problem of the drug that’s being projected as off-label drugs like sulfasalazine or artemisinin – that is when we can get a result similar to the results that we see in the cultures, in the cell cultures.

Ahmed Elsakka 51.15
A different kind of nanotechnology is used in my lab, starting from the polymeric nanoparticle. We use a polymer, like chitosan-based nanoparticles. We use inorganic materials like silicon dioxide (the silica coated nanoparticle), iron oxide, gold nanoparticle, silver nanoparticle. [And we use] lipid-based nanoparticles, which are my favourite: liposome, and lipid emulsion nanoparticles. Each one of these nanoparticles has advantages and drawbacks, and its use depends on what I need to do with the drug.

Ahmed Elsakka 51.51
[Thus,] not every drug is a candidate for nanoparticle technology. Some drugs don’t have to be in nanoparticle form. According to what I need to solve in pharmacokinetics and pharmacodynamics, I can choose what kind of nanoparticle technology I will use in a clinical setting.

Ahmed Elsakka 52.10
I will give an example with curcumin. Curcumin is the active ingredient in Tumeric roots. When they try the active ingredient inside the turmeric root in an injection form, with multiple phases of clinical trials (up to phase IV), they use curcumin with a very high dose to achieve clinical benefits. Curcumin is clinically effective as an anti-inflammatory drug; however, the problem is that there is a confusion between turmeric and curcumin. Turmeric is in the root, and it only contains 7.5% to 10% curcumin, which means if you ingest 100 grams of turmeric, you only take 10 milligrams at the maximum of curcumin. Curcumin at 10 milligrams has very poor water solubility, so we will absorb less than 1% of that. The minimum effective dosage for clinical trials is from 500 to 2000 milligrams per day. Some companies add **berberin** to turmeric extract to increase its bioavailability, but it only increases by 9%, which is still very low.

Ahmed Elsakka 53.33
So, don’t confuse turmeric and curcumin. Remember, the effective clinical dose of curcumin is about 2000 milligrams that will come from around 20 grams of turmeric, and to absorb 20 grams of turmeric, you need to digest 2000 grams of turmeric roots. So if you need to have the clinical effect of just one dose, you need to ingest two kilograms of turmeric root. So just to find the turmeric root and put it in capsules, this is nothing. You need the effective dose and you need bioavailability.

Ahmed Elsakka 54.13

Adding the berberin only increases the absorption nine times; however, you can increase the bioavailability by more than 100% if you use a very simple nanoparticle technology, like cell liposome or a lipid emulsion of curcumins, can increase the absorption and bioavailability of this by more than 100%.

Ahmed Elsakka 54.40
That’s why when liposomal curcumin came to the markets. Liposomal curcumins can actually increase the concentration of the curcumin – and we can target the inflammatory or cancer tissue to act as a photosensitizer, or to act as an anti-inflammatory agent. You can do anything with nanoparticle technology.

Ahmed Elsakka 55:09
Not only is [it useful] in drug delivery systems, nanoparticle technology can also be a very good agent in gene targeted cell therapy, detection and diagnosis, and even in biomarker mapping.

Ahmed Elsakka 55.22
That’s why, in my lab in 2023, we formulated a new dye photosensitizer agent that actually can give a fluorescent green colour when irradiated with a blue light. So we use blue-cut eyeglasses to remove the blue light from the background, and only the fluorescent tissue will be observed – we formulate the dye to target only the cancer cell.

Ahmed Elsakka 56.02
This is a high-boosted charge in alkaline nanoparticles with high selectivity regarding the tumor. We applied this dye in four different kinds of surgical removal of the tumor, one in the brain, two in head and neck surgery, and one in abdominal general surgery. If we apply this dye by injection, or even just by spraying it on the surgical field, and we irradiate it with a blue light using special equipment to remove all the blue – the fluorescent green will reveal the tumor, so we can visualise and remove it. These are the photodynamically guided resections.

Ahmed Elsakka 56.44
You can see here , after we removed the tumor, there were minimal amounts of activity at these locations. We then did a laser ablation, or a complete surgical dissection, of the tumor. We found that this dye has an extremely high selectivity to the tumor, 99.3%. (...) When it is directly applied or injected for head and neck cancers, we [administer it] via the deeply-seated lymph node using the ultrasound guide before the operation, and we target only the high fluorescent green colour. In brain glioma, we spray the dye over the tumor cavity, and we remove all the fluorescent remaining tumors.

Ahmed Elsakka 57.36
And this is the tumor after resection. You can see, we can also monitor the safety margin of the tumor. It’s something related to the nitrogen-frozen biopsy; however, this is more accurate and more easily obtained. So, when you have a safety margin, you can observe the safety margin even during the tumor biopsy.

(...)

Roger Royse 58:32
Around ferroptosis, there are a couple questions [in the chat] and I had the same question, because I actually tried a ferroptosis protocol, and I combined it with keto and with hyperbaric oxygen, and a bunch of the pharmacology that you mentioned – and I felt terrible. But other than that, I don’t know if it worked. Is there a way to gauge whether this is working, other than through scanning and imaging?

Ahmed Elsakka 59:03
Yes. So the biomarker of the ferroptosis itself needs to be monitored as a baseline before you apply the ferroptosis protocol – during and after. How do you know the ferroptosis is working? We just mentioned something related to pseudoprogression – sometimes you’re applying the scan and it’s saying that the tumor has progressed; however, actually it’s started to die or kill the tumor cells. To make sure the ferroptosis is ‘happening,’ you need to measure specific biomarkers. One marker is called MDA, this market can be monitored in a urinary sample. Urinary MDA can actually give you an idea about the cell membrane lipid stations. If you start ferroptosis with a good response, the urinary MDA should be at least double or triple the baseline. If not, you only take the side effect from sulfasalazine – there is no ferroptosis, there is no cell death. You’re only take the drug to open a metabolic pathway; however, the drug is not always delivered perfectly to the cell.

Roger Royse 1:00:28
We have a question here from Chad: If somebody is following a low methionine and low glycemic diet, what testing should be done to know? And I think maybe you just answered it.

Ahmed Elsakka 1:00:41
You need to look for homocysteine levels. The homocysteine level is a very basic test for a methionine restriction diet. So anybody with a very high homocysteine, you will know that your tumor is methionine-addicted, specifically if you take a homocysteine lowering drug dosage and it is still elevated. This means that it's not due to a defect in the cycle, but due to high conversion of methionine in diet. So, if you have a resistant high homocysteine despite the treatment, you will consider a methionine restriction diet.

Roger Royse 1:01:26
(...) Here's [another] one. Do you have any experience or thoughts on photofrin and red laser light to treat esophageal cancer? And related to that, you know, you said something that kind of struck me. You said, at low doses, I think you said red light can actually promote tumor growth, but it's only at higher doses. So those are two questions.

Ahmed Elsakka 1:02:01
Using red light, without photosensitizers, depending on your mitochondrial chromophore, is called photobiomodulation. If you use it with methylene blue as a photosensitizer, for example, it will be a kind of photodynamic therapy. So the rule of the dose is not applicable to

photodynamic therapy, it's applicable only in photobiomodulation. If you’re using red light therapy without photosensitizers, you need to be very careful about the type of device you’re using, on the total dose that’s being delivered to the tissue – because this energy delivered to the tissue is a multiplication of the laser power from the device and the time of the treatment. It can be calculated using joules per cubic centimeter squared. Anything below 35 joules/cm^3 should not be used because it can increase the tumor growth and the cell growth. In general, anything higher than 35 joules/cm^3 is safer to be used. With photobiomodulation, you will see a lot of publications giving you a warning of using red light therapy in cancer. (...) You want high influence photobiomodulation; that is, high energy of reactive oxygen species that causes that cytotoxicity effect. [You don’t want] low reactive oxygen species because that actually acts as a signalling material to increase cell cycle production.

Roger Royse 1:03:49
So there's a question. Have you considered how selenium deficiency affects methionine levels in the liver? (...) Selenium is crucial for the management of ROS, oxidative phosphorylation, anaerobic glycolysis, along with zinc and genus.

Ahmed Elsakka 1:04:07
Selenium is very essential in reducing glutathione, detoxifying the liver, and buffering the reactive oxygen species. However, if I’m intending to use the ferroptosis protocol, you need to cut off all the antioxidants: selenium (...), vitamin E, glutathione. All of these are direct antioxidants; if you’re using any other oxygen therapy – a high dose of vitamin C, hyperbaric oxygen, applying a photosensitizer or taking photodynamic/sonodynamic therapy – part of their effect is oxidative stress. At any part during the active cancer treatment, never, ever use a direct antioxidant, because this may buffer the oxidation effect that you need to kill the cancer. A lot of patients take high doses of vitamin C, but they also take glutathione with it, buffering the antioxidants. That, then, buffers the cytotoxic effect.

Roger Royse 1:05:32
Gotcha, okay. Did you have a follow up?

Ahmed Elsakka 1:05:35
By the way, there is a scientific publication called “Ferroptosis in Health and Disease.” This paper actually explains the difference between ferroptosis as a pathogen (in neurodegenerative disorders like Alzheimer’s was linked to ferroptosis cell death in the brain), and when ferroptosis can be used as a ‘friend’ in the mechanism of cancer cell death. So actually, ferroptosis can be part of a disease or it can be part of the treatment. And in this paper they describe the difference to you. I will give you another example. We had a patient with a high intracranial hemorrhage. If they were administered ferroptosis, there would be cell death of the brain. In that case, we would use an inhibitor, we give a very high dose of glutathione, a very high dose of antioxidant to suppress the ferroptosis in neural tissue. Ferroptosis is different depending on where and why.

Robb Owen 1:06:45
Interesting, yeah. I've seen some slightly different things, but it's interesting how you're looking at it. So, I did have another question, when you're doing nanoparticle technology, looking at zinc oxide nanoparticles for treatment?

Ahmed Elsakka 1:07:02
We already did the zinc oxide nanoparticles; however, we tested the zinc oxide nanoparticles from the physicochemical stability of the drug, from the distribution to the cell, and from other nanoparticle parameters, like molecular size, zeta potential, stuff like that. We didn’t start to use this for cell cultures yet, it’s only lab work – but next, in the future, we will start to apply it on animal models.

Robb Owen 1:07:30
Good. I think you're gonna find great benefit to go in that direction from the work I've been doing with zinc with patients. It's a very useful tool.

Roger Royse 1:07:46
Here's a question, is sonodynamic therapy related to histotripsy? See, I don't even know what that is. I hope that you do.

Ahmed Elsakka 1:08:23
Ah yes. It’s a different thing. There is a difference between the high flow ultrasound and the high or low focus intensity ultrasound – the sonodynamic therapy. Usually, we use the ultrasound with a low frequency just to stimulate the photosensitizers. However, there is another kind of treatment; it’s a very new treatment that we’re using: the shock wave, or high intensity ultrasound to mechanically disrupt the tumor. Anyway, they’re completely different mechanisms of action.

Roger Royse 1:09:02
Okay, I don't see any other questions in the chat. If there are, and if anybody does have a question, go ahead and use the raise hand feature. Otherwise, we went over a little bit. Okay. Ellen Miller has a question, go ahead. Ellen,

Ellen Miller 1:09:19
Hi. This may not be the right question at this time, but I’m wondering if there’s any way to sort of translate this for those of us who aren’t quite as science-y as others, just put that out there. That may not be anything for the doc to have to do, but perhaps there's someone in the lab that could [make things easier].

Roger Royse 1:09:48
You know, Ellen, I know what you're saying. And I think if you read the transcript document, it's very accessible, and it kind of goes into this, because I'm just a layman, you know. But what I

got out of this conversation is that, I guess the dose is what makes the medicine; for example, the sulfasalazine. I didn't know you had to have that high a dose to get a response.

Ahmed Elsakka 1:10:21
You don’t need *too* high, because then you’ll have a very toxic side effect. However, the minimal effective dose, when we translate the minimal effective dose from an animal model and cell culture into the clinical trial, is that you need 12 grams. So to see action, you just need to take 12 grams (24 capsules) of sulfasalazine. We didn’t do that, but we did do the nanoparticle technology, and we found that the equivalent dose when we turn the sulfasalazine into nanoparticles is from 125 to 250 milligram. That’s where we start to see the good effects – elevation in urinary MDA – which means success of the ferroptosis and minimised side effects.

Roger Royse 1:11:15
Thank you for that. It's good to know. The other thing that I'm getting out of this is that I think this is much more effective when used in a medical facility with people that are able to measure the biomarkers. You can watch this carefully and make sure you're you know, they can toggle it to get the right course. Okay, oh, Raj has a question. Go ahead, Raj.

Raj Aji 1:11:45
That was going to be my question, are there medical facilities or labs which administer the drugs or the treatment for ferroptosis that you can do this under some guidance?

Ahmed Elsakka 1:11:58
It will be at a research facility, because there is no standard of care guideline for ferroptosis even now, or for any drugs or any of these metabolic pathways. So in Egypt, we have, when I was a senior researcher at the Egyptian Foundations for Cancer Metabolic Research, I was able to apply all of this treatment because I’m a physician and scientist at the same time. However, I can’t say that I know of any medical facility doing this right now. It’s all regarding research.

Roger Royse 1:12:48
I want to thank you, Dr Elsakka, for being here. This is really interesting. It's good to know there are alternatives out there. How do people get a hold of you if they want to find out more?

Ahmed Elsakka 1:13:12
Yes, of course. It will be my pleasure.

Roger Royse 1:13:16
We'll circulate some information about where you are and who you are, and we could just go to the web.

“New Metabolic Approaches to Cancer Treatment” (Ahmed Elsakka, MD) [#120]

CHAT DISCUSSION

09:24:08 From Allen's AI Notetaker (Otter.ai) : Hi, I'm an AI assistant helping Allen Morris take notes for this meeting. Follow along the transcript here: https://otter.ai/u/PpH4kt_oEgpI_5LF9fpTVAB5fQ4?utm_source=va_chat_link_1 You'll also be able to see screenshots of key moments, add highlights, comments, or action items to anything being said, and get an automatic summary after the meeting.

09:24:23 From Robb Owen : Have you considered how selenium deficiency affects methionine levels in the liver, cysteine and glutathione peroxidases. Selenium is also crucial for management of ROS, oxidative phosphorylation and aerobic glycolysis along with zinc and genistein

09:40:43 From Scott Petinga : Do you have any experience or thoughts on Photofrin and red laser light to treat esophageal cancer? Working with an 88 yo male too weak for traditional chemo.

09:42:23 From Ellen Miller : I’m wondering how to “translate” what we are hearing to actionable steps for someone with PDAC. I admit to much of this information being above my understanding. Thanks

09:43:31 From Ellen Miller : Is sonodynamic therapy related to histotripsy?

09:44:34 From chad magnussen : If one is following a low methionine and low glycemic diet, what testing should be done to know if you are in ferroptosis?

09:46:39 From David Plunkett : Did we lose him?

09:47:34 From David Plunkett : I think he is back.

09:55:58 From Robb Owen : Have you been doing research on zinc nanoparticles?

09:56:37 From Raj : Similar to some of the questions above. What are some practical ways of inducing ferroptosis for PDAC and how do you measure whether ferroptosis is induced?

10:00:02 From David Plunkett : I'm out of time, must go, sorry.
10:08:39 From Noel Resch : I’m out of time, as well. Thank you for the presentation!
10:10:29 From Roger Royse : here is an accessible resource
10:17:15 From Ellen Miller : Thank you all!
10:17:25 From Robb Owen : Thank you for the presentation
10:17:33 From Brian Kane : Thank you!