Repurposing an Antidepressant Against Prostate and Other Cancers" (Mitchell Gross, MD, PhD) [#105]

Brad Power and Marianna Hernandez
July 10, 2024

"I led a clinical trial testing phenelzine. It's one of the oldest MAOIs, but clinically available and used. What I found was that 24% of the patients had a PSA decline. That was definitely encouraging. But even more, about a third of the patients had no progression." – Mitchell Gross, MD, PhD

Meeting Summary

Cancer researchers are constantly searching for unique characteristics of cancer cells and cancer evolution that they might be able to target with drugs. One such unique characteristic in prostate cancer and treatment-resistant cancers is high expression of an enzyme, monoamine oxidase A (MAOA). MAOA acts like a garbage disposal for certain chemicals which transmit signals between nerve cells in the brain. It turns out that MAOA also plays a role in promoting cancer growth, metastasis, and drug resistance. Elevated MAOA expression in cancer cells is associated with poorer survival. If we could inhibit MAOA, perhaps we could inhibit the growth of cancer.

Mitchell Gross, MD, PhD, Faculty and Senior Director, Clinical Translational Program, and Associate Professor, USC Keck School of Medicine at the Ellison Institute of Technology Los Angeles, is uniquely qualified to talk about the potential of MAOA inhibitors in cancer care. His group recently published the results of the first clinical trial demonstrating clinical activity of a MAOA inhibitor in patients with recurrent prostate cancer. They have also recently identified new chemical structures and drugs designed to specifically target MAOA enzyme activity outside of the central nervous system to avoid the potential for brain-related adverse effects which may be associated with these treatments.

His overall research interest focuses on applying modern techniques relating to the study of genes and proteins (genomics and proteomics) on the clinical problems faced in treating patients with prostate cancer. A particular interest relates to the androgen receptor and related proteins and pathways as key driving forces behind the development and treatment of prostate cancer. As a medical oncologist, his clinical activities are focused on therapeutic clinical trials incorporating both molecularly targeted and conventional therapies to the care of patients with prostate cancer. He serves as primary investigator on many multicenter phase 1 and 2 clinical trials. Dr. Gross has earned degrees from the University of California, San Diego (B.A.), Baylor College of Medicine in Houston (M.D.), and the University of California, Los Angeles (Ph.D. Molecular Biology). He completed a residency in internal medicine and a fellowship in hematology and medical oncology at the UCLA Center for the Health Sciences.

Why is MAOA a promising targeted approach for multiple cancer types, particularly prostate cancer?

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- MAOA is highly expressed in high-grade prostate cancer, and is upregulated in treatment-resistant cancers. It helps to control the balance of chemicals inside cells and also helps to control how genes are switched on and off. Research has shown that MAOA plays a role in promoting cancer cell growth, metastasis, and immune evasion in prostate cancer.
- MAOA inhibitors, like phenelzine, a medication primarily used to treat depression, have been shown to decrease cancer growth in animal models. It can be combined with other treatments, like androgen deprivation therapy or immune checkpoint inhibitors, to enhance anti-cancer effects.
- Phenelzine has the potential of hitting multiple targets, and it has shown to have activity in several cancer types.
- Repurposing an existing drug, like phenelzine, reduces the time and costs associated with drug development.

What additional preclinical research is needed to better understand the anti-cancer mechanisms of MAOIs and optimize MAOI use in cancer treatment?

- Detailed molecular mechanism studies to see how these medications interfere with the processes that make cancer cells run, and how they might change the cell's ability to produce energy.
- Comprehensive genomic and transcriptomic analysis to identify specific cancer subtypes most likely to respond to this treatment.
- Combination studies with existing cancer treatments to understand potential synergistic effects, such as immune modulation and their interaction with immune checkpoint inhibitors.
- How nerves outside the brain and spinal cord connect to and affect different kinds of cancer.
- More targeted variants that can minimize side effects while maintaining anti-cancer efficacy.

For which cancer patients might MAOIs be relevant?

- Patients with prostate cancer, lung cancer, breast cancer, colon cancer, glioblastoma (brain cancer), colorectal cancer, melanoma, and Hodgkin's lymphoma.
- Patients with treatment-resistant cancers, especially those with high-grade or recurrent prostate cancer.

Can you access MAOIs for cancer treatment today?

- MAOIs are not a standard approved cancer treatment. Dr. Gross's research is still preliminary, with a small pilot study of 24 patients showing some potential benefits for biochemical recurrent prostate cancer.
- While the drug exists, it's not widely available for cancer treatment. If you are interested in this approach, you would need to consult your oncologist and discuss the experimental nature of using MAOIs off-label.

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How can you learn more about using MAOIs as a cancer treatment?

- Review Dr. Mitchell Gross's published research on monoamine oxidase inhibitors (MAOIs) in prostate cancer; contact Dr. Gross at mgross@emilaorg
- Consult with oncologists specializing in prostate cancer who are familiar with repurposing drugs and with your medical team
- Follow clinical trials investigating MAOIs in cancer treatment
- Explore databases like ClinicalTrials.gov for ongoing research

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Meeting Notes

KEYWORDS

Monoamine oxidase inhibitors, cancer, prostate cancer,, repurposing, anti cancer effect, mao, brain, medicines

SPEAKERS

Mitchell Gross (68%), Allen Morris (10%), Brad Power (6%), Richard Anders (5%), Rochelle Prosser (4%), Brian McCloskey (4%), Michelle Sager (2%)

SUMMARY

Dr. Mitchell Gross discussed the potential of repurposing drugs for cancer treatment, including off-label use of antidepressants, phenelzine, and Monoamine oxidase A (MAOA). He shared his research on using antidepressants to combat prostate cancer and discussed the potential of targeting the MAOA pathway in prostate cancer patients with biochemical recurrence (a rise in PSA levels after initial prostate cancer treatment, indicating a potential return of the cancer). The challenges and opportunities involved in repurposing drugs were highlighted, including the need for funding and the potential negative effects on micronutrients. The potential of monoamine oxidase inhibitors (MAOIs) in cancer treatment was also discussed, including their location and specificity. Speakers explored the potential of using historical databases to identify interactions between MAOA inhibitors and cancer, and discussed the development of new medicines that combine the benefits of MAOIs while minimizing their adverse effects.

OUTLINE

Introductions

- Brian McCloskey connected with Dr. Gross for prostate cancer treatment through repurposed drugs.
- Dr. Gross presented his research on antidepressants combating prostate cancer.

Monoamine oxidase inhibitors and their relation to prostate cancer.

- Dr. Gross discussed monoamine oxidase inhibitors and their relation to prostate cancer and other cancers.

Monoamine oxidase A and its role in prostate cancer, including its upregulation in high-grade cancer and its potential as

- Dr. Gross explained the function of monoamine oxidase inhibitors in the body, including their role in regulating neurotransmitters.
- Monoamine oxidase A and B have different expressions in different parts of the body, and inhibitors can be specific to one or both forms.

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- Dr. Gross discussed monoamine oxidase A (MAOA) and its relation to prostate cancer, highlighting its high expression in high-grade prostate cancer and its potential as a target for treatment.
- Research shows that MLA is upregulated in treatment-resistant prostate cancer, including in animal models, and may be a promising target for overcoming resistance to Enzalutamide therapy.

Monoamine oxidase inhibitors in prostate cancer treatment.

- Dr. Gross discussed the potential of monoamine oxidase inhibitors (MAOIs) in treating cancer, particularly in combination with other drugs.
- There is a long history of MAOIs in medicine, including their use in treating depression, and their relatively rare use in modern psychiatry.
- Clinical trial results on monoamine oxidase inhibitors for prostate cancer show 24% of patients experiencing PSA decline and 33% showing no progression.
- Patients on phenelzine/MAOIs have to avoid aged avocados and Mexican food due to tyramine interaction.

Using monoamine oxidase inhibitors to treat cancer, with a focus on phenelzine and prochlorperazine.

- Researchers found that combining phenelzine with immune checkpoint inhibitors significantly accelerated anti-cancer effects in various cancer models.
- Dr. Gross along with other researchers at USC are trying to redesign MAO inhibitors to target peripheral activity (outside of the brain) for cancer treatment.

Safety and efficacy of MAO inhibitors in psychiatry.

- Dr. Gross explains the long-term safety of monoamine oxidase inhibitors in psychiatry, citing animal studies and human trials.

Off-label drug use for cancer treatment, with a focus on phenelzine and its potential benefits and risks.

- Dr. Gross discussed a preliminary pilot study on using phenelzine in cancer treatment, emphasizing the need to balance risks and benefits.
- Off-label drug use and personalized medicine highlight the need for genomics data to understand treatment efficacy.
- Dr. Sager discussed MAOA as a potential immune modulator for cancer treatment, with challenges in delivering it across the blood-brain barrier.

Monoamine oxidase inhibitors and their potential effects on cancer cells and the nervous system.

- Dr. Gross discussed mechanisms of MAOA in peripheral cancer tissues, including its role in regulating redox potential and cell differentiation.
- He raised a question of whether MAOA's effects on the nervous system could be desirable in cancer treatment, despite lack of knowledge on the topic.

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- He discussed the potential side effects of a drug, including a tyramine surge in the bloodstream, and the importance of separating the two effects to understand them better.
- He also mentioned that an MAOA inhibitor could be used to reduce the toxicity of the drug, and there is a literature on this in psychiatry dating back to the 1970s.

Repurposing drugs for cancer treatment, including challenges and potential solutions.

- Richard Anders asked about using the Medicare database for cancer research, and Dr. Gross mentioned unpublished real-world evidence from other countries.
- Dr. Gross discussed repurposing existing drugs, including safety considerations and Brian's involvement in the topic.
- Dr. Gross mentioned a nonprofit called Reboot that repurposes drugs, but faces challenges in getting them through the regulatory system.
- Brian McCloskey suggests working with Dr. Gross to update the NCCN guidelines with evidence supporting drug repurposing.
- Rochelle Prosser discussed potential micronutrient interactions with targeted therapies, including FGFR drugs and their impact on survivorship.

Using ADT in combination with Enzalutamide for BCR patients.

- Allen Morris presented a theory that women are in a better immune state than men, based on observations of autoimmune diseases, cancer, and COVID-19 outcomes.
- Morris suggests ADT class drugs, which are proven treatments for high risk BCR patients, if phenelzine is used off-label for BCR, should still be given. And highlights Dr. Gross' research that suggests synergy.

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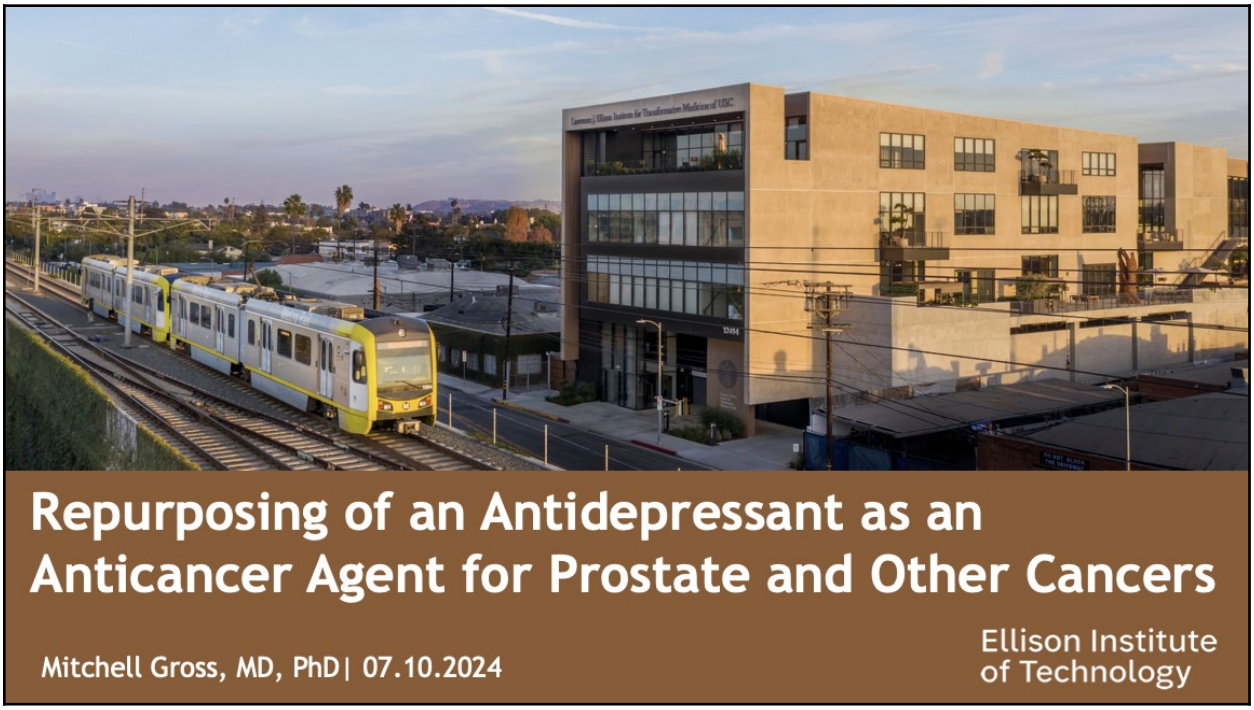
TRANSCRIPT

Brad Power
This is the Cancer Patient Lab.

Let me quickly cover our standard housekeeping items before we get started. The first is that this is not medical advice. This is for information purposes only. Everything that you hear is with a goal of allowing you to take some of these ideas to your medical team for consideration in your care.

We are a patient-led learning community. We would appreciate any donations that you might make, which you could do through our website, using the donate button.

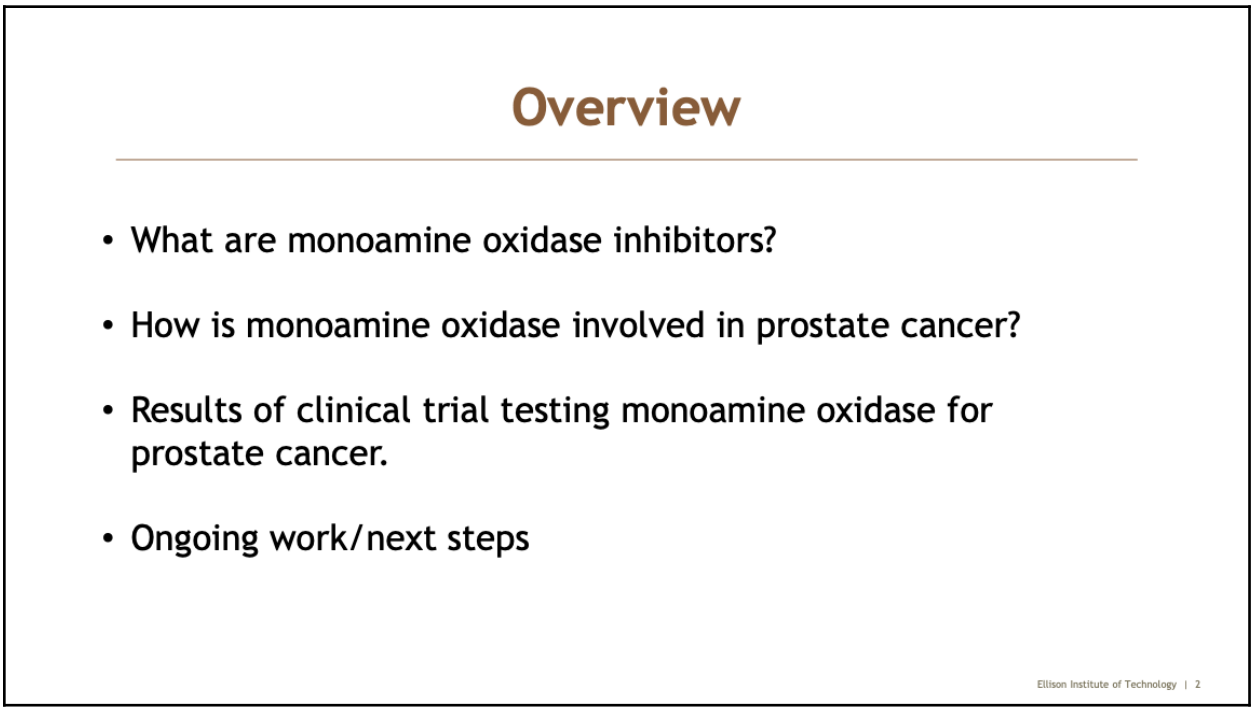
Brian, can you introduce Dr. Gross and describe how we got connected and your background with him?



Brian McCloskey 1:06
Our paths go back many years. I was diagnosed with prostate cancer in 2016. Dr. Gross was part of my clinical team very early on, I think, as early as 2017. He's been a part of my care team really ever since. But I got interested in repurposing drugs and reached out to a company called "Reboot Rx". I don't think Laura Kleiman is on this call. But long story short, I put Laura in touch with Dr. Gross, because he is an expert in the repurposing of drugs. Laura had a very interesting AI methodology for identifying drugs that could be repurposed. But of course, it requires clinical scrutiny. So I don't think that we're going to be talking about that so much. But we are going to be talking about antidepressants and the amazing research that Dr. Gross has

done with antidepressants in combating prostate cancer and other cancers as well. So Dr. Gross, thank you so much for accepting the offer to be here. We look forward to your lecture, and very active discussion from the community as well.

Mitchell Gross 2:22
That's great. Yeah. Thank you again, Brian and Brad for inviting me to speak.



What I thought I would do here was talk about the story of monoamine oxidase inhibitors (MAOIs), and how I propose that that's related to prostate and other cancers, and show you some data in prior publications that led me to this conclusion.

First, we'll talk about monoamines and monoamine oxidase inhibitors (MAOIs). Then we'll talk about how these are related to prostate cancer and other cancers. Then we'll talk about some next steps.

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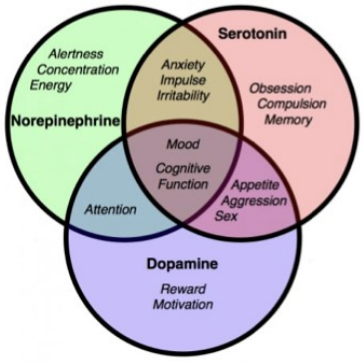
Monoamines in Health and Disease

- Monoamines are key natural signaling molecules involved in the normal function of the brain and other organs
- Monoamines include epinephrine (adrenaline), norepinephrine serotonin, dopamine, histamine
- Examples:
  - Depression may be caused by low serotonin levels in specific areas of the brain
  - Parkinson's Disease is caused by low dopamine levels in other brain areas
  - Adrenaline (epinephrine) levels surge as part of "fight or flight" response to life-threatening situation



Effects of Monoamine Neurotransmitters

https://www.open.edu/openlearn/mod/oucontent/view.php?id=77496&extra=thumbnail!figure_idm119

Monoamines are a class of natural signaling molecules in the body. There are many of these that are really important for many functions, especially in the brain. We know a lot of these in popular literature, there's what we call "epinephrine" (or "adrenaline"), that's a monoamine. Other ones are called "serotonin", "dopamine", or "histamine". These are all monoamines. These are very important molecules for lots of processes in the body that have to do with signaling, basically, telling one cell or another cell what to do.

So some examples of some of these monoamines and their diseases include depression. Low serotonin levels in certain areas of the brain are related to depression, and we use drugs that try to raise those levels. The main problem in Parkinson's is a deficiency of dopamine in one particular brain area. Again, we use medicines to raise those. We know about what's called adrenaline, or epinephrine, the "fight or flight" response. That's also driven by a monoamine, by epinephrine, which has to do with blood pressure and heart rate and attention and all sorts of things. That's the function of the monoamines in the body. Some examples of that.

What are monoamine oxidase inhibitors (MAOIs)? Well, every time you have an "on switch" in the body, you also have an "off switch". The MAOIs or monoamine oxidases are the "off switch".

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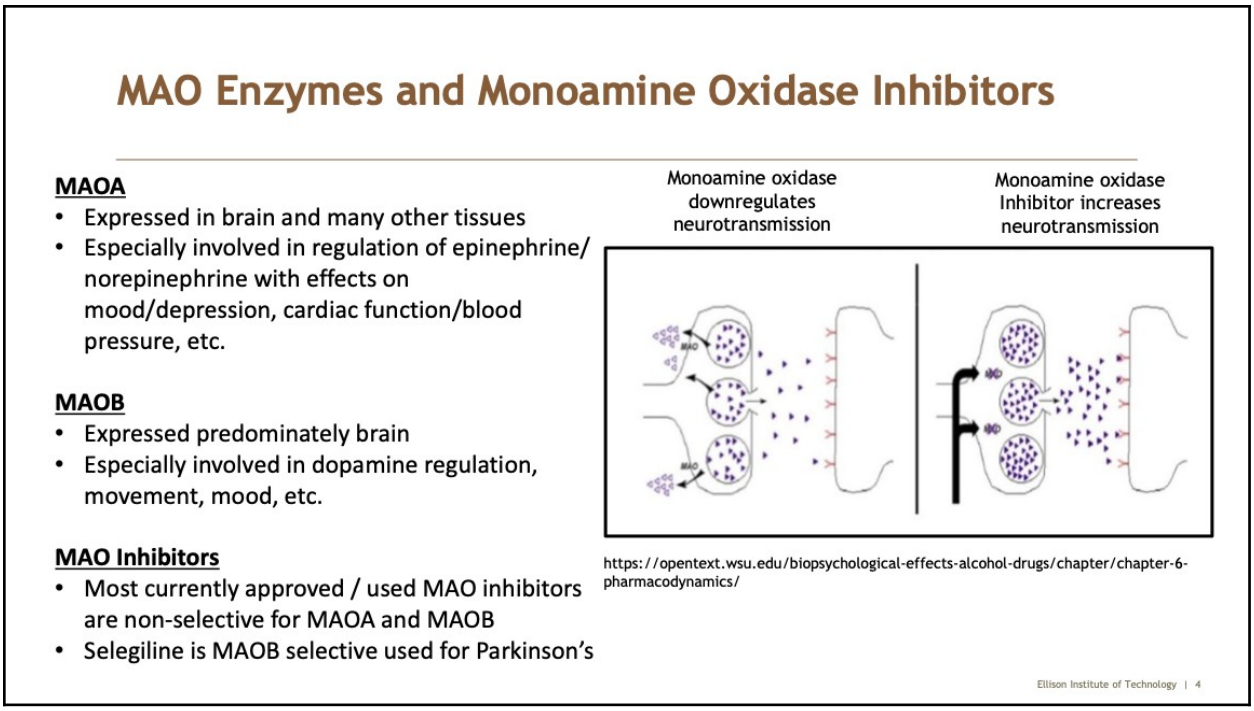

We see a diagram of the monoamine system, like two neurons talking to each other. The purple triangles represent monoamines, and they go between the cells. But then on the left, the monoamine oxidases will turn off and will inhibit those. It helps to regulate the right amount of the neurotransmitter (chemical messengers of the body that communicate across different cells in different parts of the body), as they're communicating to each other. That's the picture on the right.

On the far right is: if you have a MAOI, what you do is you prevent or block the inhibition or the degradation of those purple triangles. The purple triangles build up, you get more monoamines, more purple triangles, more signaling to the other neurons. Basically, that's what monoamine oxidase does: it helps to regulate this very important system in the body that has lots and lots of different aspects of it.

The other part to go into is there's what's called monoamine oxidase A (MAOA) and monoamine oxidase B (MAOB). These are two forms. The important thing is that they're expressed in different parts of the body, different parts of the brain, other body parts as well, but also, the chemical inhibitors that we develop can be specific to one or both of these. There's MAOA and MAOB, they have different areas, they have different functions. The inhibitors also have different activities, different functions. Most of the MAOIs, certainly the ones that are used somewhat in psychiatry now – but not so commonly used to be – are nonspecific inhibitors. They inhibit both the A and B forms. There's another MAOB inhibitor, which is much more commonly used in Parkinson's disease, called "selegiline". It's either a patch or pill, used in some patients with Parkinson's, that's very specific for MAOB. This is a complicated system, a very important system, but something that we can take advantage of for cancer treatment.

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How is MAOA related to prostate cancer?

- MAOA is highly expressed in high-grade prostate cancer [1]
- Inhibiting MAOA by genetic/pharmacologic approaches tumor formation and growth of various prostate cancer models [2,3,4]
- MAOA increased in treatment resistant prostate cancer and may be targeted to decrease growth of treatment resistant prostate cancer [5,6,7]

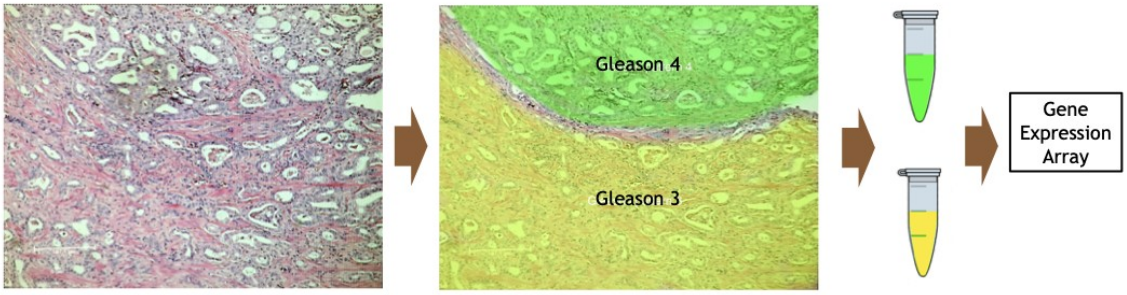
1. True, L., et al., Proc Natl Acad Sci U S A, 2006. 103(29): p. 10991-6; **2.** Wu, J.B., et al., J Clin Invest, 2014. 124(7): p. 2891-908; **3.** Liao, C.P., et al., Oncogene, 2018. 37(38): p. 5175-5190; **4.** Wu, J.B., et al., Cancer Cell, 2017. 31(3): p. 368-382; **5.** Gaur, S., et al., Prostate, 2019. 79(6): p. 667-677; **6.** Gordon, R.R., et al., PLoS One, 2014. 9(9): p. e104271; **7.** Wang, et al, Nature Comm, 2020. 11: p.2689.

How is this at all related to cancer and prostate cancer? MAOA, especially that A isoform, or the A form, is very important for prostate cancer. It's highly expressed in high grade prostate cancer. Also, our data, data that I produced, and others, show that in MAOA, in particular, can be modulated to decrease the development of prostate cancer in animal models, and also is a target of treatment in animal models, and that when cancer becomes resistant, MAOA can be one of the enzymes that's highly upregulated.

How is MAOA related to prostate cancer?

2006: "Molecular Correlate of Gleason grading.." True et al., PNAS 2006

- Laser captured microdissection to identify genes/proteins differentially expressed in high grade prostate cancer
- MAOA expression found to highly correlate with high grade prostate cancer



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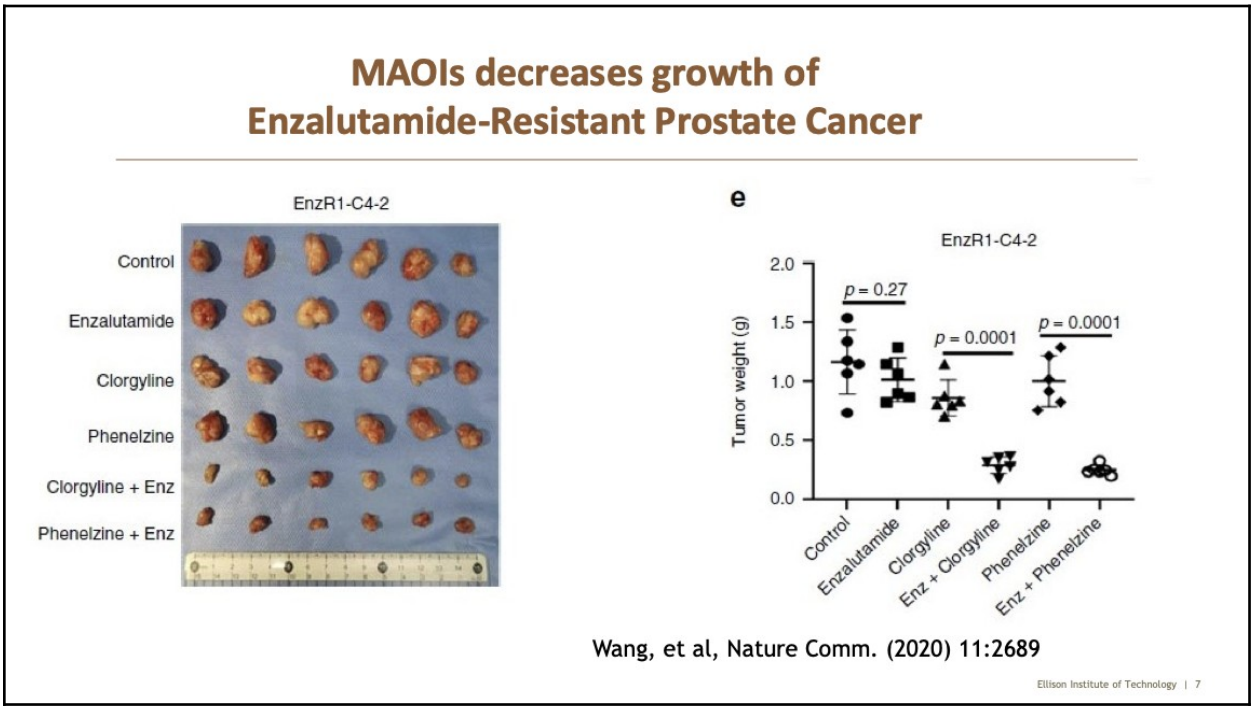
I know this is called the Cancer Patient Lab. I thought I'd do a little bit of lab history here.

Why do we think amylase is upregulated in prostate cancer? This is some very early research that was done 18 years ago. Larry True at the University of Washington said that you can take prostate cancer, and there's an area that's called low grade Gleason 3, and we know there's this kind of pattern on the lower left or the yellow that represents Gleason 3. And there's other areas that look very aggressive. We call it Gleason 4, Gleason 5, and that's in the upper right of the photomicrograph there. We can use a laser to cut away those two pieces of a low grade and high grade prostate cancer and then try to look at what we use in genetics and other features. What is different between those two areas? This was one of the first studies that did this way back 18 years ago. When they did this, they showed that one of the most important genes, the most commonly expressed genes, and also the protein that was differentially expressed was MAOA. This gene is very highly expressed in high grade prostate cancer and in many other cancers as well, but this is especially relevant to prostate cancer.

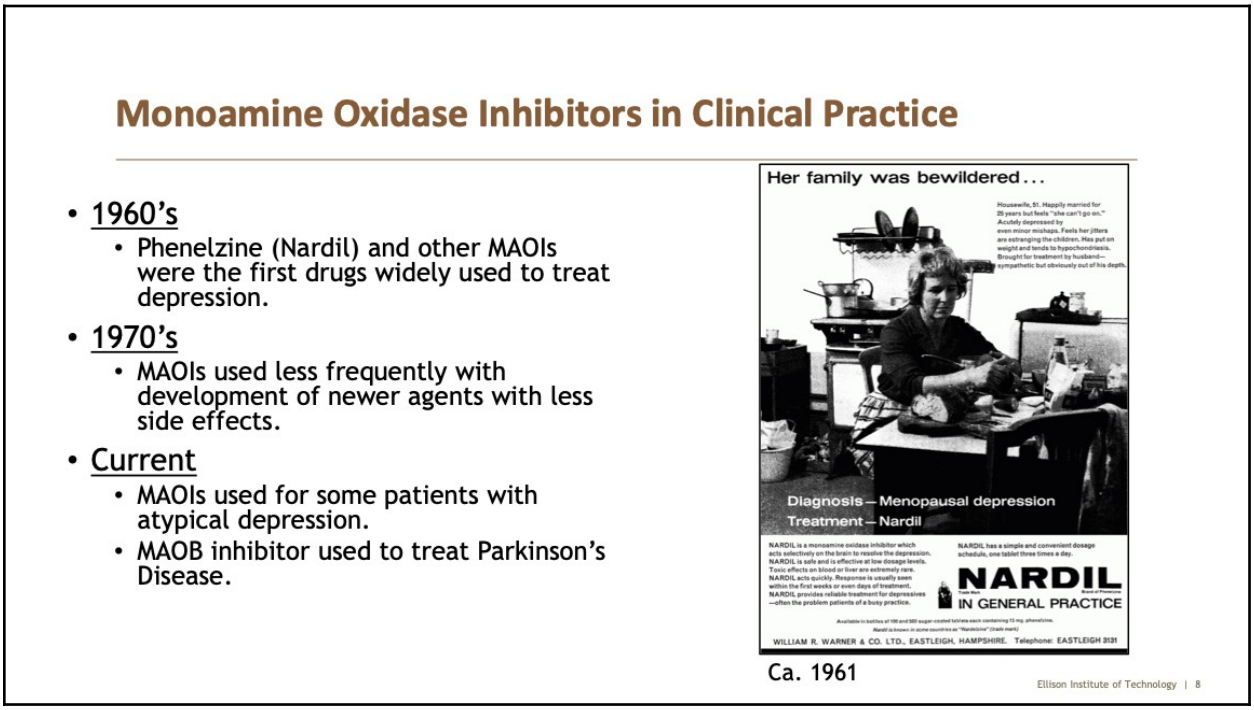


This is some other data about treatment. I mentioned that MAOA is upregulated in treatment-resistant cancers, especially prostate cancer. There are many studies that have shown this, both in patients and in animal models. This is the most compelling and one of the more recent ones.

You can grow human prostate cancer in an animal model, a white mouse. This is Enzalutamide C4-2. This is a model that has treatment-resistant prostate cancer, Enzalutamide-resistant prostate cancer. Clorgyline is a MAOA specific inhibitor. Phenelzine is a nonspecific MAOB

inhibitor. When you treat with a MAOA inhibitor, you can get some decreased growth of the cancer. That's very encouraging for sure.

But even more encouraging is if you combine the clorgyline MAOA inhibitor with enzalutamide, or phenelzine with enzalutamide, you'll get even more inhibition. This is the best data so far about MAOA inhibitors in a preclinical model.

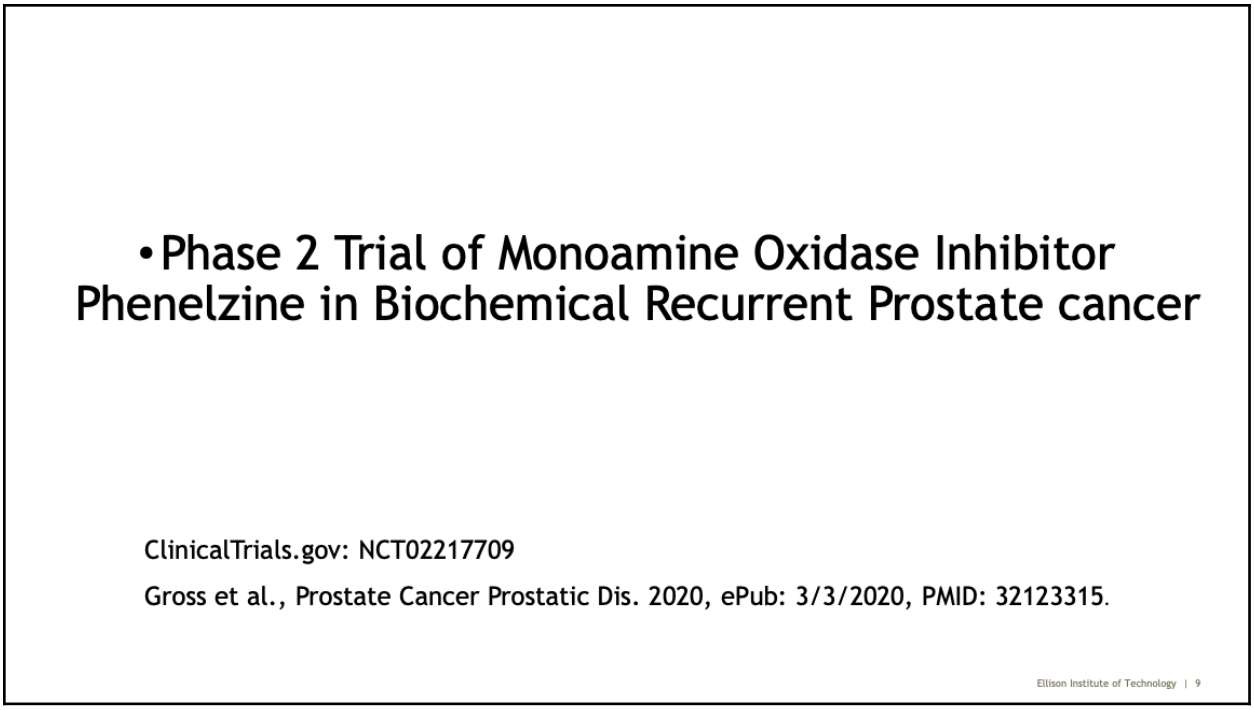


Many people might know that this is a very old field. I know in medical school, I learned that MAOIs were the drugs never to prescribe, because they had lots of problems. That's more or less maybe still true. MAOIs have a very long history in medicine. The one that I have especially studied is this one called phenelzine, Nardil (Nardil is the brand name for the generic drug, phenelzine).

This was first used in patients in 1961. Here on the right is an ad from a British Medical Journal. I think they used to allow ads in the United States, they didn't allow ads for medicines for decades. There's this woman here who's brought to the doctor by her husband, because he's out of his league and he needs the psychiatrist's help to diagnose menopausal depression. Nardil is the treatment. Times have changed, medicines have changed, but certainly, this is a very old drug.

Then if we go forward in the 1970s, MAOI and antidepressants were really changed a lot. Many new antidepressants came on the scene with less side effects and were certainly more effective. It definitely fell out of favor as a treatment. But still, MAOI, phenelzine or Nardil, is used rarely in some patients with depression. There are some psychiatrists to comment on that. But only very rarely, for something called "atypical depression". Sometimes it's used for tonic

depression. And then MAO-B inhibitors, as I talked about, are used much more commonly in Parkinson's disease (a neurological condition where a certain part of the brain deteriorates over time, causing movement problems) for neurology.



All of this background brought me to this trial that I was able to present and publish four years ago or so, that looked at MAOI in prostate cancer. Still to this day, this is the only published trial showing activity of MAOI for any cancer. In this case, we chose what's called biochemical recurrent prostate cancer.

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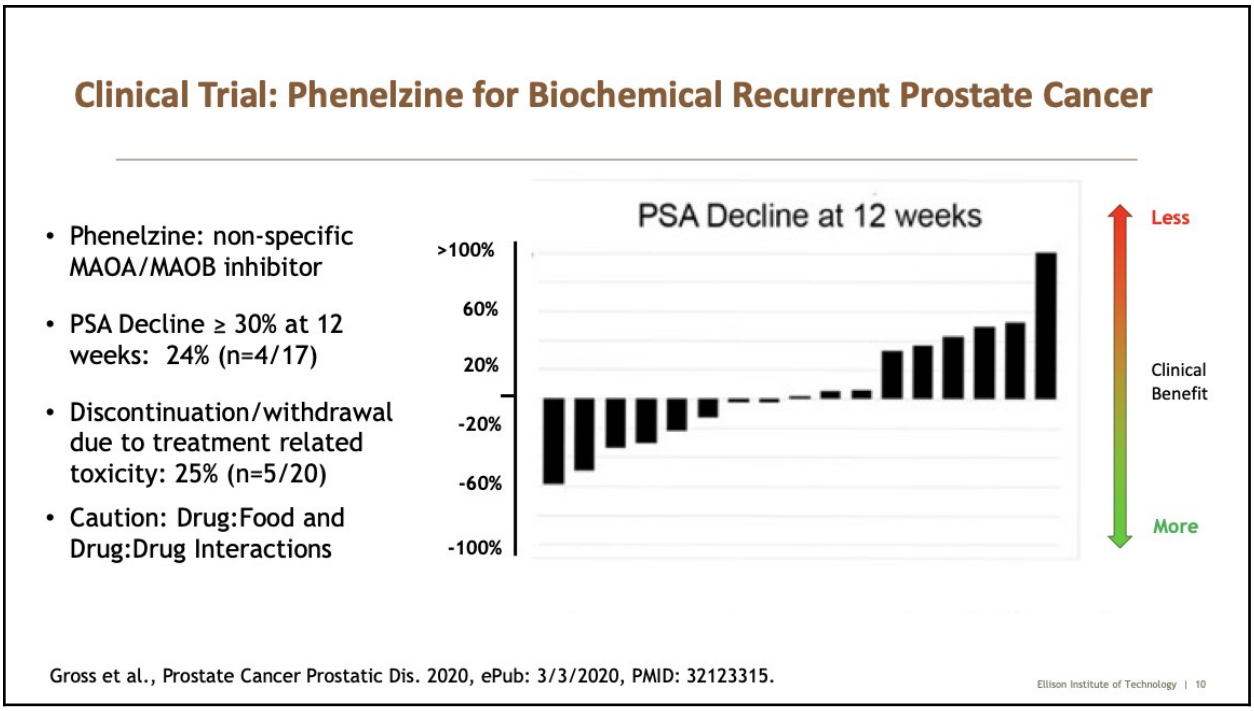


What we mean is that imaging studies are negative, but the patient has maybe had a prostate surgery and their PSA is 1, 2 or 3, or they had radiation and the PSA is around 2, 3, or 4. So this is then the cancer's coming back after primary treatment surgery or radiation. But we do scans, and certainly back then it was a bone scan and CT scan, that did not show any cancer, and we call that biochemical recurrent prostate cancer.

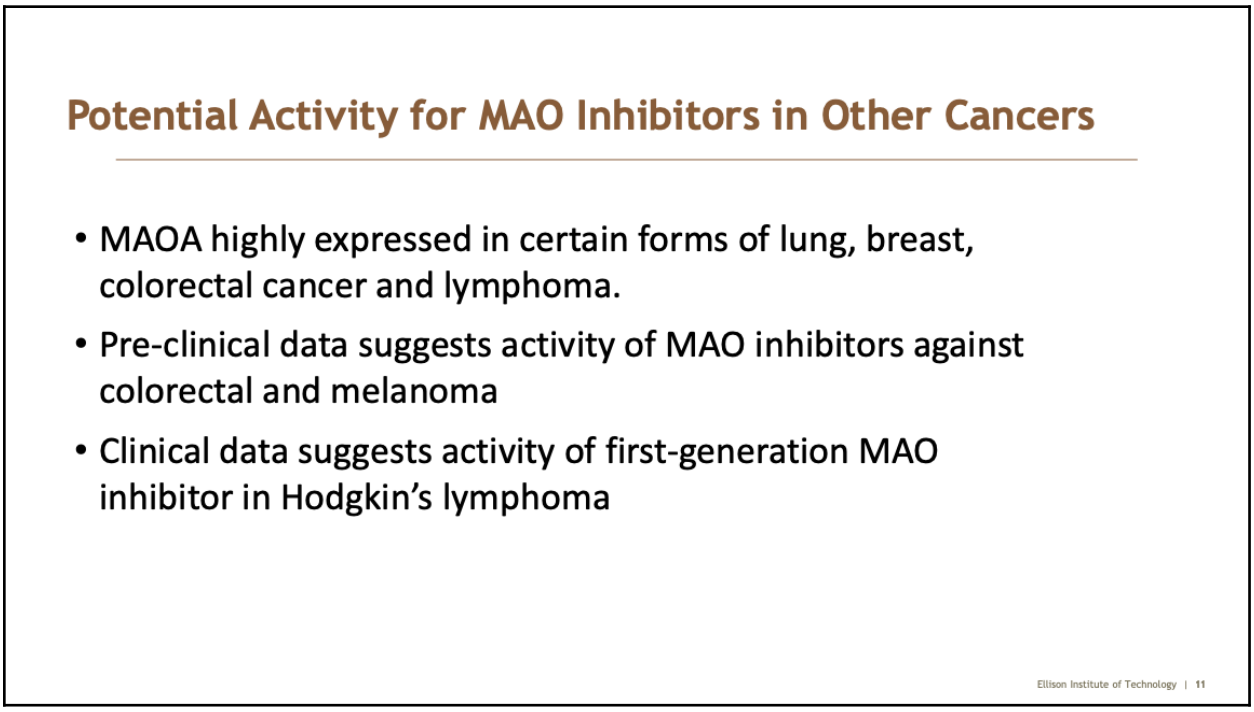
I led a clinical trial testing phenelzine. It's one of the oldest MAOIs, but clinically available and used. What I found was that 24% of the patients had a PSA decline. That was definitely encouraging. But even more, about a third of the patients had no progression.

So there was some activity of phenelzine (MAOI) in prostate cancer, but I also found the side effects of these drugs, and certainly we were aware of that when we were starting the trial. About 25% of the patients discontinued for side effects. These are patients without depression, and we're giving an antidepressant, and there's a lot of known side effects for these drugs. I know there was some discussion before about, "What are the side effects?" I mentioned a little bit, and we can talk more, but the main things people really worry about with phenelzine or MAOIs are drug-food or drug-drug interactions.

There's this very important drug-food interaction with tyramine in the diet. Tyramine is an amino acid (amino acids are the building blocks of proteins) that is part of the diet. If that goes into the bloodstream unaffected, you'll get a very high level of tyramine, which is also a precursor (starting material) for epinephrine. And that could cause high blood pressure, and wildly high and low blood pressures cause a lot of problems and in very rare cases, could even be serious and life threatening. For patients on the trial, we had a lot of education about diets that were low in tyramine. Tyramine is part of certain diets, especially fermented foods. In the old days, we

would tell patients about aged cheese and red wine, but I'll tell you in our trial, the patient that had the biggest problem with tyramine was over aged avocado and Mexican foods. Anyway, that's the drug-food interaction, generally manageable with careful education.

And there are drug-drug interactions. Certain drugs are not compatible with phenelzine, especially certain blood pressure drugs. Drugs that would be dangerous would be stimulants like Adderall and those kinds of things. There's a lot of things to worry about with phenelzine, and MAOIs in general. But still, we did see some activity.



That's the prostate cancer story. But what about other cancers? It's been shown in lung, breast, colon, even in glioblastoma, or brain cancers, as well. We'll show you some data on colorectal, melanoma, and also Hodgkin's lymphoma. Lots of things.

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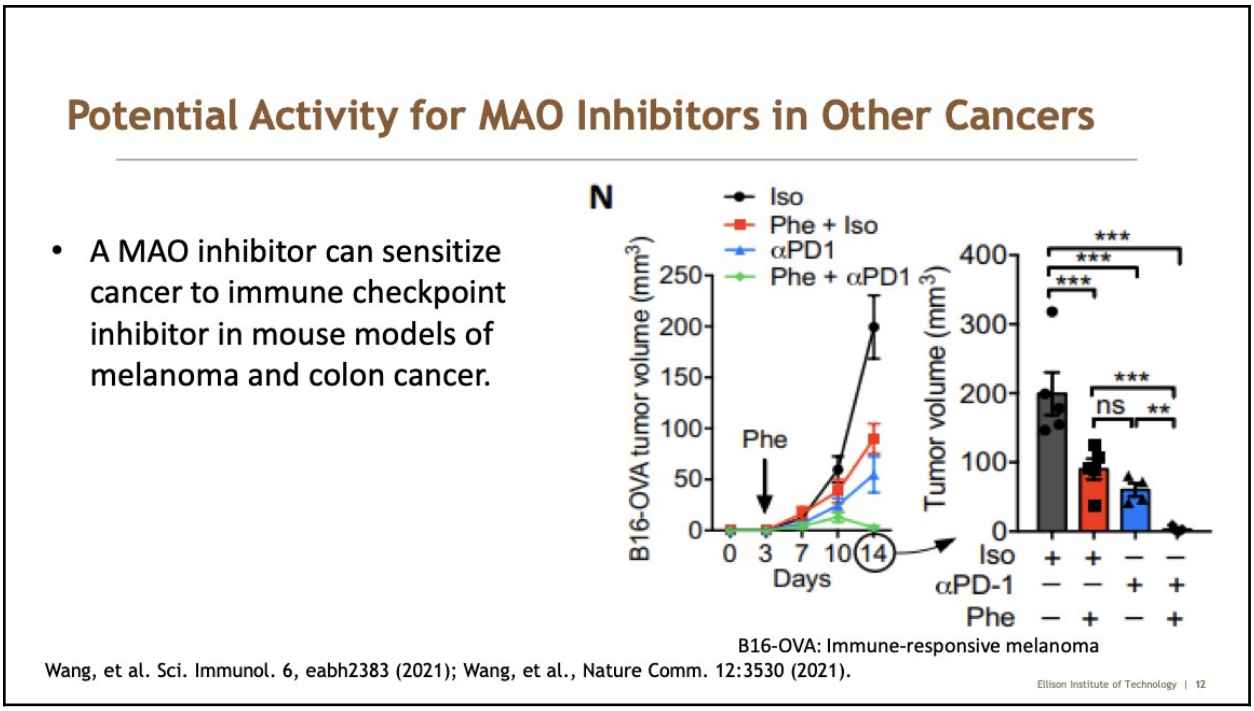
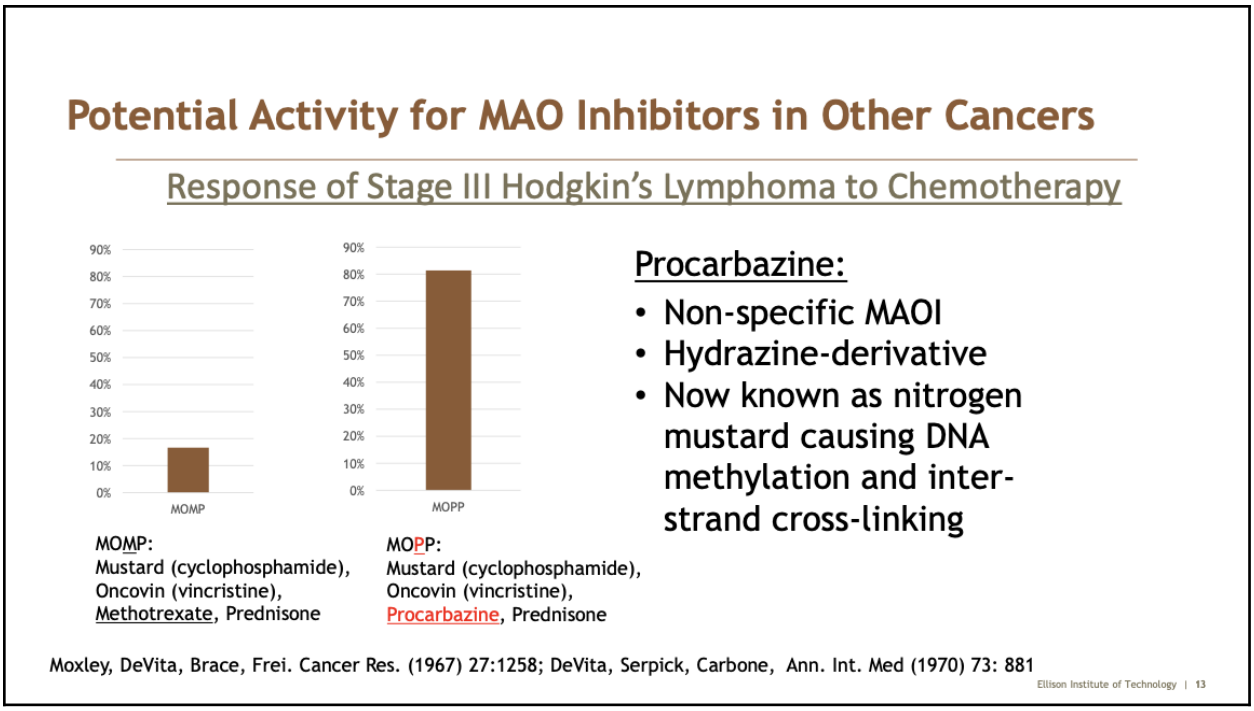


I thought I'd give you a flavor of some of the research of this more recent data. This is from 2021, a group led by Lily Wang at UCLA. We can grow mouse melanoma in a mouse. We can treat it. The black line represents the cancer growing in the mouse very fast. We can use phenelzine, again, the same drug that we talked about, that's the red line, that will decrease the growth of the cancer.

By itself, it's encouraging that it can decrease the growth. But more than that, there's this anti-PD-1 (a cell surface receptor on activated anti-tumor T cells, a type of immune cell), which is the blue line, which is kind of like this drug: Pembrolizumab (Keytruda). This is called an immune checkpoint inhibitor that stimulates the immune system. This research showed that the green line, phenelzine, plus this kind of checkpoint inhibitor, really accelerated the anti-cancer effects. This is a very striking result. They showed this also in colon cancer, I think, also in breast cancer as well.

It's very interesting that phenelzine, or MAOIs, can help promote the immune system to recognize cancer, especially in the context of checkpoint inhibitors.

Repurposing an Antidepressant Against Prostate and Other Cancers" (Mitchell Gross, MD, PhD) [#105]



This is some of the most striking data, but also really some of the oldest data. Procarbazine is a very old cancer drug. In fact, it's really revolutionized the whole theory, the whole field of oncology. Back in the day, the big question of oncology was, could we use chemotherapy to treat or even cure cancers? A representative example of that was Hodgkin's lymphoma. Hodgkin's lymphoma (a blood cancer) is still rare but an important kind of lymphoma. Back in the day at the National Cancer Institute in Washington, DC, and in Maryland, they were testing different kinds of chemotherapy to try to treat this really aggressive lymphoma and their regimen, which was a combination, the idea of combining medicines was very limited because of side effects. On the left, this was the initial data they had with a (chemotherapy) regimen called "MOMP". Those are the abbreviations of the medicines that comprise the regimen. But it was not very effective. But really tremendously what happened was when they added procarbazine to the MOP, you saw tremendous anti-cancer activity. In fact, other data showed you cured lymphoma patients a good percentage of the time by adding procarbazine, which is this drug. Procarbazine was developed as a MAOI. Later, we found it to have other anti-cancer effects. But overwhelmingly, this kind of data showed that maybe combining it could have activity.

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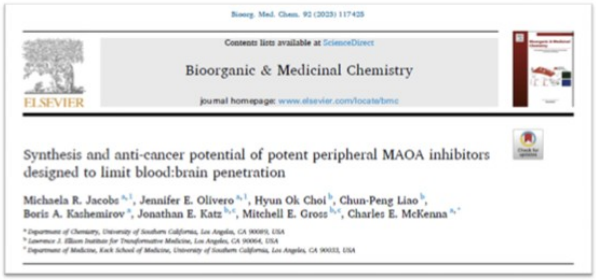
Next Steps…Peripherally Directed MAOA Inhibitor

- Design a monoamine oxidase inhibitor which avoids problems of first/second generation agents:
  - MAOA specific to minimize effects of epinephrine surge coming from tyramine in the diet
  - Minimize blood:barrier penetration to minimize "off target" effects on central nervous system



PubMed PMID: 37544256.

That was where I've been, but where I'm going is trying to develop new medicines that really design out the bad side effects of the MAOi. So this data we published just about a year ago now, working with my colleagues at USC, we basically are redesigning the MAOi scaffold, we call it and trying to get it not to go to the brain, and only to focus on the peripheral activity, which is where we'd like it to stay.

We basically designed some new medicines, and we have it submitted for a patent. And we're trying to further develop this project to look at MAOi, basically redesigned that doesn't go to the brain.

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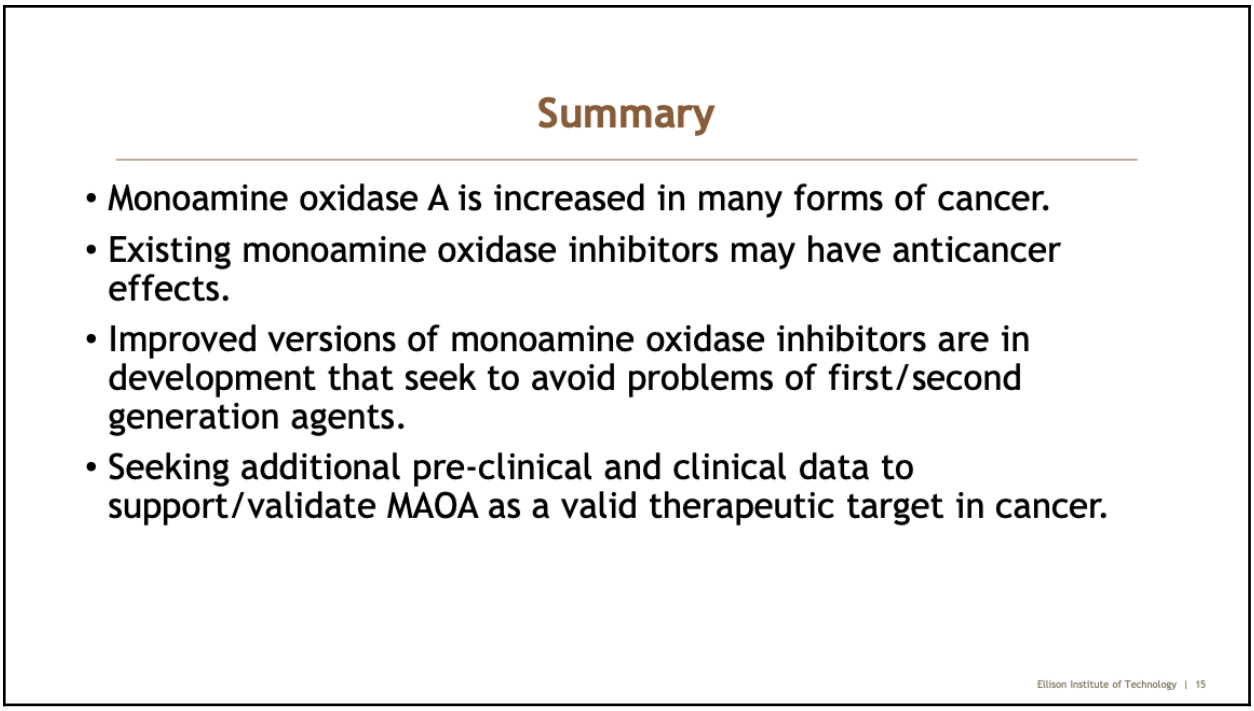

That's my summary. I know Brad wanted me to give half an hour. I could always talk more about MAOi. There are many forms in cancers, MAOA especially, as related to cancer. We can use inhibitors against the MAOis. I mentioned some of them that are used. Clorgyline is only available in research, though there were trials about maybe 20-30 years ago that did test it in patients. But now, it's only made for research.

Other MAOIs are available, phenelzine being the one that we talked about, which is a nonspecific MAOA & B inhibitor. But people are developing new versions, and especially our group is hoping to develop one, specifically looking at the peripheral activity. As always, we're looking for additional support data to help us really understand how this could be used for cancer treatment.

Allen Morris 29:28
I dragged my wife along, Michelle Sager, who's a psychiatrist. I just asked a basic question. One of the problems with any kind of phase one, phase two is not efficacy, but safety. Harkening: "to do no harm" as from Hippocrates. It turns out, psychiatrists have 50 years of experience giving these drugs and there's a reason they call things first generation, second generation, and third generation – it's because the first generation weren't as good as the second generation.
I am sorry I joined late. I presume you are not a psychiatrist and do not have long term clinical experience with MAO inhibitors. Are you a urologist? I didn't get that part of it.

Mitchell Gross 30:21
I'm a medical oncologist.

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Allen Morris 30:23
And my belief is, you're going to correct me if I'm wrong, most medical oncologists at university centers have sub-specialized in a particular organ system. Is that correct?

Mitchell Gross 30:34
Lots of academic centers? Yes. And I am a prostate cancer oncologist. Okay, good. I do genitourinary and prostate care.

Allen Morris 30:41
That's another soapbox I have about the Cancer Patient Lab. Since we're a Tower of Babel. Everybody should know, first and foremost, what your area of expertise is, you are a medical oncologist. And furthermore, you said you're specialized in prostate cancer. And therefore, I'm going to say something that might sound pejorative, but it's not, which is you do not have long term experience giving MAOi. Is that correct?

Mitchell Gross 31:12
Are you involved in any litigation?

Allen Morris 31:16
I actually am, but it's on the receiving end. But that's okay.

Mitchell Gross 31:19
No, but so, if I could answer it in the general sense. So, MAOi have been used long term in psychiatry for many patients and their patients have been on MAOi for years and years and decades. So, I think the safety of these medicines, I mean, that's one of the advantages, generally of the repurposing strategy is that we know a lot more about the safety. We know a lot more about the toxicity. But there are always uncertain questions. So overall, MAOi in animal studies and in human studies have been very safe in the long term.

Allen Morris 31:59
I looked at your study. You had 24 patients, and you had a grade 4 hypertensive episode. My math says that's 4%. Admittedly, there's a big plus or minus because your denominator is 24.

Mitchell Gross 32:11
Yeah. I mean as an oncologist, treating cancer patients, we take this very seriously. And certainly, adverse events, you know, any one is terrible, and we try to avoid them. We are trying to balance it against the benefit of treating the cancer. So, yeah, this is why, though, you know, my study was preliminary, it was pilot. It was encouraging but I didn't propose and nor would I, that thousands of patients should start this phenelzine. You definitely have to balance the risks and the benefits, any physician will know that.

Allen Morris 32:53
Do you know how many clinicians are using phenelzine?

Mitchell Gross 33:24
I don't think there's widespread uptake of phenelzine in cancer now.

Allen Morris 33:34
Why not? Do we have this off-label?

Mitchell Gross 33:35
I don't know. It's a good question. I think there's most certainly data to be explored. You know, you'll have to ask the community why? I could tell you as a practicing physician, at times I've given it to patients, but what you really have to think a lot about, as any physician does, are the risks and the benefits. In cases where we have a better option, or more safe, or a more well proven option, we would choose that option. And I think any good physician would do that.

Allen Morris 34:09
Yeah, I really have to ask you this question, because I'm stupid about this, because I'm a pathologist. We're the field that absolutely is the least familiar with therapeutics. I do not treat patients. I'm a doctor, but I don't treat patients. What is your definition of "off label" because I still, to this day, do not understand it.

Mitchell Gross 34:29
"Off label" means prescribing a medicine outside of the FDA approved label. The FDA-approved label for a medicine like phenelzine would say it's used for anti-depression or some benefit in Parkinson's. It's a little bit complicated because the ones that were prior to the current FDA regimen, meaning the current laws are sort of grandfathered in. There's a little different loophole for that, but yeah. Technically, that's what off-label use is. If you're using it for an indication that's not the FDA-approved indication, you can also adjust the doses as well. Sometimes off-label means giving the medicine for the same reason, but the doses are higher. Those are a couple of examples.

Brian McCloskey 35:32
Do we have any data that would suggest what type of patients would benefit most and least from this type of drug? We have so much data now we have genomic, transcriptomic data. It's proliferating. Is there a way for us to understand which of us would benefit and which ones wouldn't?

Mitchell Gross 36:02
That's another sort of pillar of my research. I don't have much public to say about that, but looking at genomics and response to treatment, maybe that will give us some data. In terms of the published data, there were studies that looked at prostate cancer treated with chemotherapy. This is what's called the neoadjuvant study. Basically give a patient chemotherapy, and then they would do a surgery. They asked the question, "What genes changed in the cancers, especially the ones that were resistant to chemotherapy?"

Take up a sample before treatment, and then you give treatment, and then they get a surgery, and then compare those two samples. MAOA was upregulated in those patients. Now that's not everyone. This is one of the challenges. It's one of the most commonly upregulated treatment, chemoresistant, taxane-resistant genes. In fact, there was a trial that was started, but then didn't finish at University of Washington and Oregon, that looked at giving taxotere (taxotere, or docetaxel, in the drug class of taxanes) with phenelzine. We don't really know, it seems to be very upregulated in treatment resistant prostate cancer. And in other cancers, as well, trying to identify that prospectively, I don't know it is a gene that you can look at in gene expression arrays and the protein you can look at. But this is one of the big challenges because at least in animal models, and in humans, it does work in some but not all patients.

Michelle Sager 38:06
I'm curious about how you're trying to adjust this MAOi so that it's an MAO inhibitor, but it cannot cross the blood brain barrier. I'm curious about this. The idea is that it's some sort of putative immune modulator somehow?

Mitchell Gross 38:36
It has a direct anti-cancer effect.

Michelle Sager 38:39
I guess I have two questions, then. What is your notion of its mechanism?

What is it that you're trying to do by keeping it from going into the brain? Because I'm wondering if it also has some sort of possible beneficial effect there?

Mitchell Gross 39:01
The mechanism of MAOA in the peripheral cancer tissues is one question, then the second one is, maybe this is not an off target effect. Maybe it's a desirable effect. Those are two very important questions I can speak to.

So the first one, this issue of how does it mainly work? I showed you a picture of the neurotransmitters in the brain. But how does that have to do with a cancer cell in the prostate or lymphoma or some other cell? MAOA has an intrinsic function inside cells. If this means anything, it's actually a mitochondrial resident enzyme and it regulates the redox potential (a measure of an enzyme's tendency to gain or lose electrons, which is essential for their activation) inside the cells.

MAO has a more pleiotropic (when a single gene can affect two or more unrelated traits), a wider effect, in tissues independent of the effect on modulating the neurotransmitters, that's how it was discovered. But the actual effects are much more broad in tissues. So there's a couple of published studies, these are very prominent studies. JCI is a very prominent general clinical investigations journal published about 5 or 8 years ago that showed the mechanism, or at least some of the mechanisms. Again, it has to do with redox. It has to do with transcriptional

regulation, such as VEGF (Vascular Endothelial Growth Factor, protein that stimulates growth of new blood vessels), and other pathways.

A variety of pathways are affected, but it's probably more overall the redox potential inside the cell, which is signaling the cancer cells to either differentiate or not differentiate (When an unspecialized cell becomes a specialized cell type with a specific function). And you want them to be differentiated so that they're responsive to treatment.

The second question is: do we want it to go to the brain? There is overwhelming data that you can take cancer cells in the laboratory, like grow them in the tissue, there's no brains involved. We can give MAOIs, and in many different cell lines, you'll have an anti-cancer effect. Same in animals and other things. So there is an interesting effect.

But maybe there's an effect on the nervous system in the brain. Maybe we want to take advantage of that. Yeah, again, we don't really know. The idea here was that decades of research have tried to engineer MAOi to only go to the brain, right? Because if I was a psychiatrist developing a drug, I would give the opposite talk. And I'd say, we just want to go the opposite way. We don't want it to go anyplace else.

Basically, we're kind of reengineering that for our purposes. I don't know if that answers the question. But you're right. And it's very interesting, the immune system, and the nervous system interactions are super important. It could be that MAOIs are affecting the nerves. There's a whole literature on peripheral nerve innervation to prostate and cancers, and maybe we're affecting the peripheral nerves or the central nerves. We don't really know. But well, yeah, I mean, there's a lot more to learn.

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Michelle Sager 42:19
If you had a drug that was able to separate out those two effects, then you could kind of delineate it, make that distinction and try to understand it better.

Mitchell Gross 42:31
And that's one of the things we'd hope to do with our research is try to interrogate that kind of difference.

Mitchell Gross 42:57
There's a question about whether this is for recurring prostate cancer. The research is there in the public that we showed in recurrent prostate cancer. Many of the patients, at least in 1979, did show some activity in this particular case of biochemical recurrence. But, you know, plus or minus, it's something I think you should talk about with your doctor.

Brian McCloskey 43:32
One quick follow up to Michelle's question. It seemed to me just in listening, that a lot of the side effects were probably not in the brain, but you know, sort of in adrenal and other systems that were outside the brain. So probably inhibiting the blood brain barrier interaction would still not eliminate those side effects? If that was the purpose?

Mitchell Gross 44:02
So again, the big side effect that we talked about here is this drug food interaction. So this has been really well studied going back many years. It turns out that the lining of the gut has both MAOA and MAO-B, because an important purpose of the gut is to basically remove this tyramine, the free tyramine from your diet, which is in fermented foods and meats to prevent it from going directly in your bloodstream because that can cause this problem.

The other way around this problem of the tyramine surge with diet is if you leave one of them untouched. So if you have an MAOA specific inhibitor, the MAO-B which lines the gut is enough to deactivate the tyramine. The other part of the strategy, which I didn't focus on, is to do just an MAOAi. And that way you would have less of this toxicity.

There's a literature about this in the 70s. In psychiatry, there was a class of drugs called RIMAs, that were Reversible MAOA Inhibitors, that basically avoided a lot of these side effects of the drug.

Brian McCloskey 45:31
That was actually not my question. But that was very helpful. So my question was - I used to teach life science. And, you know, I remember a professor coming in at MIT who did a large study through the Medicare database. I mean, there are these enormous databases of information. And if MAOi's are not contraindicated for a wide variety of cancers, you could do sort of historical studies, I imagine, against large databases and medical records. Begin to tease out interactions. Has anyone done that?

Mitchell Gross 46:11
Yeah, we're, as always, looking for support for that kind of research or financing. But yeah, we have talked about that. I've seen some unpublished real world evidence data from other countries. So I think that's an enticing way to do it. One of the problems is that MAOi, as we said, they're not very commonly used here in the United States. There are some countries where they're used more commonly, because they're cheap, like outside the United States and Taiwan, for example. So you could do that. And I've always wanted to do that for many years. But I just haven't had the right combination of funding.

Brian McCloskey 46:53
But the drugs are not contraindicated for most.

Mitchell Gross 46:56
They're not. No, no, no.

Brian McCloskey 47:00
Well, that would be an interesting study. I don't know how many data points you'd have. And I mean, Taiwan would probably have a good registry. But you know, a lot of countries that use a cheap drug might actually not have very good records.

Mitchell Gross 47:11
It's a practical problem.

Brad Power 47:16
Well, let me riff on that quickly, before we go to Rochelle. You're repurposing an existing drug? Can you talk a little bit about how that's been? You have safety presumably covered or the side effects and how to mitigate them. And now you're trying to find a new use case or a new application for that same drug? How's that been?

Mitchell Gross 47:41
Yeah and Brian can talk about this. And he mentioned this company called "Reboot Rx", which is a nonprofit, that really their idea is to sort of mine the medical databases to kind of find opportunities to repurpose drugs. But there's a lot of headwinds, the biggest headwind is that we take a drug that has been used for one thing, and then we're trying to use it for something else, even though the physicians or the scientific community think it's safe. One of the problems is paying for it. So you know that luckily, these off label drugs are very cheap. So that's a great opportunity. But no one would really want to pay for the research. Because if there's no patent protection, the source systems being what they are, they generally don't don't fund the research, right? There's no drug company that will fund the research. So we have to find other mechanisms like either philanthropic mechanisms, angel funding, and ideas for government funding, or consortiums, that could help fund this kind of research. So there's this very practical thing, like it seems like a no brain kind of question. You have a drug, why don't we use it for something else, and maybe it can work. But getting it through the regulatory system can be difficult. There are certain, you know, opportunities and barriers, some drugs, or it can only be

manufactured in certain ways. So maybe that's a kind of an opportunity that could be limited. The FDA does have a sort of a repurposing loophole that can give limited patent protections for certain, you know, reformulations. So yeah, there's a big practical challenge to actually making this a reality.

Brian McCloskey 49:31
Brad, maybe one of the things we could do is bring up Laura Kleiman. Dr. Gross, you could work in tandem with her on this, but she can give you an update regarding a couple of drugs that they're putting through to the NCCN guidelines. (The National Comprehensive Cancer Network Guidelines provide evidence-based sequential management decisions and interventions for cancer care.)

She has a lot of evidence to support this. Hopefully, we're going to find out soon. She may or may not want to talk about it until it's done, but it's in progress right now.

Mitchell Gross 49:56
She has ideas about how to get the consortiums involved that could help to fund this kind of research. This is a very practical problem.

Brad Power 50:07
Rochelle, you had some nice comments about connecting this with food.

Rochelle Prosser 50:23
In doing experiments with off brand use with most of the patient populations that I have had worked with in the past, and as well specifically within the pediatric population, I noticed that there would always be a micronutrient or some other food additive that we would have within the healthy components of the food, which would actually become problematic. And so I wanted to hear if there are some crosswalks that we have, now that we know what these drugs have done from first and second generations, how they affect us with the micronutrients now, and how that plays a part in targeted therapies. And maybe genomic therapies for one for FGFR (Fibroblast Growth Factor Receptor inhibitors are used to treat cancer by interfering with cell growth and signaling) drugs – the main issue is phosphorus. It breaks bones, it takes away neuropathic pathways, it unsheathes the myelin sheaths (Insulating layer around the axon of nerve cells in the brain and spinal cord, allowing for the transmission of electrical impulses.) on the neurons.

Some of these have become problematic for overall survivorship. Do you know what they are for these types of drugs?

How can we use foods to either avoid but still be healthy? Or is it the plant compositions that we're talking about?

Mitchell Gross 51:54
I guess you are thinking more about if the MAOA as a class of drugs were used? Are there micronutrients that we should be aware of that may or may not influence? Yeah, I think that's it.

Those are definitely great questions. It turns out MAOIs need nutrients to work. I'm sure there's a lot more research that could be done in the B-12 interaction with these agents. But it's something to look into.

Allen Morris 52:43
I saw your mouse model studies.

Mitchell Gross 52:51
It was published by Chawshang Chang at the University of Rochester.

Allen Morris 52:59
It showed an experiment, which is to try it with the tried and true treatments such as enzalutamide. When you combine the two, there is a greater effect. So you could use the term synergistic. Is that correct? Between the two?

Mitchell Gross 53:08
Yeah.

Allen Morris 53:09
Okay. I have this general theory, and I would like to run it by you because you are an expert physician. It's a crazy theory about immunology. I believe the female gender state is an immune better state. I don't have a good term for it. I base that on these observations.

Observation number one, women have much greater autoimmune disease than males substantially more. Observation number two men get more cancer than women do. And furthermore, women live longer. And then most recently, women fared better during the COVID epidemic than men dead did. These four things, I'm listing for my theory that women are in a better immune state.

There's a tried and true drug class in your field (prostate cancer/oncology). It's the drugs that aim at testosterone mitigation. You know, generically, ADT (Androgen Deprivation Therapy) drugs. If somebody's going to go off label and use your MAOi in treating BCR patients (Biochemical recurrence is a rise in prostate specific antigen levels after primary treatment, which indicates a potential return of the cancer.), would you also recommend that they get ADT with it? Let's say I'm BCR, which I am. Let's say I want to go off label, but I don't have the resources/access to go to you to prescribe phenelzine off label. Would you recommend an ADT + phenelzine regimen such as double hormone blockade informed by the EMBARK study (The EMBARK Trial compared the effectiveness of enzalutamide (androgen receptor pathway inhibitor) with or without leuprolide (androgen-deprivation therapy) in patients with high-risk BCR prostate cancer.), in particular, enzalutamide and Lupron (leuprolide) plus phenelzine..
[Comment: I tried to directly ask, in the non-recorded session, Dr. Gross, the very researcher-clinician, who has shown promise for phenelzine in the BCR phase of prostate cancer - if he would prescribe phenelzine off-label - I think he mainly skirted the question - but I read into it that he probably would not - which speaks to running with this information - the promise of

phenelzine to your doctor to get him to prescribe it to you in the BCR (not the end of the line state)]

Mitchell Gross 55:29
I'll answer in the general way. I would say that these drugs, this pathway, this target, I think it's very interesting by itself. And again, we didn't talk about all this data, but there's overwhelming data that the MAOA is a target in preclinical models. But it's still a gulf, but some data showing it's a target in actual patients, at least suggesting it's a target in patients.

But what is true about MAOAs to target than other targets is, I think there's a big advantage in oncology in treating multiple targets, in that you can co treat, with a combination treatment. I think you're alluding to the EMBARK study, which was enzalutamide monotherapy, enzalutamide with Lupron or Lupron alone, or general agonist antagonists alone.

It would be useful to try to think about adding MAOi to other therapies. Yes, that would be my first thought if we were to really implement this agent, or this strategy, but it's very much an open question. And testing the combinations, again, as a clinical trialist, researcher, scientist, and as a physician – it's hard to know when you add the combinations, which is better than the other, or the better combination. So this is the problem. Again, a very practical problem facing the field.