“How Hormone Receptors Affect Prostate Cancer” (Ed Friedman) [#59]

Frank Brancato, Russ Hollyer, and Brad Power
May 21, 2023

“I look at their data, and their data tells me what's going on. So far, everything I've seen fits my model. But in some cases, the author of the paper will say these results are inexplicable or paradoxical. And that's because they conflict with what they were taught in medical school.” – Ed Friedman

“It turns out that in reality prostate cancer is caused by high local levels of estradiol, <not testosterone.>” - Ed Friedman

Meeting Summary

Does testosterone **cause** prostate cancer?
Can hormones (testosterone) be used to **treat** advanced prostate cancer?

Conventional Wisdom: For decades, doctors were taught that testosterone **causes** prostate cancer. Their proof was that if rats were given high levels of testosterone, around two thirds of them would develop prostate cancer. Also, androgen deprivation kills prostate cancer.

A More Complex Model: However, in 2008 it was definitively proven that estradiol (a sex hormone, the most potent and abundant form of estrogen) acting on estrogen receptor-alpha (a chemical messenger that regulates the rate of transcription from DNA to RNA) is the primary cause of prostate cancer. Testosterone doesn’t fuel prostate (and breast) cancer, it is a messenger on the pathway that tells the prostate cells to grow, divide, or die, along with other hormones. In this more complex model, estradiol, estrogen receptors, and aromatase (the enzyme that converts testosterone to estrogen), play key roles. Testosterone, in fact, if administered in certain ways, can help **control** prostate cancer.

Dr. Edward Friedman is uniquely qualified to describe this more complex model of the relationship between hormones, hormone receptors, and prostate (and breast) cancer. He has a Ph.D. in Biophysics and Theoretical Biology from the University of Chicago. He has had four articles published about prostate cancer, two of which were peer reviewed. He has had eight letters to the editor about prostate cancer published in peer-reviewed journals. He has had one book published, "The New Testosterone Treatment: How You and Your Doctor Can Fight Breast Cancer, Prostate Cancer, and Alzheimer's" (2013).

What is a more complex model of how hormones cause prostate cancer?

Prostate cancer is more immediately driven by estradiol, rather than testosterone, though testosterone is involved. Prostate cancer starts when prostate epithelial cells (cells which cover the inside and outside of surfaces) are exposed to high local (near the prostate) levels of estradiol, creating mutations. Normally, prostate epithelial cells never divide, and prostate cells do not make estrogen. But in the case of prostate cancer, high local levels of estradiol are

produced from testosterone inside prostate cells which have a mutation (in the 5AR gene) that starts converting testosterone into estradiol. This activates the estrogen receptor alpha. When the estrogen (estradiol) triggers the estrogen receptor alpha, prostate cancer begins.

What are the practical implications of this more complex model for prostate cancer patients?

- The more advanced the prostate cancer, the more likely there are mutations that protect it from testosterone. Also, the more advanced the prostate cancer, the more estrogen receptor alpha present, which makes estradiol more deadly.
- If you still have your prostate, then it’s important to keep estradiol at low normal levels for good health and discourage additional cancer initiation. High levels of estradiol cause cell division and mutations in prostate epithelial cells, ultimately leading to cancer. To monitor your estradiol and other hormones, you can get a hormone panel test, such as the Genova Diagnostics “One Day Hormone Check”. To keep your estradiol at low normal levels, you can take aromatase inhibitors or eat Brussel sprouts.
- If you don’t have a prostate, keep estradiol in normal range for good health. You should keep your estradiol at 13-20 pg/ml. Sometimes it will become undetectable. It is a moving target if you introduce exogenous testosterone.
- High levels of testosterone act to prevent epithelial prostate cell division and can kill your cancer cells. A better way to implement bipolar androgen therapy is to keep testosterone high and cycle DHT (dihydrotestosterone, the most potent hormone among the androgens, and considered a pure androgen as it cannot convert into estrogen.)

What are possible future implications of this model?

RU486, mifepristone, a drug which blocks progesterone, could be a game changer for prostate cancer.

How do key hormones contribute to prostate cancer and how can they be controlled?

- *Testosterone*: The main male sex hormone. A messenger that tells the prostate cells to grow, divide, or die. We can decrease it or increase it as desired. Receptor(s): Membrane androgen Receptor(s) (mAR), Intracellular androgen Receptor(s) (iAR).
- *DHT*: dihydrotestosterone, the most potent hormone among the androgens, and considered a pure androgen as it cannot convert into estrogen. Almost all of it is derived from testosterone via 5AR. If we want to block it we can use 5AR inhibitors (e.g., finasteride, dutasteride). We can decrease it or increase it as desired. Usually this will also involve increasing testosterone. Receptor(s): Intracellular androgen Receptor(s) (iAR)
- *Estrogen*: Most of it is derived from testosterone via aromatase. If we want to block it we can use aromatase inhibitors (e.g., letrozole, anastrozole, exemestane). If we want to increase it we can use estrogen patches, gels, or creams. Receptor(s): Estrogen receptor alpha (ERa) – usually bad. Estrogen receptor beta (ERb) – usually good

“How Hormone Receptors Affect Prostate Cancer” (Ed Friedman) [#59]

- *Prolactin*: This hormone could be used as fuel by some castrate resistant prostate cancer tumors. If we want to block it we can use prolactin inhibitors (e.g. cabergoline). Receptor(s): PRLE.
- *Progesterone*: One of its functions is to assist in testosterone production. Receptor(s): PRa – usually bad, PRb – usually good.

How can I learn more about Dr. Friedman’s theories?

Please see his book and his website.

“How Hormone Receptors Affect Prostate Cancer” (Ed Friedman) [#59]

Meeting Notes

SUMMARY KEYWORDS

receptor, testosterone, prostate cancer, cancer, intracellular, estriol, membrane, finasteride, cell, progesterone, estradiol, receptor alpha, showed, patients, give, amplified, paper, doctor, prostate, mutations

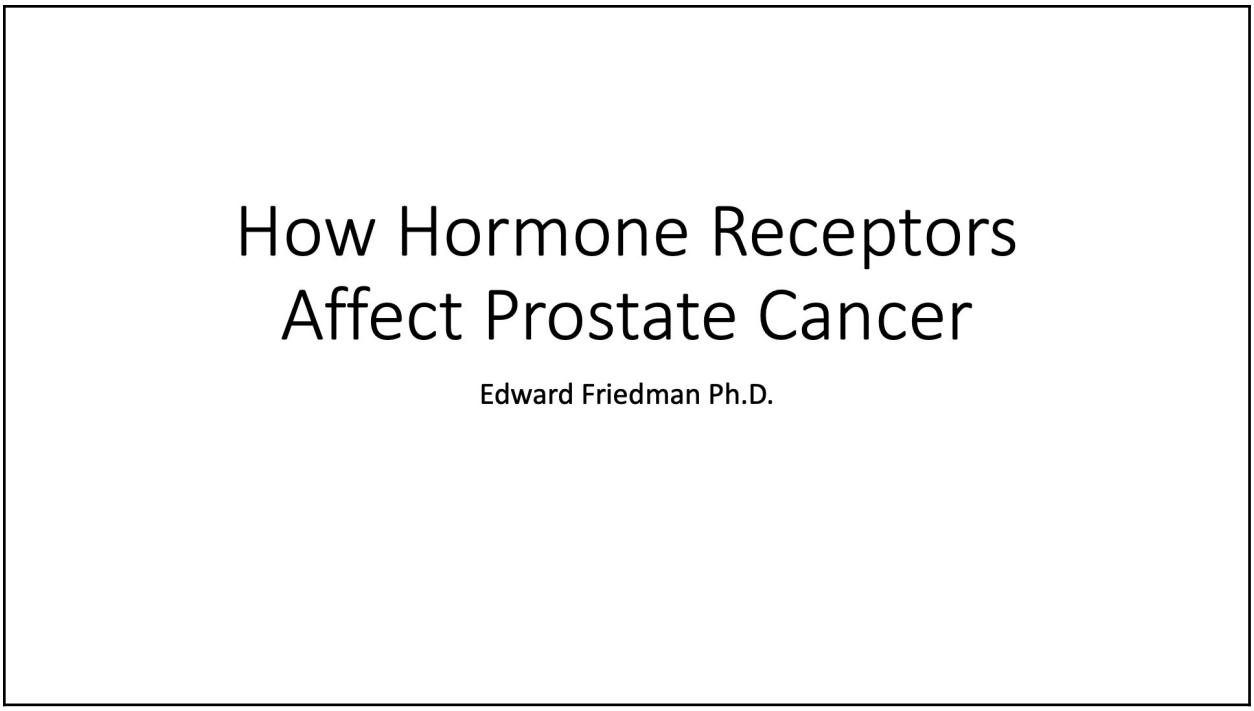
SPEAKERS

Ed Friedman (85%), Russ Hollyer (7%), Brian McCloskey (5%), John Sandiford (2%), Brad Power (<1%)

Discussion Outline

1. Introduction to Dr. Ed Friedman. (0:00)
2. Ed’s background and research. (1:39)
3. How prostate cancer originates and the role of estrogen. (5:32)
4. Hormone testing and prostate cancer. (13:07)
5. Good and bad androgen receptors. (21:10)
6. How to treat prostate cancer? (28:03)
7. How safe is estriol for men and women? (34:55)
8. Hormone sensitivity and prostate cancer. (42:29)
9. The problem with finding a doctor to treat prostate cancer. (48:29)
10. The benefits of testosterone replacement therapy. (56:18)
11. Do you know if functional testing has been done? (1:03:21)

Russ Hollyer 1:03
We have today with us Edward Friedman, PhD. He's an expert on hormones. I was so excited when he agreed to present, even though it was on Sunday. I said any day, any time, I don't care if it's 2am, or 3am, at whatever the time, on whatever the day, I will be there. He is an expert. He was the reason why I abandoned ADT and went to high testosterone, which worked for me for two years.



Ed Friedman 1:54
Let me talk a little bit about my background. I've been researching hormone receptors since 2004. My first article was published in 2005. It was on prostate cancer and the properties of the androgen and estrogen receptors. After doing that article, some people I knew came down with breast cancer. When I was doing the research for the article, there were so many papers talking about the receptors and saying that what they were seeing was exactly what they were seeing in breast cancer. So I started researching breast cancer as well. In 2007 I had my second article published, and I added progesterone receptors. Basically, all the receptors are almost identical in breast and prostate cancer. The only exception is the membrane antigen receptor, which in women decreases BCL2, and in men increases it. I'm not going to go into all the details, but it's pretty close to being the same.

Some people urged me to write a book. I had that published in 2013. One of my fans happened to be a professional English teacher teaching people how to get a book published, and he volunteered his time and helped me to find a literary agent, and eventually became a co-author to make my book more readable in plain English. Since that time, I've had three more articles that I published in researchgate.net, one of which was expanding on the role of estradiol in prostate cancer, and the latest one was looking at the BAT treatment in terms of what they're overlooking and what they're doing right. Everything I tell you is pure theory. It's based on what I'm seeing in the literature. It's not something that I'm making a guess at. “I think this.” It's like, “There are articles out there.”

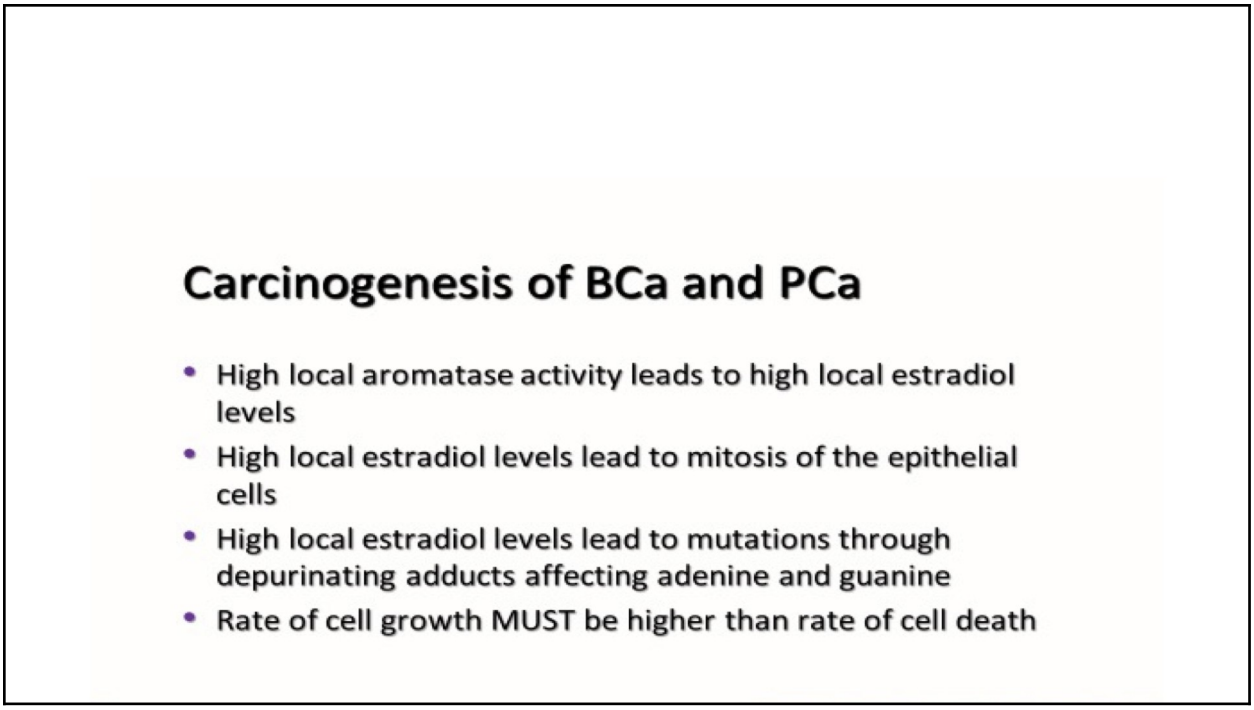
Russ Hollyer 5:09

“How Hormone Receptors Affect Prostate Cancer” (Ed Friedman) [#59]

You're a theoretician, a researcher, versus a clinician. A clinician looks at clinical results. I think they're both vitally important. You're looking at the theory, you're not looking necessarily at the practical applications.

Ed Friedman 5:31
That's correct. And the other thing is that the clinicians will publish the results without giving a clear explanation of why they have what they have. I'll give you an example. In fact, Dr. Denmeade says, it works because of the wind cap on a 402 cell line (?) and what that does, but in that paper he doesn't answer the question. “Why do you have to have an amplified intracellular androgen receptor before high dose testosterone works?” “Why can't you just give even more testosterone if the only thing that matters is what's happening in the interest of the end of the receptor?” Those are the sorts of questions that I consider in theory, in which the clinicians are totally oblivious.

So with that in mind, I basically look at what people published and ask why. “Why is this the result?” Often I look at their data, and their data tells me what's going on. So far, everything I've seen fits my model. But in some cases, the author of the paper will say these results are inexplicable or paradoxical. And that's because they conflict with what they were taught in medical school. I never went to medical school, so I never got indoctrinated in dogma, I just look at the actual data of what's been published, and work out logically what's going on.



So let's start with how prostate cancer originates. To give you a quick background, for decades, doctors were convinced testosterone causes prostate cancer. Their proof was that by giving the noble rat high levels of testosterone, they could get around two thirds of them to develop prostate cancer. So you assume they have the answer. And plus the fact that androgen

deprivation kills prostate cancer, they thought testosterone was the villain. For decades, we taught them that in medical school. They were going on that assumption.

It turns out that in reality prostate cancer is caused by high local levels of estradiol, which acts on estrogen receptor alpha. They've shown that early prostate epithelial cells, which is where the cancer comes from, never divide. They're made from stem cells. They sit there. They die off. They get replaced. They never divide. The cancer is the dividing.

They've shown you can take ordinary prostate epithelial cells, and with high local levels of estradiol, cause prostate cancer to arise. In 2008 researcher Gail Risbridger from Australia, who's done wonderful work on estrogen and prostate cancer, proved beyond a shadow of a doubt that estrogen receptor alpha is what causes prostate cancer. She used ordinary mice and when she knocked out their estrogen receptor alpha gene, she was unable to have them develop prostate cancer, no matter how much testosterone and no matter how much estradiol they were given, they simply could not develop prostate cancer. On the other hand, if you took normal mice, gave them enough testosterone so that you don't kill the prostate cells due to androgen deprivation, and then start raising the level of estradiol, she got a 100% rate of developing prostate cancer.

This should be taught in all the medical schools. All the doctors should be aware of it. They're not. Part of the problem is this article was published in a biological Journal, the Facet Journal, which is one of the two best biological journals in the world. Doctors read medical journals; they don't read biological journals.

The best you'll see is some doctor may say, “It's unclear what the role of testosterone and estradiol are in prostate cancer.” The reality is, if they read all the literature that's out there, it's very clear. There's no ambiguity. The high local levels of estradiol will cause cell division to start. That's not enough for cancer. You now need mutations, and it turns out the high local levels of estradiol also cause what's called “depurinating adducts”, which are a mild mutagen. But with enough of them heightened enough, with high level estradiol given a long enough time, even a mild mutagen will eventually lead to prostate cancer.

And the way you get the high local level of estradiol is by a high local aromatase activity. In a separate paper Dr. Risbridger has shown that the prostate cancer cell line had local high aromatase activity on a par with what we've seen in breast cancer.

Russ Hollyer 11:52
So if you simply look at testosterone, you could be easily fooled into thinking that it causes prostate cancer, if you ignore the fact that it actually produces DHT, and in this case, estrogen, so as you increase testosterone, you increase your estrogen. Is that correct?

Ed Friedman 12:16
That's correct. And most people I should point out, ordinarily, the prostate epithelial cells do not express aromatase at all. That's why the first step in prostate cancer development is the

activation of that gene. The gene is being silenced. The gene is part of the human genome. It's just silenced. So it's not expressed in prostate epithelial cells. But there are many billions of cells that are being created. One gets created with a mistake that it doesn't silence. It's not clear whether it's methylation silencing. There are various ways to silence a gene. But whatever it is, it's failing when you start to get prostate cancer.

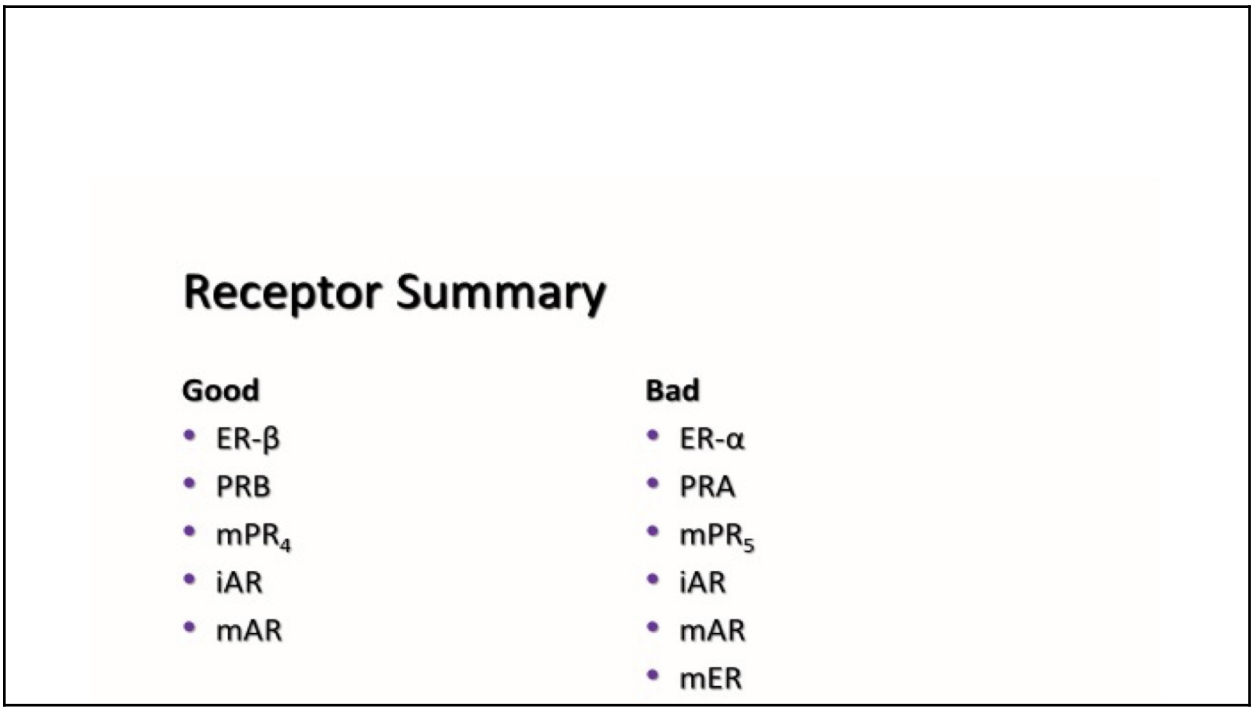
John Sandiford 13:16
This is a very fascinating thing, because I was diagnosed in 2013. Before I got diagnosed, I was feeling really weak and tired and had a low libido. I did a Genova Diagnostics Test on my complete male hormone is the name of the test. And it actually in I did a detox genomic and it showed that I had to see why p one, a one, one, b one and column T mutations, along with a gsdm glutathione, gsdm one absent, and those are all in the exact pathway that caused me to have very high bad estrogens, which close those three, four Quinones, and then the ADOX. Glutathione was supposed to be a failsafe to get rid of it, but it never did.

I presented this to my doctor, and they didn't know what to do with this stuff. It's just so sad, but it's what caused it. I was reading a paper by Lady Cavallari. You probably know her. She laid here she aircall capillary and Eleanor Wogan. They've got quite a few papers on the same subject. You probably read them. A cheese has a workaround on it as resveratrol and an acetylcysteine. It's pretty new article to 2020 tools on how to get around now those mutations and how to get rid of those DNA data actually, the three four Queen owns.

I just I'm just put my three cents out there because that's a subject that I'm trying to figure out. It's looking right at my language.

Ed Friedman 15:00
A lot of people get confused about serum estradiol and local estradiol. Your serum estradiol could be absolutely perfect. But the few prostate cells that now have high aromatase activity are going to have high local estradiol levels. And that's never going to get into the serum. Similarly, a high serum level doesn't necessarily cause the cancer in the first place, you end up having to have a pretty high level of local estrodiol to get the ball rolling. And to answer your, I guess, to address your point about resveratrol and stuff. Other researchers have worked backwards in time to figure out what age men are when they first get their very first prostate cancer cell. And it tends to be late 20s, early 30s. So that's the very first cancer cell so by the time you're aware of it, it's too late to stop the effect of the urinating Attucks, they've already created the cancer and you don't need any more mutagen once you've got the cancer growing, because cancer will just naturally mutate, and grow and keep getting worse, just natural selection. And what's interesting, of course, is that some people think, cancer, once it starts, it's off to the races, you're doomed, whatever. And the reality is, there's a race between this cells dividing and the cells being killed by your own body. A low grade. Gleason score might have something like an average, every 68 days, the cell divides, and on the average, every 72 days, our cell dies. And it's going to grow, but it grows slowly. It takes a long time, initially, for the tumor to actually double in size. When it's in the prostate, that's when it's doubling time is the slowest. When it gets to the lymph nodes, it's much faster and when it gets to the bones, that's the fastest you

can get. But again, it's always a question of the rate of cell growth versus the rate of cell death. And doing something that either increases the rate of cell death or decreases, the rate of cell growth could slowly shrink a tumor, you don't have to blow it all away. The way they do, you know, a lot of doctors like to think that we have to get all of the cancer out and get it out now. But most people have a lot of time and you just want to tip the balance in your favor. So it's, it can be slowly decreasing in size or staying the same size or slowly increasing. The idea is to die with the cancer and not because of it.



This is the heart of my work. It amazed me that no one's done this except me. For every receptor there's a researcher studying that one receptor and what it does with regards to prostate cancer, and what I did is I looked in the literature and got everything that people had put together, and am able to look at the overall scheme, what's good and what's bad. And again, in theory, we can now have different types of treatment based on it.

So let's first go through the good ones.

- Estrogen receptor beta is good. It decreases the amount of BCL two and other anti apoptotic proteins.
- Progesterone receptor B is also good. It also decreases BCL2. And I used to think it didn't have any pro apoptotic protein but I found the paper that it actually does up regulate a single pro apoptotic protein, so that's a good one.
- And then on the membrane, when I'm talking about PR for this a modification of progesterone called for preg means and they help increase the rate of cell death of prostate cancer. What's interesting is that as prostate cancer advances, as you expect, on the surface of the cell, this less of the receptors, that would take the four pregnancies so they decrease in number.

- And then the last two, the intracellular androgen receptor is actually good. It does several good things. One of the things it does, is it a Brekky up regulates a protein called as three. And what a s3 does is it just stops the cancer from being able to divide. So that's a good thing.
- Membrane androgen receptor is really good, it has quite a few pro apoptotic proteins. And can be used and has no reaches has shown that using a high androgen mode on just the membrane antigen receptor would kill like 60% of the cancer. So, every month, it's very, very potent tack on the cancer.

Now the bad receptors.

- Estrogen receptor alpha is bad. Starting the cancer in the first place. It's bad after the cancer exists, because it increases BCL two, which protects the prostate will protects all cancer cells. So to give you an example of how bad BCL two is, they found when they do high dose radiation on cancer tumors, the cells that tend to survive those five tend to have high levels of BCL two in it. So, not good to increase BCL two also progesterone receptor a increases BCL two.
- Another bad one is on the membrane of the progesterone receptor, which has five Alpha preg names that bind to it. And when that happens, it increases the risk of metastasizing, it increases the growth rate, decreases the death rate, it's a really bad one to have. And so far, no one's even thought of coming up with a drug to block it. As far as I know, no one's working on that.
- And then let me just go back and go to the jump to the bout and the membrane. estrogen receptor has been shown to increase the growth rate of the prostate cancer. So that's that one.
- You may notice that the intracellular antigen receptor and the membrane and receptor are listed both in the good column and in the bad column. And in the bad column, intracellular androgen receptors are bad because they increase BCL2. And it seems to counter all the good things in the membrane antigen receptor. And the management membrane, Andrew receptor is bad because it increases BCL two and it seems to counter the interests of anti receptor up regulating as three. So what's interesting again, just to give you the way my mind thinks, I learned that ordinarily, the normal prostate epithelial cell lives for 500 days, dies and gets replaced from the stem cell with another prostate epithelial cell. And the question I asked myself, How in the world does the you know what, what's the mechanism that after 500 days Ah, this cell just dies all of a sudden, what's going on? What could possibly explain it? And the only thing that made sense to me is that there has to be a balance between the intracellular and the membrane androgen receptor. In other words, there are articles that show that if the intracellular androgen receptor is the only one that is binding to it, nothing binds to the membrane, then the cancer can't grow. And eventually, eventually, I mean, the cell eventually just dies. Similarly, if the membrane androgen receptor is not opposed is nothing on the intracellular end of the receptor, it kills the cancer cell. And so I came up with, to me a logical assumption that for cancer to grow, there has to be a relative balance between the intracellular and membrane receptor. If you get it and balance on it, then you're going to kill the cancer cell, you're going to have an effective treatment. So

applying this to, for example, the back like I said, they don't know why it works to me. It's extremely simple. When you get amplified number amount of intracellular androgen receptor, and it tends to be like tenfold when they do the BAT treatment. And looking at the last cell line, they model it after the wind cap on a four or two, it does have tenfold more interest. So the androgen receptor, if you give it testosterone, it will not grow. And from my point of view, it's because you've just turned on as three because it's not enough binding to the membrane and your receptor, you're overwhelming it with a tenfold amount. And they know that line will not grow in the presence of testosterone. But the other thing, the kicker that shows from my point of view that I'm right, same cell line, they give it testosterone and finasteride. Okay, now that testosterone won't convert to DHT and DHT binds to the intracellular androgen receptor around 10 times stronger than testosterone does. So now we've multiplied the amount by tenfold, we've decreased the binding tenfold. We're back to normal. So what do we expect to happen with testosterone finasteride, it should grow just fine. And that's exactly what they see. And like I said, my whole theory in terms of ways to treat prostate cancer is twofold. One, if we can block estrogen receptor alpha and give an agonist test receptor beta, that should be good against killing the cancer. Another one is if we can block progesterone receptor A and stimulate progesterone receptor B, that's good against cancer. Now, you know they have to MOCs fin that we block as receptor alpha, but it doesn't block in every organ and has in some it's acting as an agonist in others and antagonists. So Tamoxifen is not ideal. I'm not sure what they may have that we block only yesterday receptor alpha. In the long term, semester receptor alpha is necessary for your health and well being so may not be a good idea, or a percent block. So receptor alpha, you know, for the rest of your life, there'll be it may cause some harmful things. Now, progesterone receptor.

Russ Hollyer 29:38
What do you think of phytochemicals like genistein?

Ed Friedman 29:48
Yeah, I mean, things like genistein. They've shown in physiological levels, it works. So for example, in physiological level because it will prevent telomere formation which ordinarily would occur if you give it physiological levels that actually promotes telomere production. So you have to be careful with the phyto estrogens. The natural estrogen in other words, I've seen a lot of people talk about ADT and adding a little bit of vest as to dial just to feel better whatever. It's actually going to be an awful lot safer to add a little estriol. estriol is natural but it binds three times stronger to beta than alpha. And so if you're going to use an estrogen product product, at this point, I would recommend estriol

Russ Hollyer 30:48
Are you familiar with estriol bioidentical estriol creams on Amazon?

Ed Friedman 30:59

I'm not familiar with those. No. I know that potentially compounding pharmacies sell estriol creams. Over the counter, they sell progesterone cream. I didn't know that they were selling estriol cream.

Russ Hollyer 31:16
They say it's bioidentical, but I wouldn't expect that they can sell a prescription drug OTC.

Ed Friedman 31:21
The only way you get estriol is with a doctor. The only way you get progesterone is over the counter. I thought you needed a doctor's prescription for estriol unless they changed it. But what's interesting on progesterone receptor is Mr. Chris stone blocks progesterone receptor A does not touch B. So the question becomes what happens if we give progesterone receptor I mean, give up a combination of Mr. Pistone and progesterone. And what they showed is that basically, the myth of histone helped, like, with Blink tap, it slowed the growth down. And when they added progesterone on top, it greatly slowed it down, it was a huge thing. And other people have written papers on other cancers. Showing that that combination, they talk about it as a synergistic effect is if there's some magic that happens when you combine the two, I look at it, I don't look at it synergistically. I just say, look, you're blocking progesterone A is stimulating the, of course, good things are gonna happen. What's fascinating, there was one paper that showed it was very effective, even when there were no intracellular progesterone receptors. So from that, I have to assume the only way that could happen is if it blocks the membrane receptor for five Alpha preg name, and doesn't touch the membrane receptor for pregnant it's. So that combination is one crying out to be used. And in fact, in one article, I saw the doctor not only, or researcher not only talked about the good results, when the discussion pointed out that when you translate what he was using in these animals, and what's going to have to be used in humans, he was saying like an ordinary 200 milligram crystal dose is going to be all you need to combine with the progesterone to make things happen. Now, why has no one done it? Well, many years ago, Mr. Chris Stone, lost it, it's a patent, it's now considered a generic drug. And to do the sort of testing to show this combo is going to be great, is going to be costing hundreds of millions of dollars. And at the end, they're not going to be able to reap the reward. And then of course, you know, following it politically, it may be banned totally in this country. So no one's doing the research on it. But that's a combination that in animal studies in the xenograft of human cancer cells, prostate cancer cells, shows it's a great combination to use.

Russ Hollyer 34:42
That’s one of my backup plans. So I will be trying that on myself, at least potentially sometime in the future. Assuming I can get a hold of it. Do you think estriol has the same bone density and hot flush properties that estradiol has (e.g., Climara patches)?

Ed Friedman 35:15
I’ve never seen anything negative about estriol at all, any jokes, okay, in terms of safety and humans, a pregnant woman will make SQL at a level 1000 times more than they do normally. And of course, it does no damage. And there's no reason to do any damage to males, either. It's just, it's basically, you know, going off on a tangent a little bit, you may be aware that too much

as to dial men can damage the heart, whereas women as to dial is very beneficial to the heart. Some researches and it turns out, this applies to animals too, not just humans. And some researchers did a study where they took the female animal and knocked out estrogen receptor beta. And now they found that estradiol was just as ineffectual as it was in males. So females without su receptor beta, just as you know, estrogen was just as worthless as it is to males. So that's

Russ Hollyer 36:39
That’s why women don't get prostate cancer. Laugh.

Ed Friedman 36:44
That's why women who benefit from Estradiol don't have to worry about the heart attacks men do. But the yes or no, again, in theory, it's possible SQL may help protect men from heart attacks, because you'd be hitting the beta, because you have beta. But obviously, it can't be as much as it is in women, otherwise, estrogen would have been hard protected there, too. So let's go to the next slide.

Brian McCloskey 37:15
Actually, Dr. Friedman, just before we move on, once, your things that we know about any cancer is that every advanced prostate cancer patient on this call has a different makeup of prostate cancer as defined by their DNA alterations, or their RNA expressions or protein expressions. So if we were to take this, this theory here and this receptor summarizing and apply it to the patients on this call, are you saying it's a one size fits all model? Or can we combine this theoretical approach with, for example, my RNA expression where, for example, I have, you know, I've got a very low expression of BCL two. I mean, like, I'm in the, you know, 2% range for, you know, against 1000 prostate cancer patients who've had their RNA expression sequenced. How do we, how do we apply this theory, particularly given what we now have, relative to transcriptomics, proteomics, and genomics?

Ed Friedman 38:30
Basically, you throw everything in the kitchen sink at it. In other words, it's hard to believe that you're going to get a mutation. In every single one of these things, typically, the cancer is going to grow by knocking out one of the things that's hindering it, and gives it a selective growth advantage. So, for example, you're not going to see cancer with lots and lots of estrogen receptor alpha, unless you start treating the patient with estradiol. And you do that and initially, you'll get a high level of estradiol which gives you androgen deprivation because it stops the production of testosterone. But ordinarily, the initial prostate cancer cells have mostly su receptor beta and just a little extra receptor alpha, but if you keep treating them, now you're going to see a surviving population with lots of extra receptor alpha. In terms of the progesterone receptors, again, it's hard to say how the cancer is going to get around it. Cuz usually, in other words, the mutations are usually made in order to give an advantage to the cancer. So the poppy population is going to have something in the way of mutations that are advantageous to it. And, you know, one example. In fact, the D 145 strain of prostate cancer has no intracellular androgen receptor at all. They got it from a man who died in spite of years of

being on androgen deprivation. And when these researchers in 2005, took this cell strain, and just gave it testosterone. It again killed like 60% in a month, it's like, this patient died because doctors were so afraid of testosterone that have never occurred to him. That when the androgen receptor is not present inside the cell, that's the time to give them high testosterone and kill

Russ Hollyer 41:11
Do you think this should be a sequential type operation or just a combinational approach like everything at once?

Ed Friedman 41:36
At some point, you have to reverse. In other words, if you stick with just one treatment, eventually, the cancer is going to adapt to that and it's going to respond totally. But the advantage of something like that is that you are switching treatment, you're going from an amplified into sort of anti receptor, hit it with the high testosterone and then take that away, because you keep it up, the androgen receptors are not going to be amplified anymore. Eventually, they're amplified because they're exposed to low testosterone. So you want to switch it up.

Brian McCloskey 42:33
I guess what I'm trying to get at is like, for example, Dr. Antonarakis has shown us a couple weeks ago, that roughly two thirds of patients that he's seen, are going to receive some level of benefit from just from cypionate. Right, some are going to see their PSAs go down dramatically, some are going to like level up, but then they get hormone sensitivity. But then there's this third, where their PSAs and their cancers can really just take off. That's a gross feeling. It's a one size fits all approach. And so I'm trying to figure out how to fine tune that model, using this theoretical approach to mitigate against the rest of those 30 patients that are seeing really aggressive growth.

Ed Friedman 43:30
Anything you can imagine, in terms of mutation will exist in someone, you know, the limitation is just what you can imagine. And you can end up with a cancer that ignores all the receptors and just grows uncontrollably, and there is nothing you can do, whether it's androgen deprivation, or high level this or you know, any drugs to block any specific receptor. That's a death sentence and that can happen, it happens. More likely. The more cells you have, the sooner you can start attacking the cancer. That is more likely you are to have success in terms of the person dying with the cancer instead of because of it. And if you've, you know, for those who've read my book, I admire the philosophy of Dr. Robert Liebowitz. He took the stance of hitting the cancer early with everything. And then he on maintenance would go high testosterone plus a five five AR inhibitor. Now let's look at what that does based on my receptors model. Five AR inhibitor means progesterone is not going to come five Alpha pregnant again because it needs a five alpha reductase to do it. So, five AR inhibitor protects your membrane progesterone and allows the for pregnant pregnancy to help control the cancer. Similarly, because I should point out, while DHT binds the intracellular receptor is 10 times stronger than testosterone, both testosterone and DHT bind equally well to the membrane, androgen receptor. So, by having

high testosterone plus a five AR inhibitor, he developed an imbalance with a membrane Andrew receptor has, you know, like suddenly 10 times more effect and a head because you had a balance where there was enough membrane and receptor to balance out the intracellular energy receptor, assuming there was testosterone, which inside the cell converts the DHT. Now you block that conversion, so you don't have the DHT you get 10 times more than the membrane antigen receptor. And either you know, depending on the individual, you may see a drop in the PSA or the PSA much may just very slowly rise and in fact, Dr. Liebowitz his patients often would go many, many years on high testosterone with a five AR inhibitor and not have to go back on to Andrew deprivation. His initial approach was injured deprivation and if it was an aggressive cancer, he would add chemo right away whereas most doctors wait for chemo until the patient's almost dead. And then they hope to give them a few more months of life. Dr. Leibowitz took the approach, let's hit it with everything initially. And he had incredible success. He had a paper where not paper he presented at ASCO conference, a study where he showed a 1.5% prostate cancer death rate with people who started with average PSA of around 12 or 13.

Russ Hollyer 47:44
Do you know of any doctors who might be practicing his approach? The outfit appears to be more standard of care (SOC) today.

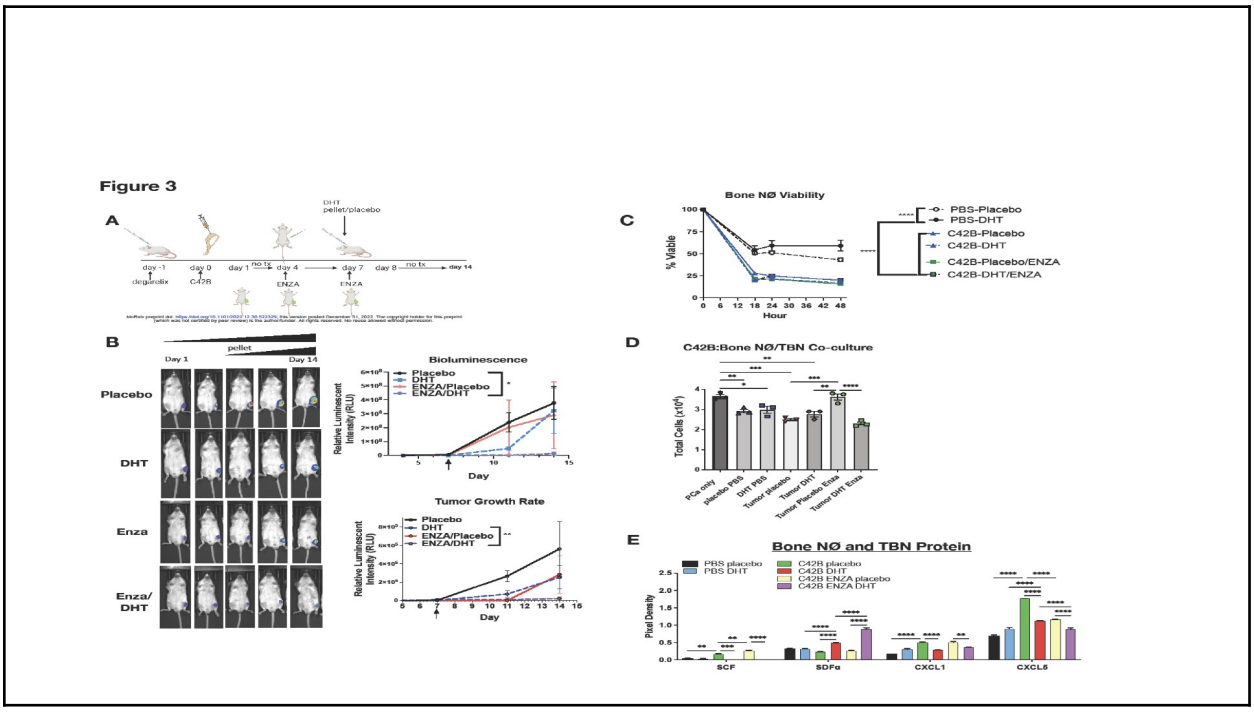
Ed Friedman 47:59
Dr. Leibowitz has retired and Dr. Eshagion has taken over. He might be convinced to try with Dr. Liebowitz. From what I understand he's continuing to treat the patients who started with Dr. Liebowitz in the same way. In other words, since they have success. As a doctor, he's not going to do harm and take away what's been working. Whether he's going to start a brand new person on it, that's a different story. But yeah, the problem in all this is finding a doctor to do it. You know, as a theoretician, I could say in theory, this is what we do. As patients, you've got to go find a doctor that you can convince, this is what you should do. And that's not not at all an easy chore. In fact, I was contacted by one doctor out in Oregon, I believe, who was losing his license because he was giving testosterone to prostate cancer patients. And the medical boy took offense and, you know, he asked me for help and I'm building you know, I can't, you know, I have no power over what they're doing to you. Men can point you to the literature that what you're doing makes sense. You know, I pointed him to like the Morgan Taylor's studies where he gave as the first treatment testosterone to prostate cancer patients and they had, initially a decrease in PE PSA. More recently, there have been articles where doctors took patients with lower grade Gleason Scores who wanted to win. Radical prostatectomies, and half of them got testosterone, half didn't. And they expected going in and they were going to prove how bad testosterone is for prostate cancer patient and they found the people who got testosterone had a much longer delay to biochemical failure and some, you know, never got it it you know, it was no question that testosterone was very beneficial to prostate cancer patients after their prostate was. That's not what they expected when they went into the study.

Russ Hollyer 50:40

“How Hormone Receptors Affect Prostate Cancer” (Ed Friedman) [#59]

Even if you take the stance that it's the exact identical outcome (and I don't believe that's true), would you rather have testosterone or not?

Ed Friedman 50:56
Quality of life is there's no question about it. Quality of Life was one of the things that Dr. Liebowitz was a big proponent of; he never recommended surgery. And he prided himself on having his patients live for years with an intact prostate.



On the left, this is an interesting paper, it's not been published, it was a Bio Archive website where it's been small in advance of publication. And if you look at the bottom left, figure three B. These are human zener graphs of bone metastases. So this is the fastest growing prostate cancer you're going to see. And, you know, if you look at the bottom one, Enzalutamide cut the growth rate and half death. But if you look real carefully, at the very, very bottom, there's a purple dashed line, representing the combination of Enzalutamide and DHT. And that combination, they only did this for like, one week. It wasn't that long an experiment, I wish they had gone longer, but it was virtually no growth at all. With that combination. In the paper, they had absolutely no explanation for this result, and even tried to hazard a guess that if Enzalutamide is blocking the intracellular receptor and not the membrane receptor, then this is what I would see. And if they went out 30 days instead of seven, I'd expect to see an actual decrease in the amount of prostate cancer that showed up. Which brings up the point of how do we get something like binding to the intracellular receptor and not to the membrane? Well, they've shown that the drug flutamide definitely does not block the membrane receptor, but it does block the intracellular receptor. So combination of testosterone with flutamide should have a very beneficial effect, although you probably want a five AR inhibitor, because the testosterone will be converted to DHT, which would compete with the flutamide because

flutamide isn't that strong a blocker of the interest of the NGO receptor. Now this suggests, because no way prove that and Saluda might block the intracellular but not the membrane. I wish someone would do a test on all this like five drugs now, at least that block the interesting ng receptor that are being prescribed. And I wish someone would check to see which ones do not block the membrane receptor because that gives you a very powerful combination. So in terms of what to do in terms of a theoretical treatment. If I'm right, and this is what's happening, if you block the membrane receptor but not the membrane, then the way the cancer that survives is going to adapt is it's going to decrease the amount of membrane receptor. Because of the membrane receptors, what you're using to kill it, all it has to do is decrease the amount of membrane receptor now, it's not going to work. Now what happens when you decrease the amount of membrane receptor? Well, now you can, it should be extremely sensitive to that, because the amplification of the intracellular receptor is going to make it huge ratio of binding to the intracellular receptive versus membrane. And now that's going to be effective and the cancer won't be able to grow. And the only way you can grow in that circumstance is going to be to increase the membrane receptor. And so I view a treatment protocol, we know what sort of mutation you're selecting for, that's going to lead to cancer, survive or thrive in the condition you give it, and you steer it that way. And then you yank off the frog and go the other direction. And I should point out, even though you know, Denmead is doing very low testosterone in order to get the amplification, there was a paper published in the journal the prostate that showed if you use finasteride alone, in 30 days, you've got the amplified intracellular receptor. In fact, I wrote a letter to the editor who got published the the journal authors were going this is horrible, we've amplified the interest of the end of receptor and everyone knows that's a bad receptor. And I wrote an article going Oh, it's wonderful. Look at the limb cat 104 Or two, if you've got an amplified just say intercepting, you can just hit it with high testosterone. And suddenly, you're getting the benefits. When I grow blender, the editor back didn't exist yet. But right now, basically, you can get the same benefits from that without the lower quality of life. In other words, having finasteride is not as debilitating to the body as having castrate levels of testosterone. So sorry, in answer to your question, there's some things like MyFord prestone, plus progesterone, that tell you that there's no way the cells can develop anything that gets a selective advantage from that combination. But by alternating, hitting the membrane edge of the receptor to use more binding to the membrane receptor to kill this cell non binding to the intracellular receptor to kill it, you can alternate between the two. And you know that most of the cancer that survives, is going to move in a direction that's going to be susceptible to other treatments. But you know, in an ideal world, if a pistol, progesterone estriol and flipping back and forth with the bat, but with the IRS, right now, the only thing we know is testosterone plus flutamide. But hopefully, at some point, someone finds one of the more effective drugs, mod insurance. They're awesome, too, and do not affect the membrane receptor. So that's basically what I've worked on, and my thoughts on cancer. And if you have any questions, feel free to ask.

Brad Power 59:30
Let's suppose this was a graduate course you just gave, and there was a lot of stuff I didn't understand because I don't understand molecular biology or molecular pathways. Are there any

papers that you've written or any interviews you've done that are at an introductory level that might be accessible?

Ed Friedman 59:51
You can go to my website. I've got a lot of stuff there. It's math that you Chicago dot EDU till the end, and you can click on the prostate cancer, I also have done, I have links to studies showing that testosterone actually prevents heart attack strokes as well as preventing prostate cancer. And yeah, thank you, Brian, that is the correct website. I also have a section on myths of different people, which is alright, so my second I think it's called ru 486. And combining that with progesterone, you can see what people have done. But yeah, my website, my website is in plain English, and I link you to the actual articles backing up what I say when I you know. So for example, men with a serum testosterone level below 350. If they're given testosterone replacement therapy, they're more than threefold less likely to develop prostate cancer. And I point out that if you consider all the men in that study, probably the same percentage of them had cold tumors, which is too small to be detected. The fact that you see a three fold reduction, where it's not just a delay before they see prostate cancer never comes out. That indicates that the testosterone is actually killing the cold tumors for some of these men. In other words, once it starts out, at the very, very beginning of prostate cancer, it's very susceptible to testosterone. It's just later on that, you know, basically the there'll be mutations that the cancer makes to make it able to grow better and better and testosterone because men have testosterone, but initially, it's it's barely squeaking by and you know, you're not going to see prostate cancer, people with teenage levels of testosterone, it has to level has to drop in order through the cancer football. Also, my book, if you haven't read that my co author put everything into pretty plain English. For people that want the hard science, the footnotes, most of the time, take you to an area where I'm talking about the actual hard science behind everything.

I mean, I wish there were doctors doing more of this, I wish there were researchers doing the sort of research that should be done. But the problem is having this knowledge while sort of nice intellectually, pragmatically, it's not going to help your treatment unless you can find a doctor that you can convince that this is the right way to go. And that's the long haul.

Brian McCloskey 1:03:49
What if, you know, we've had one patient who's built an organoid. I'm just thinking about testing some of these theories, using functional testing methods, whether it's organoids or other means, do you know if that has been done, because that can help to build a case. And within healthcare that is so resistant to this type of orthogonal thinking?

Ed Friedman 1:04:22
I don't know that it's been done, like I said, as far as I know, I'm the only one making these conclusions with regards to the receptors. No one's no one's really actively doing the research. And a lot of the time it's a question of money. To do it right, to bring to bring things to a FDA approval of whatever method you're doing, costs a lot of money, and especially, you know, 50 Talking about how great estriol has, well, you know, estriol, dirt cheap, you know, no one's going to get rich no matter how great it works. And so no one's gonna even try to do this study. I

think for us, it said he's at one point, he's going to try high testosterone with flutamide. And I'd be very interested to see what that combo does.

Russ Hollyer 1:05:27
And I was wondering about constant high testosterone? What do you think about cycling finasteride on and off? It has a short half life.

Ed Friedman 1:05:38
That was one of my ideas that in looking at that they showed that regular testosterone level with finasteride you get amplified intracellular receptor, okay. That's just a known fact. And they showed it not just for cancer cells, they showed it for normal prostate cells, it's like it's one of the few situations where the amount of a hormone receptor gets changed based on its environment as opposed to selecting for a genetic change. It adapts and actually makes more which also happens when you take away testosterone. But I wish someone would do the experiment of let's take high testosterone plus finasteride and see if that also amplifies interest. So receptive because if it does, you can go with like you just said high testosterone all the time, on and off with finasteride or in the worst case, normal testosterone with finasteride, alternating that with the high testosterone, no finasteride because you don't want finasteride when you're trying to hit the intracellular am Andrew reset receptor active it's been amplified, that that's been shown to be totally ineffectual.

Russ Hollyer 1:07:43
They did the studies on finasteride alone.

Ed Friedman 1:07:49
, yeah. On my web page and look at the links with okay. Okay, you'll see that this letter to the editor about you know, their finasteride paper, it's pretty new. I forgot the title, but it's pretty obvious. You'll see what my letter to the editor is. You click on that you'll see with the reference the prostate unfortunately, the state's not open source. So you'd have to get it from a library or something. Or you can read the summary you know, the abstract but it was pretty clear that finasteride only amplifies you know, they they said for 30 280 days. So I mean, they they kept waiting to see if it would stop amplifying and it didn't. But is it just an open question whether it's going to work when you got high testosterone? It'd be great if it did, it'd be a wonderful quality of life to just go between those two. Yeah.

Russ Hollyer 1:08:53
What would you suggest the timing could be? Maybe three months on three months off?

Ed Friedman 1:09:07
I go by the guesses. I mean, if you know if the if the PSA starts going up too much, you switch to the other

Russ Hollyer 1:09:22
Okay. Based on your PSA. Okay. I like that.

Ed Friedman 1:09:27
Right? Because, right, because I can't tell you the months because we don't know. Okay, well, no, I mean, no one's done it but you don't want to stick with something when the PSA starts going up and then you switch.

—

“How Hormone Receptors Affect Prostate Cancer” (Ed Friedman) [#59]

Evidence for a More Complex Model of the Role of Hormones in Prostate Cancer

Dr. Abraham Morgentaler used testosterone to treat men with untreated prostate cancer. 13 men with prostate cancer and low testosterone (238) were treated with testosterone (664). After a median of 2.5 years, the average PSA drop was over 33%. None of the men experienced a rapid PSA increase. This study demonstrated the falsehood (still being taught to medical students) that giving testosterone to men with prostate cancer was like adding gasoline to a fire.

Even more impressive are the results of a 12 year study in which 412 hypogonadal men received testosterone, with a control group of 380 hypogonadal men did not. Prostate cancer was detected in only 2.7% of the treated men, as opposed to 8.9% of the untreated men. All of the cancers in the treated men were detected within the first 18 months and all but one of those men had a Gleason score of 6 or less. None of the untreated men had a Gleason score under 7. There can be no question that both groups of men should have had approximately the same percentage of occult tumors at the start of the study. This means that logically, the increased level of testosterone either was killing prostate cancer cells or was slowing down their growth rate to such an extent as to prevent detection.

A recent retrospective study of 189,461 non-diabetic men aged 40-60 showed that testosterone therapy reduced the risk of prostate cancer. They concluded: "increased use of testosterone therapy is inversely associated with prostate cancer".

A study showed that for men who received a prostatectomy, testosterone reduced the risk of recurrence.

Researchers at Johns Hopkins have had some success in using high levels of testosterone to treat men with Castrate Resistant Prostate Cancer. While this article only presented results from 4 men, 2 of which had a greater than 50% decrease in their PSA. A newer study with more men still shows a 50% positive response.

Researchers have shown that low-risk prostate cancer patients who have undergone robotic radical prostatectomy lower their risk of recurrence if given testosterone.

Researchers have shown that supraphysiological levels of testosterone induce cellular senescence in human prostate cancer cells through the Src-Akt pathway. Also, researchers using human prostate cancer (PCa) xenografts in nude mice concluded that " Higher levels of serum T inhibited PCa cell growth."

In 2008 researcher Gail Risbridger, PhD, a professor at Monash University and Sir Peter MacCallum Cancer Centre in Melbourne, Australia, proved that estrogen receptor alpha is the cause of prostate cancer. (See: Prostatic hormonal carcinogenesis is mediated by in situ estrogen production and estrogen receptor alpha signaling. https://pubmed.ncbi.nlm.nih.gov/18055862/). When she knocked out the estrogen receptor alpha gene in mice, she was unable to have them develop prostate cancer, no matter how much

testosterone and no matter how much estradiol they were given. On the other hand, when she gave mice enough testosterone so that they didn't kill the prostate cells due to androgen deprivation, and then started raising the level of estradiol, she got a 100% rate of developing prostate cancer.

“How Hormone Receptors Affect Prostate Cancer” (Ed Friedman) [#59]

Subsequent Email Discussion on Hormones and Bipolar Androgen Therapy

I realize that I never really explained why I advocate the protocol of Dr. Leibowitz instead of BAT. I am putting a link to a file of patient records who used his treatment. If you look at the starting status of the first man, I think that you would agree that nobody but Dr. Leibowitz would ever had been able to save this man's life, especially with T levels well over 1000 and PSA well below 4. I should point out that Dr. Leibowitz always used 5AR inhibitors when administering T. His anti-angiogenic cocktail was daily injections of Leukine plus Thalomid every other day.

See: https://web.archive.org/web/20210309193444/http://compassionateoncology.org/pdfs/TRTcase_reports-05-09.pdf

“How Hormone Receptors Affect Prostate Cancer” (Ed Friedman) [#59]

Subsequent email Discussion on hormones and breast cancer

Unlike prostate cancer, in which the number of intracellular androgen receptors (iAR) can be modified depending on the conditions that the cells are exposed to, e.g., a low androgen environment leads to an increased number of iAR, I'm not aware of any evidence that exposing breast cancer to a low estradiol environment will affect its number of estrogen receptors.

However, I don't believe that any of this is necessary. Dr. Rebecca Glaser has had remarkable success in treating breast cancer using supraphysiological levels of testosterone coupled with an aromatase inhibitor. Her website is https://hormonebalance.org/ and I consider her the best (and most knowledgeable) breast cancer expert in the world. Dr. Glaser is located in Dayton, Ohio, and typically sees her patients 4 times a year.

One of the reasons high T is so effective in BCa is that both iAR and mAR downregulate bcl-2. In PCa, iAR downregulates bcl-2, but mAR upregulates bcl-2.