

Evolution 2.0 Podcast

How to Halt Cancer at Stage Negative 1 with Dr. Azra Raza

Welcome to the Evolution 2.0 podcast, where we explore the intersection of art, technology, business, biology, and spirituality. Here you'll discover new trends in evolution that are changing the way we think about everything. This is your host, Perry Marshall, author of *Evolution 2.0, 80/20 Sales and Marketing*, and guides to Ethernet, Google, and Facebook. I'm founder of the Evolution 2.0 prize, a quest for the missing link between earth science, the information age, and life itself. Let's join the conversation now.

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Perry: Hello, I'm here with Azra Raza, who is an oncologist at Columbia University in New York. I interviewed Azra a year ago and it was a very surprising interview. I didn't know her, she didn't know me. I read her book *The First Cell* and it was a very – well, it's hard to describe this book if you haven't already read it, but it is "Oncologist cuts a vein and bleeds about her frustration with a calcified system that is essentially stuck in the 1970s."

This is a person who cares very deeply about her patients. I think if you really know doctors and surgeons and people like that, it's very easy for people in the medical field to emotionally wall themselves off and isolate and just go into their head and be professional and not really deal with the emotions and the trauma and the heartache and the suffering.

It's perfectly understandable that somebody who has to go to work every day and deal with dying people would do that. It's not like any of us can't understand that that happens, but Azra has not done that. She has chosen to keep her heart open, which is a much more painful road. She becomes friends with her dying patients and then, as a result of her husband dying of cancer and her daughter's best friend dying of cancer, it suddenly pushed her to decide, "I have to talk about this."

We're not going to cover the old ground that we covered last time. If you want to hear all of that story, you should go back and listen. It's at evo2.org/azra. There's a transcript so you can read it, you can listen to it, you can watch it on video, and I encourage you to do that. It's probably the best interview I've ever done, I think. Again, it just kind of caught me by surprise. It just came out the way that it came out.

Another thing Azra talks about is that over the last 30 years she's collected 60,000 tissue samples of patients who – am I correct? – they had to have marrow extracted from their bones in order to get these tissue samples. Not all of them had to have this done, but you got permission and they did it. It was painful, so everybody has skin in the game. And not only that, but you paid for the freezers to put all this stuff in, with your own money to make this happen.

Another characteristic I found of revolutionary scientists is a very high propensity to spend their own money or to take severe reputational risks in order to further their research, because even though nobody else believes in it, they believe in it. So Azra is a 'skin the game' scientist, too.

So that's the set-up, and about a month ago Azra said, "Perry, can we have another interview?" and I'm like, "Sure, in a hot second. What do you want to talk about?" She said, "I don't want to talk about what's wrong with cancer today. I want to talk about what's right. I want to talk about what we can do that's new."

Just before the interview went live we were talking about – “If we really have a good model, if we really have a good theory, we don’t need a platoon of PhDs from Caltech in order to understand it. We ought to be able to explain it to a high-school dropout.” I was like, “Okay!”

So I have an idea, but I don’t really know what she’s got today. She’s got a PowerPoint and she’s got some videos. Azra, you have the floor.

Azra: Wow, what an introduction. Perry, you never let me down. You always outdo yourself and you have managed to intimidate me with those wonderful prominently-displayed 80/20 and Evolution 2.0 books – my favorite books. I’m a big admirer, as you know. You are one of the most unusual people I’ve met, really. We haven’t met physically yet, but I feel like we’re old friends.

I think one of the most important things you said just now is about our connection to the human angle in all of the conversations we have. I have tried to look at everything regarding cancer through the prism of a patient’s anguish. My working principle comes from Emily Dickinson. “Surgeons must be very careful when they take the knife, for underneath their fine incisions stirs the culprit – Life!” That’s what we’re talking about.

I asked permission from Perry to share a few slides with you to show you the kind of different models that I would like to present today regarding cancer.

Until now, causes of cancer are some hereditary susceptibilities like BRCA1 or 2 genes causing women to be susceptible to breast or ovarian or uterine cancer, or some pathogens. Hepatitis-B virus can cause liver cancer. Of course, exposure, everyone knows, can cause cancer. But with all of this, it only accounts for like 20% of all cancers, so where are the other 80% coming from?

The current working theory is that, “Oh, it’s these spontaneous mutations.” What are spontaneous mutations? Every time one of our bodies’ trillions of cells divides it has to double its DNA, and the DNA enzyme can make copying errors, which is a mutation. These mutations start to build up as we age because more and more cells are dividing.

The current idea is that these are spontaneous random mutations that build up, and eventually cancer is a disease of old age. That’s where they have become numerous enough, or by chance one of the mutations happens. DNA copying error means that the double strand of the DNA has to open up and a preliminary machinery of proteins will walk down and add the complementary bases, and it can make a mistake. One mistake is all it needs, and the mistake is called a mutation.

I’m basically challenging this model, first of all. It is not a random mutation.

Perry: No, it is not!

Azra: I’m saying it’s a deliberate response of normal cells to what? To stress. What kind of stress? What I just told you – infections, inflammation, autoimmune problems, toxins.

In the 1970s model it’s a very reductionist approach, that a cell dividing makes a copying error and there’s the DNA mutation now, right here. Then this is accompanied by giving a growth advantage to this clone of cells. They resist, they keep dividing, they lack growth control, they make new blood vessels, invade and go to other organs. These are the six hallmarks of cancer that have been proposed

by Weinberg and Hahn. These have now been increased to 12. Then Henry Henk takes this apart in his beautiful book, showing they can keep increasing. They're up to 18 now.

The whole idea of treatment, Perry, so far has been the reductionist strategy to simply retrace our steps back to that first mutation, and then use a magic bullet to target that mutation. This reductionist strategy turned out to be an unmitigated disaster because it worked in a couple of cancers early on – a chronic myeloid leukemia, acute promyelocytic leukemia, but those are exceptional things. Cancer turns out to have thousands of mutations.

I just want to show you in the form of a Darwinian tree. A normal cell divides into 2, gets a mutation, gets a growth advantage, and every time it divides it gets more mutations. It's capable of picking up more and more, so by the time we are diagnosed with cancer we're somewhere up here with thousands of mutations in the cells, and we are trying to target it with one magic bullet that's going to attack one of these mutations.

Wouldn't it be better to go here? That's the whole concept of early detection.

Another thing I wanted to do, Perry, is something I appreciated that Denis Noble said, that artificial intelligence can never compete with cellular intelligence, because in the cell there are a trillion molecules that are floating in a liquid medium. I want to show you just 10 seconds of this video. [video plays]

Basically the idea is that this is all happening in one cell. There are a trillion molecules floating and exchanging information. We're trying to replicate that on a solid silicone chip.

Perry: And not only that, a chip with one input and one output!

Azra: Yes! I would love for you to comment on this and tell me where to go.

Like you said, I started by studying acute leukemia. I went to study pre-leukemia because I thought things would be simpler and I could intercept these patients from developing leukemia. At least the one good thing it did for me is I started to collect tissue on my patients and now I have over 60,000 samples. They are longitudinally obtained as patients go from pre-leukemia to leukemia, or die of their MDS.

The tissue repository is supported, of all things, by patients. They want to give me money and I said, "No. Contribute to the tissue repository," and they do generously. It costs \$1 million just to maintain the repository.

Perry: What? I didn't know that. \$1 million per what?

Azra: Per year, because look, I have to pay for the space I'm occupying for all these freezers, maintenance of freezers, and constant addition of new samples. From the moment a bone marrow biopsy tray is opened up, Perry, I pay for everything because they say, "Oh, you're going to take extra tissue for your research, then pay for it." I have to pay for every single bone marrow I do, the runners who carry the sample to the lab, people who separate cells – it's very expensive. That's why no one does it.

I can do it because I held my first fundraiser when I moved to New York in the home of Hugh Jackman. He is so supportive of our work. I mean there are people who step up to help in these things. I'm

basically supporting the entire tissue repository for all these years based on philanthropy and money I've raised from all over the place. No government institution – nobody supports this kind of thing.

Perry: Azra, everybody's got this stereotype of, "Oh, you're a rich doctor from New York City and you probably have a house in the Hamptons or something," and Azra is making friends with Hugh Jackman and doing fundraisers in New York City so she can spend \$1 million a year to freeze tissue samples.

I was sort of wondering vaguely, and I sort of knew that you had this thing and I thought, "I don't know, it probably costs a few thousand bucks a month for all those freezers. Where do you put them? Do they have an uninterruptible power supply with generators and stuff?"

But \$1 a million a year, and you didn't tell me this? Oh my word!

Azra: Yeah, it's a lot of money. That's why nobody does it. I'm the only single investigator in the world who has collected all these tissues, and I know, Perry, that no one appreciates it now. Only after I'm dead and gone will somebody realize, "Oh yeah, she was the one who did this. Nobody was doing it," and I've been doing it since 1984. It's not just today.

The kind of longitudinal retrospective analysis we can do is so unique. Not a single cell is contributed by another oncologist. Like you said, I do every bone marrow myself with my own hands, and draw the blood myself, and do the buccal smear myself for germline control.

Perry: You need to now explain why this is useful and what we can do with this. I don't want to sidetrack you too much, but you've got to explain the medical research significance of this.

Azra: The most important thing, Perry, is how do you study cancer? You can try to make models of cancer, try to grow cancer cells in the lab to study them, but they die. So then people started studying cancers in animals, but that has been an unmitigated disaster because those kinds of models have nothing to do with humans.

That's why 95% of the clinical trials that we bring, the drugs we bring from such models to the patient's bedside, 95% fail outright, and the 5% that succeed should have failed because they're only prolonging life by a couple of months for 20-30% of people by and large. Now, there are a few exceptions. That accounts for a few thousand patients that are helped by those things out of 1.8 million newly-diagnosed cancers every year.

I don't want people to go home thinking negatively that I don't think any progress has occurred. No, tremendous progress has occurred in understanding the biology of cancer, but very little in terms of improving treatment. I think the only way to improve it will be by studying human tissues.

You know what Norbert Wiener said in 1940? "The best model for a cat is another cat, preferably the same one." We know, Perry, that if you eat ice cream and I eat ice cream, you may put on 10 pounds and I put on nothing because my microbiome is different than yours. It's metabolizing things differently. It metabolizes drugs differently. It responds to cancer differently.

Given that we are such individuals really in our responses to things, we have to think the same way, "preferably the same cat" kind of approach, and that we can do by examining this spectrum of these patients as they progress in the natural history of their disease. We trace our way back to the very first

cell and then ask the question, “Why did this person who was perfectly healthy even get pre-leukemia? What is unique?”

My approach that I’m going to show you now will make it possible to do it just with 10cc of blood. Sitting at home you should be able to detect whether you have early steps of cancer or not.

The problem right now is that cancer is a silent killer. A 1-cm tumor has 3 billion cells, and a 0.1-mm tumor already has 300,000 cells, so how am I planning to find the earliest cell? How do you find the first cell?

Perry: This is a very big deal because if you can find that one needle in a haystack as soon as it happens, it would be very, very easy to fix it, right?

Azra: Yes, exactly. That is the point. The problem with our screening methods like mammograms, PSA, Pap smears, and colonoscopies is that they only detect, at best, Stage 1 or 2. I’m talking about years before Stage 1 and 2.

Perry: So Stage .1 or Stage .01? Is that what you mean?

Azra: I’m saying the first cell.

Perry: So Stage .001 cancer.

Azra: No, even pre-cancer. I’m saying the earliest changes that would lead to cancer and formation of the first cell, and I’m saying it’s a natural evolution of what we have been doing, is to go to the next step and go really early, which means even pre-cancer. In fact, monitor wellness to detect the disease perturbed changes, and diagnose illness before it becomes clinically apparent.

One way we can do it, Perry, is very interesting. To catch the first cell you simply have to look into blood. Use blood as a window into looking at changes in disease. One of the things everyone must realize is that in fact the earliest formation of cells for cancer start being shed into the blood, and they can be isolated by size because they’re larger than blood cells, which are the smallest cells in the body. You can use a ‘coffee filter’ technology. They get trapped on it, and smaller cells go through.

My very wonderful colleague, Patrizia Paterlini at the Pasteur Institute developed this machine called isolation by size. That’s what it looks like. The idea is that some very large studies have been done looking at people at high risk of cancer – for example, heavy smokers who already have COPD. You do a liquid biopsy, which simply means 10cc of blood, and pass it through this Iset machine which isolates by size. Imagine, Perry, you can detect one cancer cell from 50 billion normal cells.

Perry: Wow!

Azra: And this study was published in 2014 with lots of patients. I want to show you just one patient from there. He’s a 54-year-old male, heavy smoker, COPD. They do a liquid biopsy on him in 2009 and what do they find? A giant cell. In fact, 47 circulating giant cells like this. Compare this giant cell to the size of the normal blood cell. Now you know what I’m talking about. Clearly he felt okay.

The oncologists saw this and they said, “Sure, this is cancer. Where’s the lung cancer?” All kinds of things are being done to find lung cancer like CT scans, but nothing is found for four years. Then a CT

scan detected a tiny tumor. This is removed and the patient who had invasive cancer but Stage 1A is cured for nine years now, Perry.

What it showed was that the first cell could be detected four years before the actual cancer appeared on the CT scan. See what I'm talking about?

Perry: Go back to that giant cell. I've got a question. This cell, you said it's not quite actually cancerous yet?

Azra: No, I didn't say that. I'm going to show you. Hang on.

The first thing to notice is that these cells can be detected before the tumor arises, four years before. They are giant in size and they have many copies of chromosomes because they have multiple nuclei. Giant cells were never detected in a normal sample, and they ran like hundreds of normal controls, so if there is a giant cell in the blood, there's cancer somewhere.

Now, what are these giant cells? They were described first in 1858 with beautiful pictures, but they're so rare, Perry. They lie on the side of thousands and thousands of cells. There will be one giant cell in the corner. People just kept dismissing it by saying, "Oh, that's a dying cell."

Then many people started noticing that after we give chemo and radiation to solid tumors like lung cancer and pancreatic cancer, then they relapse after a while. When that relapse is occurring you see a lot of giant cells.

I want to show you now a video, but first let me explain the video. Ken Pienta, the brilliant head of the urologic oncology program and prostate cancer program at Hopkins – and you know him very well, of course, Perry, but just wanted to say it for the audience – he developed his amazing technology. You inject prostate cancer cells here and they go and land into these little diamonds, one cell at a time, and start growing there. Then you inject a drug from the other end, but the drug is injected at a gradient of concentration that goes from high to low, which means the concentration of drug is highest in this area, for example.

This is Ken's movie. I just want to share it. Of course it's all available on YouTube. You can watch it. I want to now focus on this tiny area at the right lower bottom and take you to the next slide and show you what happens.

The highest concentration of drug was around here. These prostate cancer cells start dying, and now you see that the area becomes pretty much black compared to this diamond, for example. You can see that. You suddenly see the appearance of these rapidly moving giant cells that start coming, and very soon, Perry, what you see is something never seen before, that these giant cells start birthing smaller cells.

All these smaller cells start coming from the giant cells, and before you know it this whole area now start getting filled up more and more with the smaller cells, and the giant cells go away. Now this whole tumor has come right back. You see what I'm saying?

Perry: Actually I probably didn't completely understand that. Maybe the last 30 seconds I'm not sure I was completely following about the giant cells coming back.

Azra: I'm going to show you another picture about explaining it. Basically I'm saying that these polypoidal giant cancer cells – polypoid simply means many nuclei or many copies of the chromosome. Giant cancer cell formation happens because when a normal cell divides into two, it doubles its DNA and chromosomes and then the nucleus divides into two and then the cell divides into two.

If there is a cell, Perry, that is a normal cell that is being stressed – what's stress? Infection, inflammation, some kind of toxins in the environment, which are going to kill the cells, so a normal cell will receive a signal – fight or flight. Either you develop a strategy to survive this swamp or this poison, or you're going to die.

The way giant cells are formed, giant cell formation is a normal response to stress. In two ways they're formed. First, and this will explain your question, the first way is that the cell will keep doubling its DNA but the cell won't divide. The nucleus will divide and the cell becomes larger and larger and now has many nuclei and becomes a giant cell, but it doesn't divide. Why? Because it's kind of hibernating.

The most vulnerable part of the cell is when it's undergoing mitosis, when it's actually dividing into two. That's when they get killed. They're most vulnerable. So these cells just divide the DNA but they don't undergo mitosis, which means the cell doesn't divide.

Another way is smaller cells simply fuse together. Again from Ken Pienta, look at this movie. Concentrate on these two cells. These were prostate cancer cells that are given chemotherapy, and look what happens. They're under stress. You see how they've merged? Fusion. So that's another way. Basically, Ken has shown these huge polypoidal, which means many nuclei, large giant cells – compare them to the blood cell size. These are from metastatic prostate cancer courtesy of Ken.

So how come no one talks about these giant cells? Actually there are hundreds of papers. Jinsong Liu, Henry Henk, Ken Pienta, all these people have been talking for years about giant cells. It has been reported they appear after chemotherapy. My hypothesis is no, they don't appear only after chemotherapy. Giant cells are the first cells.

So what about leukemia? I'll show you a few pictures from my lab and then I'll shut up. We CRISPRd in a mutation, which is very common. 90% of patients have this mutation if they have a certain kind of MDS. We introduced this mutation through CRISPR in K562 cells, which are just leukemia cells growing in a Petri dish, already abnormal anyway.

But when we introduced the mutation it caused stress. Then we treated the cells with chemotherapy and it caused more stress, and the result both times was giant cell formation. These are the wild type cells growing happily. When we CRISPRd the mutation, see how many giant cells appeared. Again, they're happily growing. When we treated with chemotherapy, see how many giant cells appeared.

In fact, these giant cells are wild type, meaning normally growing, and then this is the mutated, K700E, giant cell with multiple nuclei, lots of chromosomes. Henry Henk calls it genome chaos, but to me chaos sort of sounds like the cell is confused. I'm saying no, this is a very well-conserved normal response. It's genome reorganization. Cells are finding strategies to survive the stress.

I'll just show you this beautiful picture from my lab. We fixated our camera onto one giant cell and followed it for days, and nothing happened until three days later. We saw it started birthing these tiny

cells. Jinsong Liu at MD Anderson calls it somatic cell pregnancy. Basically here you see many giant cells birthing these – they literally are getting pinched out from these giant cells.

Again from my lab. Look at one giant cell, Perry, and how many cells it's given birth to. Then after a few days, all we see are these small cells. The problem is this is where we diagnose cancer and we missed all the first cell business.

Perry: What are these small ones?

Azra: That's the real cancer. These are the ones that cause relapse of the disease. If you were looking at prostate cancer, these would be the prostate cancer cells, and they are the ones which are the small cells. They're not giant.

Perry: So it's like the giant cell is the queen bee and the little cells are the worker bees, and now it's swarming all over the place with worker bees and it's basically all over.

Azra: Yeah. And remember that the giant cell has many, many nuclei, so it can give copies of its DNA to be two mDNA now. Most of these kinds of cancers have just two mDNA.

So what is the new model? I'm saying that the first response to major stress is wholesale genome-wide aneuploidy, not genome chaos. I call it genome reorganization, but it's the same thing. It's the same thing that was proposed 100 years ago by Boveri and has been championed – and by the way, Perry, I covered this extensively in my book where I talk about the aneuploidy model rather than this reductionist one tiny mutation which is a random DNA copying error. No, I'm saying absolutely not. That model we have been working on for 50 years and it hasn't helped. It's time to change the model.

Basically it's a conserved response to stress, and recurrent genetic mutations that we are obsessing over all the time – sequencing, sequencing, sequencing – is a late step. Cancer is not due to DNA random errors. It's the result of a conserved response, and the gene-centric model has not proven to be correct.

A new model is proposed that first there's some kind of stress. We don't even look for that in patients with cancer. We're just so concentrated on the cell, but actually the cell is responding to some stress in the tissue around it. We need to study that.

Then cells are either fused together – I showed you the video from Ken – to ride out the stress, or they keep doubling DNA but do not divide. I showed you that. Giant cells are produced. If the stress goes away, giant cells go away. But if the stress persists, they wait silently until one of them – 1 in a billion will start producing smaller cells. That's why cancer is so rare, even though giant cell formation is not rare because tissues are being stressed all the time. Smaller cells are when we diagnose.

This is all shown in solid tumors by our colleagues. No one has looked at liquid tumors. What are liquid tumors? Leukemia, pre-leukemia, what I study.

I have had this machine, Perry, for 3-4 years and I've studied tons of patients, and I started finding these giant cells and they look exactly like solid tumors when you saw the first giant cell. I'm finding these giant cells all over the place now because I'm looking for them. You see the difference? You find what you look for.

This is the Kristen Walen paper, "Cell Cycle Stress in Normal Human Cells: A Route to First Cells." We can talk about this in a minute. I'm coming to my end. I published this paper about giant tetraploid cells back

in 1985, along with my late husband, Harvey Preisler, so no one can blame me for being a newcomer to the scene. I'm an old hat, I admit.

Now, it's important to get other people on your side, because otherwise lone voices die, so I built consensus by organizing The Oncology Think Tank and have 30 leaders from academia and industry. We had lots of meetings and we published an opinion paper, which was published in Scientific American in January, a couple months ago, and there are all these authors with me.

What is the idea? The idea is very simple. We need to screen for the first cell. Early detection is the name of the game. Identify a group of individuals at high risk of developing cancer. Who are they? Now, I don't want anyone to get scared, but 1 in 5 new cancers appear in a cancer survivor. Instead of getting scared, I think you should help find the first cell so that we can prevent it from happening. Do the math yourself, Perry. If there's 1.8 million new cases which will be diagnosed in America this year, 350,000 will appear in a cancer survivor.

All these eight institutions are the major institutions in the country. MD Anderson alone sees 80,000 cancer survivors a year. No one is looking at their liquid biopsy. Blood is all you need to see if we can find the first cell. Dana Farber, University of Chicago – these are the top institutions. We are proposing to have a First Cell Center for cancer survivors. Simply start a tissue bank.

All of us are seeing cancer survivors. How non-invasive can you get? Just 20cc of blood, saliva, urine, and feces every six months. 40,000 samples will be collected in three years. 5,000 to 8,000 cancer cases will appear. This is not recurrent cancer. It's not like someone had lung cancer and now it has recurred after three years. This is a new second cancer. That's what I'm seeing.

The best example is my own husband, Harvey. He had his first cancer at 34, survived it, and gets the second one at 57, which kills him. All we're saying is now you'll have 5,000 to 8,000 patients who have developed the second cancer, but we have all their samples. We can go pull them out, look at those captured giant cells, and basically we have to trap the giant cells and do the MultiOmics on the giant cells, the transcriptomics, metabolomics, proteomics, genomics – not on those tiny little cells the way we are doing, but on the giant cells.

And I'm saying that eventually the stress that is causing the giant cells to form – stress will change the metabolites and [inaudible 35:50] That's what we need to look at. What is the stress the organ is facing that it's making giant cells?

That's where I wanted to stop, and at the end I hope I have about two minutes to show this video about why I'm so invested in this. I can show it now or later. You decide.

Perry: Go ahead.

Azra: In my first broadcast with Perry we talked extensively about this young man, Andrew, who at 22 got diagnosed with a brain tumor which was 9 cm. It couldn't be removed completely so it means we knew from Day 1 that this poor boy's chances of surviving are 0.00. There's nothing we can do to fight this malevolent malicious enemy.

For me it was particularly important because Andrew was the best friend of my daughter since they started 8th grade. Andrew was not Scheherazade's boyfriend. Andrew was gay, and at 22 he gets

diagnosed with this horrendous brain cancer, and then he died the most tormented, the most painful death possible at 23 years of age.

His sister, who's two years older than him, 25 years old, she put together this movie. I want everyone to see this. You know why? Because four years later, two weeks ago, his mother Elena, who's standing here with Andrew, her only son – Elena called me two weeks ago, Perry, and said, "Azra, you won't believe it but now my best friend has just been diagnosed with glioblastoma multiforme, the same tumor Andrew had, and it is extensive."

She said, "Azra, have you made any progress in the last four years? Can we offer something different to my friend?" How ashamed I felt. We have made zero progress since this poor boy died. Why? How many Andrews have to die? How many people have to die?

It's just about two minutes of this little video to remind ourselves that this is why we're doing what we're doing. This is why there's an urgency. This is why I ask all of you – and I'm so grateful to Perry for letting me speak.

[video plays]

Perry: Wow...

So what do you think about your First Cell Center and its ability to help a person like Andrew? Does this apply to Andrew's cancer?

Azra: Of course, every cancer. And first let me say, Perry, how much I appreciate the few moments of silence you gave to the memory of Andrew. It means the world to me. Secondly, yes, I'm asking for so little. Eight credible institutions have come together to say, "We will give you all the samples of our cancer survivors, Azra. Let's do it. Let's make the Center."

Even if I'm proved wrong for everything I said about giant cells in my new model, let's say it's all proved wrong, we still have the samples. We'll find something new. And what am I asking for? A couple of million dollars a year for three years, and no one wants to give that. I don't understand, Perry. In this rich and affluent country, why am I constantly out there with my begging bowl? Why, when 95% of resources are being wasted on mouse models and all kinds of mindless research?

Perry: I had a therapist who told me, "An addiction is anything you lie to yourself about."

Azra: Very true.

Perry: I don't have any words that are adequate to respond to that little film clip. That was beautiful. Everybody knows some version of Andrew. I know a bunch.

Going back to something you said earlier, when I wrote *Evolution 2.0* it's what I like to think of as a 'bottom of the swamp' book. You go as far down into the depths of a question as you know how to get, and you find something down there. What I found was that this random mutation idea is literally the biggest mistake in the history of science. As an engineer I could understand, "No, nothing works this way. How on earth did literally a million biologists and doctors get indoctrinated with this idea?" but they are.

I found that people actually started getting what I was trying to say when I started talking about cancer. I was like, "No, those cancer cells aren't just random. They're trying to figure out how to survive. They're smart." The word 'intelligent' has been banned from biology forever, but those giant cells are smart. All you're saying is, "I've got a coffee filter and I can find 1 in 50 billion."

So tell me if I got this right. I see a total 80/20 in this. The 80/20 I see is 20% of post-cancer people are going to get cancer, but only 20% of 20% of pre-cancer people are going to get cancer, so you've got an 80/20 just by picking the people that are coming back for their 6-month check-up. These people are four times as likely, or maybe more – maybe it's 16 times as likely, but they're way more likely to get cancer than the average person. So since we know this, every time they come back we want 20cc of blood and some saliva and stool samples. They're already coming into this thing.

By the way, everybody here doesn't know all these people you're talking about are members of our cancer and evolution group. I know all these people. I'm kind of amazed that I know all these people, but here we are. They're all willing to cooperate, and if we can get together a couple million dollars a year we can have the First Cell Center.

Now tell me if this is right. This isn't stage 0.001, this is stage negative 1.

Azra: Yes, that's the way to say it.

Perry: It's like, "You've got Stage -1 cancer, which isn't even cancer yet, so we call it a first cell. Mrs. Johnson, don't get scared. Don't get worried." I'm future-pacing this, so maybe two or three years from now.

"Not only have we detected this, but we're actually starting to find some ways to reverse-engineer the stresses in your system that are causing this. We can nip this in the bud with some medical intervention right now, but we can also put you on a program to reduce your stress, like your pancreas is not happy right now, and your liver is not happy right now. With certain nutrition, or maybe you need to do mindfulness, or maybe you need to exercise, or maybe you need to forgive your ex-husband or whatever, but you're not going to get cancer. And if I have anything to say about it, Mrs. Johnson, you're going to stop doing the stuff that was giving it to you in the first place."

Do I have this right?

Azra: You have it perfectly right. I'm going to copy you in my next talk.

Perry: I'm sold on this. I think this is great.

Azra: Thank you, Perry. As you said, it is a collaborative effort, but I have put out a bold model. Other people have been too cautious. They're saying, "Oh, this causes relapse in solid tumor. This causes drug resistance." I'm saying, "No, this is the first cell. Prove me wrong. Let's go prove me wrong."

Eventually what I want to do, and this can happen within two or three years because we'll have all the samples in two or three years – I'm not talking pie in the sky 10 years later, I'm talking now. What I want to come out of these samples is a very quick, very simple test from just the 10cc of blood, serum markers, metabolite markers, to show there is stress, what kind of stress, and for the first time, like you said, Perry, we will actually deal with what's causing cancer.

That tiny little cell is not causing cancer. It's the stress that's forcing these cells to react badly. It's not random, for God's sake. You and I are soul mates in this, that we don't believe such an important issue in biology is random. I just don't buy it, and I'm the one fighting this in biology.

Perry: No, it's demonstrably stupid, but it has become the foundation of an entire field of science. It's also in viruses. That's a whole other thing. Virus macromutations aren't random either, but that's a whole other subject. This thing has tentacles that go everywhere.

What I'm thinking here as we're talking is you get your First Cell Center and you find, "There's 100 causes, but these are the 12 most common that are like $\frac{3}{4}$ of everything, and we can put people on these 12 things." Then imagine if, as a result of this, we had a comprehensive scientific model of stress itself.

Azra: Yeah, the holistic way rather than the reductionist way. So much can be done with this whole model of facing up to reality and saying yes, there is stress. There could be internal stress in the organ just as a consequence of aging, because we're not handling garbage disposal in the tissue as well. Our immune system is a little less efficient and misses a few things, and there are mutations also contributing, but those mutations even are not all random.

I just can't explain and I don't know what made me come to you. I came to you, Perry, because I know that you and I think alike about these things, and you will provide me the podium to be able to say all this, because other people are even scared to let me speak up.

Perry: Right now we have an epidemic of cancel culture. There's social media and people getting banned. I look at this and I'm like, "This ain't new to me!"

In science, if you're friends with the wrong people, you're out. I've been watching this for a long time, and the evolution space I think is the worst. It's getting better, but 10 years ago it was hideous.

So here we are in cancer and the thing that impressed me most about you was that you got away with writing *The First Cell*. I was like, "So you didn't have to go move to an island off the coast of Newfoundland and get security guards? How did you not get taken out by the mafia for saying this?" I still don't know why you didn't get taken out, but the profession actually respected what you had to say.

So here we are, and we're calling out the elephant in the room. "This is not working, but..." And you're taking another stand, which you didn't really go into in *The First Cell*. You're like, "These giant cells, we can detect them. We can figure out the stresses. We can nip Stage -1 cancer in the bud and we're going to do it. All we need is a platform of people that will listen to us. And guess what – the NIH is not going to fund us, and NSF is not going to fund us because there's too much legacy stuff."

This has all kinds of parallels in business, Azra. Entrepreneurs totally understand this. Think about it. IBM should have led the world with PCs, and DEC should have done it before them, and they didn't. And the taxi industry should have come up with Uber, and they didn't. And the hotel industry should have come up with Air BnB, and they didn't.

Reform never comes from the inside. I know this, my friends know it, my colleagues know it, and we expect it because when you have a business – think about it. I sold my car three years ago and I take Uber. For me it totally makes sense. In fact, it's less expensive and I can get stuff done while I'm going

somewhere. I can type on my computer, I can read a book, so I'm much more productive. Now, I would never, ever, ever have sold my car and taken a taxi. The pie is 10 times bigger now.

Think of Uber Eats in a pandemic. That's been a big help for restaurants and people who want to eat a pizza and can't go to a restaurant because all the restaurants are closed. Look at that. The taxi industry would have never come up with it. Why? Because they're making too much money on the old model, and the new model kills the old model before the new model becomes 10 times bigger.

This is the problem the cancer industry is in. I've had this conversation with 50 people. Chemo costs \$60,000. Let's say we come up with a cure for cancer that costs \$6,000. What's the new wing of the hospital going to do when their \$60,000 upsell becomes \$6,000? How are they going to pay their bills?

Azra: They'll have meditation centers to reduce the stress.

Perry: Right, but meditation centers don't cost \$60,000, right? So this is where we're at, and it's going to take outsiders to do this, and Azra is asking for money. We need generous philanthropists, and the philanthropists are going to be outsiders.

There's people that are going to watch this video and they can stroke a \$1 million dollar check without breaking a sweat, and they're probably going to do it because their wife died of cancer two years ago and nobody could do anything, and they watched her get down to 86 pounds and all of that dreadful hell. They're like, "Yeah, I'll do anything to fix this, even if might not work, so here you go."

So how do we get in touch with you and how does this work?

Azra: I can't tell you how much I always feel deeply moved talking to you because, Perry, in the final analysis really people are dying right, left, and center. I'm glad you always keep bringing that up. It's your friend whose wife died, or my cousin who just died. It's got to stop somewhere, so I'm very moved. Thank you so much.

The ask is very little. I'm asking everybody to guide me how to raise this money and support all these institutions. It's just to collect the samples. Once we have the samples, you see I want to capitalize. I want to bring capitalism to early detection. We set a new goal and we finally incentivize that goal, and everyone and their grandmother will want to rush that way. How do we do it? You tell me. You're the chief in this.

Perry: I've got a couple of thoughts here. Anybody who's a science geek will know the term 'emergent property.' An emergent property is like it would not be obvious if you were studying water molecules and you didn't know anything about water that if you have mist in your refrigerator it's going to condensate into a snowflake, and that every single snowflake will be different than the other ones.

Well, guess what? The snow and the trees and the mountains – that's an emergent property of water getting cold. It's like you create a set of conditions and something completely new happens.

This happens in business all the time. I just described it with Uber. You start with, "What if a taxi was just an app and anybody could be a taxi as long as they had an app? What would happen?" It's really hard to fast-forward five years and figure out, "What would happen is they come up with this thing called Uber Eats, where the people with crappy cars that you don't really want to ride in can deliver pizza." Then a

pandemic comes along and then this becomes the only way for a restaurant to survive. That is an emergent property. Nobody can roll the tape and quite figure that out before it actually happens.

Apps are an emergent property of a cell phone, which is a combination of the internet and microprocessors, so this is how it always happens.

If you go, "How is the medical industry going to survive if we can just detect cancer and prevent it from happening? What are we going to do with all these people and these facilities?" Oh, trust me, they'll find something useful to do. There's not like any lack of problems in the world, but you may have to take all that biology and genomics and chemistry and go apply it to something else.

But what would happen if we knocked out cancer and we weren't spending 5% of the Gross National Product killing people with chemotherapy? Then what would we do? Trust me, something really great. People just have to have the faith to do this.

I'm going to jump the gun a little bit. You barely even know anything about this. In December I formed a 501c3 called Science Research 2.0, and we fund cancer research and science research that the traditional academy won't fund because it doesn't fit the old models.

I had a scientist tell me, "I hate applying for funding at NIH and NSF and the government. Here's why. I tell my grad students, 'Do not let on that we're doing anything revolutionary, or we won't get the money.'" It's just like give Homer Simpson the donuts and the revolutionary stuff is just going to have to hitch a ride. He goes, "I prefer getting money from private sources instead."

Azra, when I talk to my friends they all understand what I'm talking about. They don't have any difficulty. Everything I'm describing to you, this is their life experience. They know disruptors, and nobody wants a disruptor. To us, maverick is a cool word. In medicine, maverick is like a crazy person. Yeah, we're crazy, and so was Einstein and so were the founders of Google and so was Bill Gates and so was Steve Jobs. They were all crazy. Azra, you're crazy and you're going to change the world, or we're going to at least bet on it. I want to help you do this.

If you want to fund Azra's project, email evolution@evo2.org and we'll figure it out. John Correll is the new CEO of Science Research 2.0. He's been helping me with this. Actually, I've got a bunch of entrepreneurial friends that have been helping me with this, and this has to happen. I didn't know I was going to be saying this. I'm going to have to call John like, "John, guess what? We have a new project!" but let's see this thing happen, because this totally makes sense.

This is totally right now in the fairway of what we believe in. I've been studying evolution for 17 years. I've been studying cancer for one year. This lines up with everything I've seen, and everything that the cancer and evolution group has been saying, and it's time for a change. Let's have the revolution.

The Martin Luther of cancer, Azra Raza, thank you.

Azra: Thank you so much, Perry. It's been a pleasure. I just want to add that everyone can also go to my website, AzraRaza.com, or The First Cell Center or just TheFirstCell.com, and you will have a Donate button, but send me a message. Tell me what to do and how to do this properly, just like Perry did. In such a short period of time you've given so many new ideas and laid into context what I'm dealing with really.

I really need help to get this done in the next two or three years so Elena, Andrew's mother, and other people don't have to call me and ask me, "What have you done in the last four years? Any improvement?" I shouldn't have to be saying no.

I really am deeply, deeply grateful to you, Perry, for everything that you're doing through your podcast, for how you're trying to change people's thinking, because if we really start a radically different approach then I'll end by saying this, that once we bring the word processor, no one's going to worry about the typewriter.

Perry: Yes! Yes! Perfect, yes!

Thank you, everybody, for listening. Thank you, Azra.