Demetri Kofinas: 00:00:00 Today's episode of Hidden Forces is made possible by listeners like you. For more information about this week's episode, or for easy access to related programming, visit our website at hiddenforces.io and subscribe to our free email list. If you listen to the show on your Apple podcast app, remember you can give us a review. Each review helps more people find the show and join our amazing community. And with that, please enjoy this week's episode.

Demetri Kofinas: 00:00:48 What's up everybody? Today's episode is unusually specific in that it deals with a specific type of cancer known as CLL, which is a type of blood cancer. But it's also universal in that it deals with something we all have in common, which is our mortality.

Demetri Kofinas: 00:01:09 Dr. Koffman is extraordinary in many ways. First, he's extraordinary in the medical sense, in that after 12 years of battling cancer, doctors can no longer find a single trace of malignancy in his entire body. He is 100% cancer free going on almost two years thanks to an experimental therapy that wiped out his cancer conclusively in less than a month. And this is a cancer which is metastatic on day one, which means it had already spread and could be found anywhere and everywhere in his body.

Demetri Kofinas: 00:01:51 But there's another way in which Dr. Koffman is extraordinary and that is in how he has handled his diagnosis. The impact that he has had during the last 11 years as the tip of the spear, not only in so far as seeking out and trying the most cutting-edge experimental therapies on himself, but also turning the camera on himself and sharing that experience with the world. First, by blogging about it and eventually by leaving his medical practice behind and dedicating his life entirely to being a CLL advocate for cancer patients everywhere. I want to encourage everyone to listen to this episode. Even if it seems irrelevant or inappropriate for you, I can promise you it's not.

Demetri Kofinas: 00:02:43 Some of you already know my own story, that I'm the survivor of a brain tumor that caused me debilitating psychological and physical distress. But which also empowered me to change my life and to make decisions about what was important to me, where I wanted to spend my time and who I wanted to spend that time with that I don't think I would have made otherwise. I now know that my time in this world is limited and that's not just true of me, it's true of you. It's true of all of us. We're all mortal and how we choose to spend our precious time in the face of this reality is what gives our lives their meaning. It's what distinguishes my life from yours and yours from everyone else's.

Demetri Kofinas:	00:03:36	Dr. Koffman has made his choices and hopefully he will have many, many more to make. His story is one of perseverance, leadership, generosity and service to a cause greater than himself. But besides serving as an important source of information and optimism about a very serious illness, I hope that his story and this conversation provide you with cause to reflect on your own life. On the things that matter most to you and how you want to spend your remaining time on this planet. And with that, please enjoy my very inspirational conversation with Dr. Brian Koffman.
Demetri Kofinas:	00:04:26	Dr. Brian Koffman, welcome to Hidden Forces.
Brian Koffman:	00:04:29	Thank you so much for having me here. I'm excited.
Demetri Kofinas:	00:04:31	How are you doing?
Brian Koffman:	00:04:32	I'm doing good. I'm good. It's always great to be back in New York.
Demetri Kofinas:	00:04:36	Are you a regular visitor of New York or the New York area?
Brian Koffman:	00:04:39	I'm lucky that I get to come to New York fairly often. There's a lot of the work that I do as a patient advocate and dealing with some of the pharmaceutical industry, dealing with patient advocacy organizations brings me to New York pretty often.
Demetri Kofinas:	00:04:55	So, my audience may or may not know this based on the intro that I write for this episode, but you were connected to me through a friend who found you because his cousin had fallen ill with CLL and he told me that I should look into your story, that I would find it very interesting. I did and it opened the door to many things that I think are interesting. So, I put together this conversation for us today, but maybe you can start us off with your story and how you got into your current role now as a major advocate for CLL patients.
Brian Koffman:	00:05:32	All right, so let's take one giant step back and remind people that CLL stands for chronic lymphocytic leukemia, which is the most common adult form of leukemia. Having said that it's the most common adult form of leukemia, it doesn't come close to the number of patients with breast cancer or colon cancer or lung cancer or prostate cancer, which is an issue. It's an orphan cancer, so even though it's quite common in the elderly population, the average age of a CLL patient is 72 years old. It's still a relatively rare cancer in that regard.

Demetri Kofinas: 00:06:08 What does orphan cancer mean?

Brian Koffman: 00:06:10 Orphan disease is a disease below a certain threshold, a certain number of patients in the US. There's about 22,000 people a year diagnosed with CLL.

Demetri Kofinas: 00:06:20 What about though, from what I understand from my research, CLL also often leads to secondary cancers.

Brian Koffman: 00:06:27 Right. That's a good observation. Chronic means that it's slow growing. Lymphocytic means that the lymphocytes are one type of white blood cell in CLL, specifically cancer, the B lymphocytes, which is the type that forms antibodies and it's a leukemia in that it lives in the blood. Leukemia just means white blood. But it is also a lymphoma because it comes from the lymphocytes. It's a lymphoma like Hodgkin's diseases lymphoma, non-Hodgkin's lymphoma. I tell patients that's a good thing because we get the research from both leukemia and lymphoma, we get the research dollars in the interest. So, we have this double cancer that has two different names.

Demetri Kofinas: 00:07:13 I'd love to walk through the biology here because you throw out a lot of things, lymphocytes, those exist in the lymph nodes. You mentioned B lymphocytes, these are B-cells. There are also T-cells. And also, the bone marrow plays an important role in this cancer. Can you walk me through the biology of this disease?

Brian Koffman: 00:07:32 Yeah, absolutely. Maybe it would help if I told a little bit of my own journey and how that evolved. So, I'm a family doctor. I'm not a hematologist or an oncologist, a cancer doctor, I'm a family doctor, retired family doctor. And 14 years ago, I was feeling the back of my neck and I noticed some lumps. They were sore, they were mobile. And when you think about cancer, you think about hard, fix lesions that shouldn't be like they're there. These just felt like a cyst or something. I wasn't terribly worried about them, but they persisted for a few months. They say that the doctor who treats himself has a fool for a patient, but I went ahead and ordered some blood work on myself and I remember getting the blood results back and being very pleased.

Brian Koffman: 00:08:16 My cholesterol was great, my blood chemistries were all within normal limits, but my white blood cells were elevated. So, I went on to have a more sophisticated test, which looks at the immunological fingerprint, immunophenotyping, which is done by a test called flow cytometry. And it proved that I had a monoclonal population of a particular type of B-cell that was consistent with the diagnosis of CLL. And like most family

doctors, I didn't know very much about CLL. I knew a little bit. I recently took my board exams for recertification as a family doc and 1% of the exam is hematology. So, you can imagine that most family docs aren't busy studying that. Normally when we have a patient who has hematological malignancy, we're quick to refer that rather than try to handle it ourselves. So, I was in that category until I had, pardon the double entendre here, blood in the game and then suddenly I wanted to become an expert in CLL. So, I quickly learned a lot about CLL when I was first diagnosed.

Demetri Kofinas: 00:09:23 What was that like, the diagnosis?

Brian Koffman: 00:09:25 It comes as a complete shock. Like most people with CLL, nowadays, it's most commonly diagnosed when patients are asymptomatic or have very minor symptoms. Like I had some lumps at the back of my neck, which turned out not to be cyst, but lymph nodes. And if you did a more thorough exam you'd find that I had enlarged lymph nodes where you might expect them in the armpits or the axilla, in the groin. I had other lymph nodes that were enlarged in the neck that were harder to feel, but they were definitely there. The medical term for that is adenopathy or swollen lymph nodes. So, I had this minor symptom and I felt great and I had a very healthy lifestyle. It was this, how can I have cancer? There must be a mistake here. There's this denial that this can be really happening because you feel great.

Brian Koffman: 00:10:16 Now, this is different than 50 years ago when people were diagnosed with CLL and people weren't running to the doctor all the time and having routine blood work and having well woman exams and well man exams and having a complete blood count on a regular basis. And most people then presented with symptoms. They were tired, they were running fevers, they were losing weight, they're having the symptoms of more advanced and the disease was being diagnosed more advanced. But most people now are diagnosed and they're asymptomatic or have very minor symptoms at the time.

Demetri Kofinas: 00:10:47 Is it similar in a sense to pancreatic cancer where in the case of pancreatic cancer diagnoses often happened much later because it doesn't present as early or the symptoms? I think the same thing as a stomach cancer. There are certain cancers that are not diagnosed much later. Is this similar?

Brian Koffman: 00:11:05 The similarities are somewhat limited because pancreatic cancer often when it presents is already spread and it's too late to do much about it. The same with some gastric cancers, but

they can be asymptomatic for a long time and when you catch it sometimes and often it's too late to do anything. The other piece that's so different about this, and this is a real important point that separate CLL from a lot of other cancers, is there's already this cognitive dissonance that you've been diagnosed with cancer but you feel great. You meet with the doc and he says, "You've got this chronic lymphocytic leukemia, you've got CLL. It's not curable. There is no cure for it." "So, what are we going to do doc?" "We're going to do nothing. We're just going to watch it." And you're left saying, are you really a doctor? I mean, we've caught this cancer early. It's not causing me any problems. Why don't we jump on it?

Brian Koffman: 00:11:58 You would never say to a breast cancer patient, well, your lump is really small. We're not going to worry about it now. Let's wait and see if it grows. No, you get it out. Why do we send patients for mammos or Pap smears or colonoscopies or skin checks? To catch it early and knock it out. But in CLL, we get the diagnosis and the standard care for the vast majority of patients is what's called watch and wait or active observation or what patients call, watch and worry because they need to be monitored. So why do we do this? And this gets into the biology of disease, the first word in CLL is chronic because a significant percentage of patients never need treatment. They have the same life expectancy as someone without chronic lymphocytic leukemia. Then that's not the majority.

Brian Koffman: 00:12:49 The majority will need treatment and the disease will progress, but why would you treat 15%, 20% of patients who would never need to be exposed to potentially toxic medications if they're going to have a normal life expectancy and their disease will never need treatment? The other piece of that is that there's no evidence that early intervention makes people live any longer, which is entirely different. If you look at a woman with stage one breast cancer versus stage four breast cancer, there's a huge survival advantage to catching it early.

Demetri Kofinas: 00:13:22 Is that because there isn't a particular location of the malignant tumor or the malignancy? It's already spread because it's a blood-based cancer?

Brian Koffman: 00:13:28 Absolutely. All blood case cancers are metastatic on day one. They've spread throughout the whole body. So CLL, when it's found, it's in the blood, it's found in the lymph nodes, it's found all over the place. So, it's already spread. That's one issue that's there. But the other issue is that there's again, no evidence that intervening early makes a difference. The therapies that we have now seem to be equally efficacious. Whether you start

them on the day one or you start them when, Oh oh, you're getting anemic, Oh oh, you're having symptoms, let's start the therapy now. It seems often to the advantage to wait until you need treatment because none of these treatments are free of their toxicities. So, waiting and give the patient a long time to wait and if the patient is most of that time asymptomatic and just waiting till they become symptomatic, that's when you start to intervene. This also grows out of the history of CLL because in the old treatments we have in the old days were just a little over a decade ago.

Brian Koffman: 00:14:35 The only treatments we had were chemotherapy. You'd get a chemo and then the clock would start ticking and that chemo for most patients would stop working after a few years, maybe five years. Some people were lucky and had longer, and then you'd get a second chemo and that would work for less time. And then you didn't have a third option. So, you wouldn't want to start that clock ticking until you absolutely had to because you had limited options. Things are different now and patients are doing better. So, this whole idea of active observation or watch and wait as being reexamined. But for right now, there's this weirdness that you get this diagnosis, you're not expecting to have cancer and then you're told by your doctor that we're not going to do anything for it.

Demetri Kofinas: 00:15:21 So when you're saying the therapist we have now, you're talking about the standard of care, which is chemo and bone marrow transplants. You're not including some of these new targeted or immunotherapies?

Brian Koffman: 00:15:33 The treatments we have now for CLL are radically evolved. I mean, the therapeutic landscape has changed radically in CLL. What treatments we have now have changed how we should be approaching this disease. When I was diagnosed 14 years ago, there was nothing that was shown to prolong life, let alone cure CLL. There was nothing shown to add any therapy that I had could get me into remission perhaps. But when the disease came back, it would come back more aggressive and my total life span would be the same as if I hadn't had that treatment.

Demetri Kofinas: 00:16:10 Was that even the case for, let's say successful bone marrow transplant, let's say where you had a biological twin? Were there cases where you could be cured in the past?

Brian Koffman: 00:16:21 In the past, and still may be in the present though, there's some controversy about this that we can get into. The only proven curative therapy is a bone marrow transplant. If you think of CLL, CLL is a cancer of the B-cells of the lymphocytes and that's

part of the immune system. So, you have this corrupt immune system and the immune system, and I'm going to talk about this with my own personal story, is not good at attacking itself. The immune system is not working well. So, the only potentially curative way until quite recently was to throw out that immune system and import a new, like if you have corrupt police force, you don't ask them to monitor themselves. You bring in an outside authority, a different police force and you throw out the old police force. That's what a bone marrow transplant is. You get it from someone else. They look in and say, that doesn't look right over there. That looks like a cancer cell, that looks like a problem and it attacks and wipes out the cancer.

Brian Koffman: 00:17:23 The problem is you can get what's called graft versus host disease, so you get the graft versus leukemia, which is desirable, which is a potent immune response and it's durable because these new cells become your new B-cells. Somebody else's B-cells become your B-cells. But it can also attack your gut, your liver, your eyes, and that's called graft versus host disease.

Demetri Kofinas: 00:17:47 This is the situation where this immune system that you imported doesn't recognize the body and it views the entire host as a foreign agent that it used to attack.

Brian Koffman: 00:17:56 Right, the graft versus the host.

Demetri Kofinas: 00:17:58 And that can kill you basically.

Brian Koffman: 00:18:00 That can kill you and if it doesn't kill you, it can make you miserable. When you talk to transplanters, they talk about different groups of people. There’re the miracles, the people who had two feet and one arm in the grave that get pulled back with a transplant. Then there's the tragedies where people die of treatment related mortality or it just doesn't work and the disease comes back. But there's patients who say, "This wasn't the deal that I asked for." They may have their disease knocked back, but the graft versus host is so horrific that they're on so much immunosuppressive meds. Those immunosuppressive meds can lead to infections and to other complications.

Demetri Kofinas: 00:18:38 Because they have to suppress their immune system-

Brian Koffman: 00:18:40 From attacking themselves. Or they're just miserable with skin problems, with GI problems, not being able to eat, with liver inflammation.

Demetri Kofinas: 00:18:48 There's way to walk that back once you did the transplant?

Brian Koffman: 00:18:49 Once it's in, you can't get the toothpaste back in the tube, it's there. So, CAR-T therapy, which we're going to talk about a little bit later, grew out of this saying, we know what works. Cellular therapies work because they're durable, the cells stand around, they chase down every little bit of cancer. But is there a way to get to this without having graft versus host disease? So, we can talk about that. When I was diagnosed 14 years ago, I looked around and there was no evidence that anything would be helpful and transplants have a significant treatment related mortality, TRM, about 15 20% of people die in the few months after a transplant. So, it wasn't something I was going to rush into. But my disease progressed and mine behave more like a lymphoma. I had to grow a big Santa Claus.

Demetri Kofinas: 00:19:38 Over what period in time, you were diagnosed in 2005. When in 2005 were you diagnosed?

Brian Koffman: 00:19:43 In September of 2005.

Demetri Kofinas: 00:19:43 September of 2005.

Brian Koffman: 00:19:45 Right.

Demetri Kofinas: 00:19:45 A date I'm sure you don't forget. In fact, I think you've talked about in terms of a paradigm shift.

Brian Koffman: 00:19:51 Right. I was diagnosed just a few weeks before my oldest daughter's wedding. And I'm Ashkenazi Jewish, which by the way, CLL was more common in Ashkenazi Jews. There's a teaching in the Talmud, which is a commentary on the Hebrew Bible that says, "When a funeral and a wedding come to the same corner at the same time, the wedding takes precedent, you choose life over death." So, it was very difficult for my wife and I, because I'd gotten this horrible diagnosis and it was just a couple of weeks before this huge celebration. All the kids are coming back from college, all the families flying in, people are flying in from all over the world for my daughter's wedding and I couldn't say a word, couldn't say a word to my kids. Couldn't say anything until the wedding was over.

Demetri Kofinas: 00:20:37 That's hard. You didn't tell your family.

Brian Koffman: 00:20:39 Yeah, I don't want to spoil their honeymoon. I don't want to spoil what's going on. So, we waited till the wedding was over because we wanted the joy of that occasion to be what people remembered. I'm still around 14 years later and my daughter is giving me granddaughters.

Demetri Kofinas: 00:20:54 You have two kids?

Brian Koffman: 00:20:55 I have four kids.

Demetri Kofinas: 00:20:56 Four kids?

Brian Koffman: 00:20:56 Yeah. Two girls, two boys. We're really blessed that way. So, we kept it quiet. And again, because I was relatively asymptomatic, there was really nothing to do. My lymph nodes kept growing and I had to grow a big Santa Claus beard to hide the lymph nodes in my neck and my patients could notice them. They were saying to me, "Dr. Koffman, are you okay? What's going on?" My blood counts got a little bit worse, but not too bad. But my spleen enlarged and I got full easily and I had some GI issues and stuff.

Demetri Kofinas: 00:21:30 And this progressed over what period of time?

Brian Koffman: 00:21:31 Couple years.

Demetri Kofinas: 00:21:32 Couple years.

Brian Koffman: 00:21:32 Yeah.

Demetri Kofinas: 00:21:33 It was a steady progression.

Brian Koffman: 00:21:34 Steady, slow progression. But then one day, I noticed some little red dots on my legs and I was aware these are broken blood vessels called petechiae, which are like tiny little bruises, which can be from inflammation, the blood vessels called vasculitis or problems in the clotting system. So again, like I said, the doctor who treats himself has a fool for a patient, I ordered a complete blood count on myself. I was on call that night, and I remember this very well. I got a call at about 2:00 AM in the morning and they said, "Dr. Koffman?" I said, "Yes." He said, "We have a critical lab level on Dr. Koffman" And my platelet count, and the platelets are what helps your body clot should be over 150,000 and mine were nine.

Demetri Kofinas: 00:22:19 Yeah, that's crazy.

Brian Koffman: 00:22:20 That's crazy.

Demetri Kofinas: 00:22:21 That's the lowest number I've ever heard of.

Brian Koffman: 00:22:22 Mine had been lower. I mean, sometimes they'd been six and four and sometimes not measurable. This is not compatible with

a happy life. When we're driving to the hospital, I realized if I get into a little tiny fender bender, I could internally hemorrhage and lead to death.

Demetri Kofinas: 00:22:36 Bleed to death.

Brian Koffman: 00:22:38 That led to multiple hospitalizations and all kinds of treatments, high dose steroids and IB infusions and nothing seemed to work for me. I had an emergency splenectomy because the spleen filters out the platelets that didn't work. I bled internally and my hemoglobin, which was about 14 grams, which is normal, dropped seven grams in 24 hours. My belly swelled up because I was bleeding internally. I looked like I was six months pregnant except I was black and blue from all this internal bleeding from the surgery. I mean, it was touching. There was a lot of nights that I went to bed when I didn't know whether I'd wake up in the morning. So, I had this really bad auto-immune complication of CLL called ITP or immune thrombocytopenic purpura. So not only is my cancer leading to immune deficiency, it's leading to my immune system acting out and attacking my platelets. It's a rare complication to CLL, one to 2% of CLL patients get it. But I was unlucky and got it and it led to my platelets crashing.

Demetri Kofinas: 00:23:45 As I understand the biology or as I thought I understood it, the negative impact on the platelet count for CLL patients is a derivative of the fact that you have an explosion of the growth of B-cells. It crowds out blood cells and platelets. Is that accurate or am I misunderstanding?

Brian Koffman: 00:24:03 That's accurate for some patients. There are many causes for low counts, whether it's the hemoglobin, the red blood cells or the platelets or the neutrophils, a different kind of white blood cell. The most common is the bone marrow is the factory floor as you suggested. And if the bone marrow is 90% full of CLL, the body expands. It starts building red blood cells and white blood cells and other parts of the bone marrow that it normally wouldn't do in adults and it compensates. But at some point, it can't compensate anymore. And that leads to gradual increases and there is a tipping point. But a more sinister and rare cause of those low platelets or low hemoglobin, in my case the platelets, is that the body attacks itself and that's an autoimmune complication of CLL. Now that same ITP, immune thrombocytopenic purpura or low platelets from an immune cause can happen outside of CLL, but it happens more commonly in CLL. And that tends to lead to a more precipitous fall of the platelet, some more life-threatening fall. And that's what I had.

Brian Koffman:	00:25:10	I had this ITP that was very, very difficult to control. I was getting multiple treatments for that ITP and we finally came across a combination of two drugs that seemed to work for, one was an antibody, it's an immune therapy called rituximab. So, on the surface of CLL cells, there are-
Demetri Kofinas:	00:25:34	Malignant B-cells. Correct?
Brian Koffman:	00:25:36	Right.
Demetri Kofinas:	00:25:37	Can you tell our listeners what B-cells traditionally are supposed to do? What part they take in the immune system?
Brian Koffman:	00:25:44	Our immune system is complicated and there's all kinds of parts to it, but one part is the lymphocytes. The lymphocytes are really divided into three categories. The B-cells, the T-cells, and the natural killer cells.
Demetri Kofinas:	00:25:55	Most people have heard of T-cells. That's like the killer cell. That's the soldier of the immune system.
Brian Koffman:	00:26:01	It's the cellular therapy, and we're going to spend a lot of time on that when we talk about CAR-T. But the B-cells are the humoral, which comes from the Greek humors, the four humors, and it's the liquid part of the immune system. What they do is they make antibodies. So, when you get a flu shot or if you were a kid and got a Measles shot, you formed antibodies and those were formed by B-cells that matured into what are called plasma cells and formed these antibodies. The normal B-cells form antibodies, CLL is a cancer of the B-cells and they're dysfunctional and they can crowd out the normal B-cells. They can crowd out the T-cells-
Demetri Kofinas:	00:26:38	They're like Scouts, they scout the body and they tag, let's say foreign or pathological agents that the T-cells then attack. Is that a...
Brian Koffman:	00:26:46	Well, they get messages to say there's antigens or just proteins that they get presented and say, Hey, here's a problem. Let's see what we can do. And it's all part of a coordinated system with the T-cells and B-cells. There’re all kinds of redundancies built in. We can live without B-cells. I don't have B-cells, cancerous or non-cancerous.
Demetri Kofinas:	00:27:07	We're going to get into that when we talk about CAR-T.

Brian Koffman: 00:27:08 Right. So, the B-cells form antibodies. Like for example, I don't get a flu shot anymore because I don't form any antibodies. It wouldn't do me any good. That's the role of the normal B-cells. What happened with me is my immune system not only became nonfunctional, it became dysfunctional and started attacking my own cells. In my case, my platelets, other people it attacks their red blood cells. Mine, it attacked my platelets and we tried to turn it off. We tried to turn it off by using an antibody that would kill some B-cells. And the same antibody is used to treat autoimmune problems like rheumatoid arthritis by calming down the immune system.

Brian Koffman: 00:27:53 I had another drug called Cyclosporine, which suppresses T-cells and it's most commonly used when people have kidney transplant so the body won't reject the foreign kidney. It knocks down the T-cells. This combination of rituximab and Cyclosporine worked and seemed to calm down my ITP. When I had a bone marrow biopsy done, my CLL had gone from 90% of my bone marrow down to about 6% of my bone marrow. This was unexpected. And though rituximab has some activity against CLL, it's usually pretty weak.

Brian Koffman: 00:28:29 It doesn't usually have great effect in the bone marrow. Cyclosporine, there's been some papers, some anecdotal cases of Cyclosporine having anti CLL activity, but generally it was not used to treat CLL. Suddenly I was in the significant remission and I'd almost died-

Demetri Kofinas: 00:28:47 This was 2007, 2008?

Brian Koffman: 00:28:48 Yes. Yeah, about then. I was in the significant remission. So, what to do at this point? I took a radical approach, and what you're going to find out from me is, I'm an early adopter of things, is we started this conversation. The only known curative therapy was a transplant. So, I'm 57 at this point and I'm thinking, there are no therapies particularly going to be helpful for me.

Demetri Kofinas: 00:29:13 You never considered chemotherapy seriously?

Brian Koffman: 00:29:16 CLL is an extraordinarily heterogeneous or variable disease. So, there's that 15%, 20%, 25% who never need treatment and there's some who have a very aggressive disease. While we can't predict for individuals, we can predict for groups. I was in the group that was a very high-risk group. So, I had these prognostic and predictive factors that look at the inside the cell and see what chromosome abnormalities I had and I was missing certain chromosomes. I was missing the long arm of the

11 chromosomes. That's an 11Q, the short arm of the 17 chromosome 17P. These are very bad prognostic markers. I also later had next generation sequencing which showed that I had mutations in certain things, certain kinds of oncogenes were mutated. I didn't have the apparatus to turn myself off. The way that chemo works is by damaging the DNA the same way the radiation works. Then the cell gets a signal, my DNA is damaged. They have something called TP53, which is a protein which goes in and tries to fix that and if it can't fix it, turns on the cell suicide, program cell death.

Brian Koffman: 00:30:31 If that chromosome lives on the short arm of 17th chromosome, if you're missing the 17th chromosome, you're missing that ability, which means chemo won't work. Or if you have the short arm of the 17th chromosome, but that TP53 protein is mutated, chemo won't work and that was my circumstance. So, there was really no role for chemo with me. I also had something else, which is another predictive factor called unmutated IGBH, which is a marker would suggest that chemo was less likely to give me any durable response. So, I was in this circumstance where the best I could hope for would be a couple of years of chemo and likely that would be optimistic. That's why I moved when I got into this remission, I went for a transplant upfront. This is very unusual because usually transplant, because of the treatment related mortalities associated with it, was seen as kind of a hail Mary pass, a last stitch effort.

Brian Koffman: 00:31:36 So why is Brian doing this upfront? Well, because I didn't have other options. I just did a logical assessment of what's going on. I said, if I don't do anything, if I do chemo, if I follow the regular path, if I looked at the survival curves based on the data at that time. It's entirely different now. So, I'm anxious to get to that part. But if the data at that time, my chances of being alive in about five years were about 5%. About 5% of people like me were alive in five years, one out of 20. With a transplant, even though I had maybe a 15%, 20% chance of dying in the next three to six months, where if I didn't have a transplant, my chance of dying next three to six months was probably one or 2%, my chances of being alive in five years from now was about 50, 50 and my chances of being cured were just a little bit less than that. So, it seemed to me like a no brainer decision.

Demetri Kofinas: 00:32:26 You couldn't just wait. It didn't make any sense to wait and not do chemo because you had such a great response to the other drug.

Brian Koffman: 00:32:32 Yes, I had a great response to the other drug. First, chemo wouldn't work if I waited or didn't wait.

Demetri Kofinas: 00:32:37 Right, sure.

Brian Koffman: 00:32:39 At this time, so this is about 12 years ago, there was no even twinkle in the eyes of researchers about any new kinds of therapies coming. There was no CAR-T therapy, there was none of these small molecules that have revolutionized the care of the CLL. So, I really didn't have a lot of options.

Demetri Kofinas: 00:32:59 I hadn't heard of ibrutinib the time?

Brian Koffman: 00:33:01 Nobody had heard of ibrutinib at that point. I spoke to the researcher who actually developed the molecule and the molecule was just being made at this time. It wasn't in any human trials at this point.

Demetri Kofinas: 00:33:14 So you decided to roll the dice on a transplant.

Brian Koffman: 00:33:17 I rolled the dice on the transplant because the odds-

Demetri Kofinas: 00:33:19 This was 2008?

Brian Koffman: 00:33:20 I think 2008, I think is right. Yeah, yeah.

Demetri Kofinas: 00:33:24 So you decided to roll the dice and what happened?

Brian Koffman: 00:33:27 What's interesting, and you brought up the issue of chemo because most people who had transplants had had chemo before. The chemo is toxic to any fast-growing cells, including bone marrow cells, and it damages your T-cells, which are the cellular part. Like you talked about, the soldiers and the captains of the immune system. I'd never had chemo. Ironically, even though my immune system was corrupt and inadequate, it was adequate enough for me to reject the graft because I hadn't been beaten up before with chemo. So, I got the graft, it started to do a little work, but within months I ended up rejecting the graft and never becoming the other person. I lost the graft and went back to being myself again.

Demetri Kofinas: 00:34:13 When you have a transplant like that, do they put you on immunosuppressants? Do they try and suppress your immune system in order to help you take the graft?

Brian Koffman: 00:34:22 Yes. There’re all different kinds of transplants. The first thing in CLL, the only ones that have been shown to work are what are

called allogeneic, which means from someone else because you need the graft versus leukemia response. If you take it from your own cells, an ontologist transplant where you use your own cells, those don't work. But the kind of transplant I got, thank God, was called the reduced intensity or mini transplant, some people call this. And what they do is they give me just enough chemo, not to knock back the CLL, but to clean out my bone marrow a little bit and knock down my immune system so I won't immediately reject the graft.

Brian Koffman: 00:35:01 So the graft goes in and then they give me all kinds of immune suppressive drugs to keep the graft and you stay on those depending on what's going on for months and months. And if you get graft versus host sometimes they push those up and those can be things like I mentioned before, cyclosporine, but also steroids and tacrolimus and sirolimus, those all kinds of different drugs that they give you so you won't lose the graft. But that didn't work for me and I ended up rejecting the graft. Within a few months my CLL started to come back. Even though I got a nice response, it came back pretty quickly. My ITP, my platelets all came back, but it bought me some time. It was like I'd reset the clock and I had a few years of just the CLL slowly coming back and the ITP slowly coming back, but not single digit platelets.

Demetri Kofinas: 00:35:52 How are you doing emotionally during this time? Because you're also talking about a time where there really wasn't anything on the horizon. Like you said, you weren't in this phase where a lot of people are today, which is they're hopping from one therapy to the next with the hope that they can eventually ride one comment out. How were you doing?

Brian Koffman: 00:36:13 When you get the news that you've relapsed after a transplant, it's pretty depressing, but you have to keep your eye on the ball and try to figure out, okay, what am I going to do? How do I get to the next step? You just try to move forward. One of the things I do as a physician is try to be very Zen about this and detach. I tell patients, you really have to underreact because you're going to get good news during the journey and you're going to get bad news and you just got to underreact and keep going, and I tried to. I turn on the nerdy side of myself and become analytic and say, what would I do with a patient like this, and try to be self-analytic without getting too emotional. Sometimes I'm good at it and sometimes I'm not so good at it. But I just try to step away from it and look at, how do I move forward? And it's not like you have a choice. Like people say, well, you're so brave to do this, that's completely bogus.

Demetri Kofinas: 00:37:14 Does that part being level-headed, learning to underreact, does that actually get easier with time because you're in it?

Brian Koffman: 00:37:24 It can get easier with time and it can be difficult sometimes to turn off because then you can get emotionally detached from things you should be emotionally attached to. I mean, you develop this Teflon coating, but can you turn it off and on?

Demetri Kofinas: 00:37:38 It also becomes hard to be... Are you suggesting that it gets hard to imagine that they get very hopeful because you're trying to keep your expectations low?

Brian Koffman: 00:37:47 Right. Because you want your hope to be grounded in reality and look like anybody. I'm looking-

Demetri Kofinas: 00:37:52 You don't want to have your heart broken.

Brian Koffman: 00:37:53 Yeah, you don't have your heart broken, but you're also trying to be optimistic about things and look forward and be upbeat, but you've just got to be realistic. Any cancer patient, anytime you get a scan or a blood test, your heart's in your hand until you get those results back and you know things are stable. You're waiting for that, what did my CT show? Did anything come back? What did my blood count show? Is the count still stable? This is the way it is. So, no matter how cool I try to be, it was never all that cool. But you don't have a choice. It's not like people say to you, well, what did you want to do when you must've been so brave to? It's not like I'm brave. It's like, what could I do? A transplant seemed like a logical thing and the transplant didn't work and I thought about a second transplant and I thought about some other things that I just thought about, okay, this didn't work. What's my next move? It was my way of coping, was being analytic and trying to figure out what's the next thing I do?

Demetri Kofinas: 00:38:52 How soon after your initial diagnosis did you reach a point of acceptance?

Brian Koffman: 00:38:59 I don't know that you ever reach a point of acceptance. There's always, it's just something that you deal with. One of my favorite quotes is Gilda Radner said, "If it wasn't for the downside, everyone would want cancer." And it's true. If cancer wasn't life threatening, the world that I live in, Like I'm here in New York, sitting, talking with you Demetri. I get to travel around the world and talk about my story and my journey. My world is much bigger. It's more exciting. I move with really

interesting scientists. I get to do really exciting research. I live in this much bigger world.

Demetri Kofinas: 00:39:38 You're also more appreciative, right? I think that's what Radner was suggesting as well, I imagine.

Brian Koffman: 00:39:42 Right. So, the other piece is, and this is something that I know well, and if I can say so, I think you know too, is that I've gone to bed at night not knowing whether I'm going to wake up in the morning. All of us know our time here is limited, but none of us believe it until we get cancer. Then when you have cancer, you realize, Oh, this is for real. Nobody gets out of here alive.

Demetri Kofinas: 00:40:06 You decide to stay radical.

Brian Koffman: 00:40:07 Right, yes. We all are going to die. And in our case, it could be tomorrow. It could be, I don't get off the operating table. It could be, my platelets don't go up again. It could be, I could have a major hemorrhage during the night. I remember if I bumped my head lightly, it would be like, oh my God, is that going to lead to a major bleed? Everybody says, don't sweat the small stuff, but when you have cancer, it's all small stuff in comparison. So, what really matters to me it's your family. It's the good works that you do. It's the advocacy stuff that you can be doing to move things forward. What really counts and what can you drop away that no longer matters?

Demetri Kofinas: 00:40:47 I watched a very moving presentation by your wife. It was actually during a lecture that you were giving. You brought her in and she presented your son's comic strip, which is actually beautiful. I found it very moving and I was trying to understand kind of why I felt that way. I think his love for you came out in the detail of that comic.

Brian Koffman: 00:41:11 Thank you, thank you. That was fun. My wife scripted that.

Demetri Kofinas: 00:41:13 Your wife's narration also, her love for you came out in that. So, that's a way of asking really, what was the family dynamic during this time for you? How was your family coping with this and how were you working with them through this difficult time?

Brian Koffman: 00:41:29 It takes a family to get through this and you cannot do this on your own. Let me give you an example of this than I can from the CAR-T. It's kind of jumping ahead in the story, but when I had the CAR-T therapy, it's done on an outpatient basis.

Demetri Kofinas: 00:41:49 Maybe this will be a good opportunity to tell. We'll jump around, but maybe you can tell them what CAR-T therapy is.

Brian Koffman: 00:41:54 CAR-T stands for chimeric antigen receptor T-cells. This is a new angle cellular therapy. CAR-T therapy is a living drug. It's a biologic. So, what they do is they take the T-cells, which we talked about earlier, they take them out of you through a process. It's like a panty centrifuge called the leukapheresis machine, and they spin off the T-cells and they purify them. Then they infect them with a lentivirus. That means like a slow virus. This is a cousin to an HIV virus. This is fooling around with your genes and it's inserting new genes in there. It's inserting new genes to take these lazy T-cells that aren't doing a good job of fighting the cancer and turn them into serial killers.

Demetri Kofinas: 00:42:44 This is an evolution of the innovation in bone marrow transplants. It's not a direct lineage, but in terms of the fact that both are an attempt to turn your immune system against the cancer.

Brian Koffman: 00:42:57 Right. Cancer is very good at hiding from the immune system and turning off the immune system. What the CAR-T does is skip some steps so the T-cells don't have to recognize the cancer. They're taught to recognize the cancer. They're born-

Demetri Kofinas: 00:43:14 Because you cannot like teaching a dog to sniff out cocaine or bombs or something like that. They get the scent and then they're put back into the body and they know where to find the cancer and to attack it.

Brian Koffman: 00:43:25 That's a very good analogy, except the difference here would be is that they keep going. They're serial killers, they see a cancer cell and they do another, so they grow these cells outside of you. There's all kinds of purity and sterility checks and stuff like that and these cells and they get a certain count, certain number of millions of these cells that had been trained to attack the cancer.

Demetri Kofinas: 00:43:50 They're remarkable.

Brian Koffman: 00:43:51 Yeah, it's gene therapy in one, I'm in a clinical trial for this. This is not approved in CLL at this point. The FDA demands that I be followed for 15 years because we don't know for certain where all the new DNA was inserted into my genome. I'm part mouse now. I have these mouse genes and-

Demetri Kofinas: 00:44:19 Can you explain that. I don't really understand that. So, I understand that they've taken T-cells out of your body, they've modified them so that they can attack the cancer. But I'm not clear exactly on how that's risky in any way in the way that you're describing. Can you explain that to me?

Brian Koffman: 00:44:32 Sure. So, when they take the genetic material, so there's my T-cells that are outside of me, and they try to purify it. So, it's only T-cells, but there might be a couple of B-cells and natural killer cells and other cells in there. Then they put the virus in and the virus inserts something to recognize a marker on the surface of the cancer cell. It also is on the surface of B-cells, and we'll go into that later. Now, it puts it in, but they don't have control over it as it puts one copy in, five copies in, where does it put the copy in? Maybe it splits it in a spot that turns some gene on. Maybe that's what's called an oncogene or a cancer gene. There's been tragedies before in gene therapy where perhaps we're turning something into a cancer. So, it's tough to fool around with mother nature and when you start fiddling with the genetic code-

Demetri Kofinas: 00:45:30 In other words, you could create cancer in the lab and be inserting it into the body.

Brian Koffman: 00:45:32 That's correct. That hasn't happened and there's all kinds of safeguards against it. Also, they want to make sure that there's no virus left. So, it's not still doing it. It's only in these T-cells, it's not anywhere else and it's only attacking this particular thing. But things can wrong and things can get out of control and there can be unintended consequences. So that's why they want to follow me because they've manipulated my genes, not all my genes, just the genes in my T-cell. So, if you took a cheek swab from me, my cheek genes would be the same. If you looked at my DNA in a biopsy of my skin, it wouldn't show that.

Demetri Kofinas: 00:46:08 So these new T-cells that they insert in you, they begin to replicate and they replace the existing T-cells in your body?

Brian Koffman: 00:46:16 Well, I have T-cells left in me. But what happens is, so they grow these outside of you, then you get what's called lymphodepleting chemo. So just like with the model that we talked about with the transplant, we need some chemotherapy to prevent me from rejecting these new T-cells. Even though they're my T-cells, they've been genetically modified. So, I might see them as a stranger and my body reject them. This makes room for them. They go inside you and it's very disappointing you're getting this thing that you've been waiting for forever and you get this little infusion over 10 or 15 minutes and

nothing happens. Nothing. They just are dormant. They just sleep there for a while. I was blogging about this and recording about this. I remember saying, wish me ill, because you want to get this inflammatory response where the T-cells start expanding and get into a killing frenzy.

Demetri Kofinas: 00:47:11 Why do they initially remain dormant?

Brian Koffman: 00:47:14 I don't know the answer to that for sure.

Demetri Kofinas: 00:47:16 Okay. So, you said --

Brian Koffman: 00:47:16 They could be dormant for a couple days or sometimes a couple of weeks, but usually in five to 10 days they wake up and start attacking.

Demetri Kofinas: 00:47:22 You wrote on your blog, wish me ill because you wanted these T-cells to wake up and to begin to attack the cancer?

Brian Koffman: 00:47:28 Right. And when they attack the cancer, there's a killing frenzy that goes on and there's all kinds of toxic things that can happen. The contents of the cancer cells can spill out and cause kidney problems and other things, but the body reacts with inflammation. So, you can feel flu-like. Where I had it done, which was the Seattle Cancer Care Alliance, the Fred Hutchinson or the Hutch in Seattle, it's done on an out-patient basis. I developed these flu-like symptoms and my wife had this very clear protocol about what she was supposed to do, take his temperature, ask these questions, do these things. I met certain criteria, so she called and said, "The doctor on call said bring him in a hospital." I was hospitalized for about four or five days and I felt flu-like, achy, pretty bad. Like a horrible flu.

Demetri Kofinas: 00:48:19 You got the infusion in Seattle but you went back home.

Brian Koffman: 00:48:21 No, no, no. When I say I went back home, I went back to the hotel that we were staying.

Demetri Kofinas: 00:48:26 You were staying near the hospital.

Brian Koffman: 00:48:27 Yeah, you're not allowed to be more than 20 minutes from the hospital, which in Seattle is about one block with the traffic because it's pretty bad. We were staying in like an extended care hotel for two months.

Demetri Kofinas: 00:48:38 Sure. This is obviously a huge commitment. We're talking about this and I want to capture as much of the biology as possible

and we're really, I think, selling short the emotional toll that this has taken throughout the course of these years that we're talking about here. But continue please.

Brian Koffman: 00:48:59 So when these CART-Ts wake up, they start killing and they lead to release of inflammatory molecules that are called cytokines. It's called the cytokine release syndrome. The old-

Demetri Kofinas: 00:49:14 CRS.

Brian Koffman: 00:49:15 CRS, the old non-PC name for this was a cytokine storm. We're not supposed to say that anymore. So, I went through this, I got better just on my own, nothing really bad, and then went back to the hotel and about five or six days later I was getting achy and sore and really in a lot of pain and having trouble moving. It migrated around my body and I remember-

Demetri Kofinas: 00:49:42 Now you were expecting something like this.

Brian Koffman: 00:49:44 Well, I thought I was through it. I had been in hospital for five days and this is about four or five days later.

Demetri Kofinas: 00:49:49 Were you worried that your response wasn't strong enough?

Brian Koffman: 00:49:52 Well, there's no one-

Demetri Kofinas: 00:49:53 Like you said, you wanted to feel that you got ill.

Brian Koffman: 00:49:56 Yeah. So, important question. The data is scant on this. There're not many people who've had it, but the data seems to suggest that what's important is that you have some reaction. But the depth of the reaction doesn't seem to make that much of a difference. What matters is how much the cells expanded, how durable they are maybe a factor, but it was mainly how much those cells expanded. Some people have done very well with just minor aches and pains. Other people have had terrible CRS, cytokine release syndrome and not done well at all. It's not a one to one correlation.

Demetri Kofinas: 00:50:30 Is there any way to predict the extent of the response based on the proliferation of the cancer? Is there any way, in other words, to get a sense of how much cancer is in your body so that you can prepare yourself for the type of response that you're going to experience?

Brian Koffman: 00:50:44 Well, there's algorithms that can look at the number of lymph nodes you have and their size and some aid that, and look at

what your white blood cell count is and they can do that. And there's some suggestion that the more disease you have, the stronger the reaction is, but it's still a lot of hit and miss. Some people with tremendous burdens of disease have had very mild reactions and other people with very little disease have had very severe reactions. It's very much in its infancy and there's more unknowns than there are knowns.

Brian Koffman: 00:51:15 What happened with me is only been described in one other person. After I gone through this cytokine release syndrome, clearly done that, I was back and feeling better. And then about four or five days later, I got these aches and pains, which progressively got worse. I remember I had to go to the bathroom, I needed to sit down on the toilet and I was standing in front of the toilet for 20 minutes because I couldn't move, I couldn't sit. And my wife said, "This isn't normal." I said, "This is the kind of denial I'm in and I'm out of it." I'm saying, "Well no, no honey, it's normal for me to take 20 minutes to sit down on the toilet." I just had no idea how out of it I was and what was going on. To her credit, she ignored my advice saying, don't call the docs, I'm going to be okay. Because I don't know what's going on.

Demetri Kofinas: 00:52:04 You're experiencing neurotoxicity.

Brian Koffman: 00:52:05 Neurotoxicity or what now called neural events. It's like they like us to use that language.

Demetri Kofinas: 00:52:10 There was a cognitive decline going on.

Brian Koffman: 00:52:12 Right. I was toxic. I didn't know what was going on.

Demetri Kofinas: 00:52:14 Cytokines in your blood were causing the toxicity.

Brian Koffman: 00:52:16 And there may be some brain swelling and some inflammation. That's different because there's not a one-to-one correlation between the cytokine release syndrome and the neuro advance. But my wife called and I ended up going to hospital and then I was really sick this time. I couldn't move. I was in excruciating pain when the sheets hit my legs, I was screaming in pain. I had massive edema. I looked like swelling of the legs. I looked like the Michelin man. My joints were red hot. They put a needle in, they aspirated my knee to see what was going on. I had all kinds of inflammatory white blood cells, consistent with a septic joint.

Brian Koffman: 00:52:55 They put me on antibiotics while they're trying to figure out what's going on. Nothing grew out and they never quite figured

out, but they figured out it could be some kind of inflammatory reaction that was triggered by this. I couldn't move. My inflammatory markers were tens of thousands of times what they should be. They were incredibly high. My CAR-T cells had massively expanded. I was really sick. I was in excruciating pain. I was on Dilaudid, which is a heavy opioid around the clock. I was hallucinating.

Demetri Kofinas: 00:53:27 You remember this?

Brian Koffman: 00:53:29 I remember some of this. Some of this is from what my wife and daughter came up to reliever were telling me, but I was hallucinating. I'd been up to the Olympic peninsula. I was in the forest, I was talking to monks and caves. I was in this museum being interviewed. The doctors would come in and talk to me and I say, "Leave me alone. I'm being interviewed in a museum." I was completely out of there.

Demetri Kofinas: 00:53:51 And you remember some of these hallucinations?

Brian Koffman: 00:53:52 Yeah, I remember them because sometimes I think it's important to know what your subconscious is saying to you.

Demetri Kofinas: 00:53:57 Sure, I agree with that.

Brian Koffman: 00:53:57 My son really encouraged me to say, "Dad, write some of this down so you remember-

Demetri Kofinas: 00:54:01 The same son who created the comic.

Brian Koffman: 00:54:02 No, the different son. Different son.

Demetri Kofinas: 00:54:02 So you've got very creative children.

Brian Koffman: 00:54:05 Yeah.

Demetri Kofinas: 00:54:06 Artistically inclined children.

Brian Koffman: 00:54:07 Yeah, so he did the videos and stuff. That's all my other son, Dan. And William did the drawings.

Demetri Kofinas: 00:54:13 What a great family you have?

Brian Koffman: 00:54:13 I'm really blessed. I'm so blessed. I try to remember, but I had a conversation with one of my docs and he called me like a week later and said, "Did you talk to anybody last week?" And I said, "No, I hadn't talked to anyone." I had a 45-minute conversation

with them. And my daughter said she had to call him back and said, "Dr. Bird, please excuse Brian. He doesn't know what's going on." I wrote a blog post and it's complete gobbly gook. It's like Alice in Wonderland stuff. But I had no idea. When you're out of it, you don't know that you're out of it. You don't know how far gone you are in and also being a physician and I might say at the risk of being a gender insensitive, being a male physician, I was in denial about all this stuff. Well, I can handle all this. This is pretty normal. But I was completely out of it. So, my wife had to take control. I was very sick. I was lying. So, I've got a blood clot in my lung. What's called a pulmonary embolus. I was really sick.

Demetri Kofinas: 00:55:07 What caused the blood clot?

Brian Koffman: 00:55:08 Well, blood clots happen when you're immobile. I couldn't move. I could not move. I could not lift my leg off the bed. I had to be catheterized-

Demetri Kofinas: 00:55:16 Were you ventilated at some stage?

Brian Koffman: 00:55:18 No, no, no. I never was in the ICU and my blood pressure stayed stable. I could talk and breathe, but I couldn't get up. They had to use a special harness. It took three people --

Demetri Kofinas: 00:55:26 You're basically at death's door in this process.

Brian Koffman: 00:55:28 Well, I'm not on death's door, but I'm not doing well. My daughter, who's an architect, my oldest daughter and my wife talking, we going to have to revamp the house because daddy can't walk anymore. I had to get around in a wheelchair. I couldn't move. It took three people to get me into a chair. Or if I had to go to the bathroom, took people to stand me up to urinate. I mean, it was-

Demetri Kofinas: 00:55:48 How many days was this going on?

Brian Koffman: 00:55:49 This went for about four days and I was on Dilaudid around the clock and they finally said, "Let's see what's going on, let's see if we can reverse this." And they gave me some anti-inflammatory medications, a steroid called dexamethazone and then something that blocks interleukin six called Tocilizumab, which is used to treat rheumatoid arthritis and other diseases and then more dexamethazone.

Demetri Kofinas: 00:56:09 Anti-inflammatories.

Brian Koffman: 00:56:10 Anti-inflammatories, and swelling and the pain melted away and I didn't need anything. Just something like an Advil strength stuff afterwards from being on dilaudid. In fact, it got better so quickly that I went through opioid withdrawal because they stopped the opioids and I've been getting them. I remember I was getting shaky and goosebumps and anxious and my daughter said, Dad, it looks like you're going through some kind of withdrawal or something." Because I was really shaking. They gave me some IV Valium and I woke up six or eight hours later and felt better. But I had to learn how to walk again. I had to use a Walker and I had the belt around me. Like you see an older people.

Demetri Kofinas: 00:56:52 Now, when you say you had to learn how to walk again, what do you mean you had to learn it? Was it that-

Brian Koffman: 00:56:57 Well, I couldn't walk. I didn't have the strength. I had pain in my legs, I hadn't walked for days and I couldn't walk normally. I didn't have the balance. I was still, I was way better --

Demetri Kofinas: 00:57:09 From the physical exhaustion. It wasn't from --

Brian Koffman: 00:57:10 Or from the inflammation that had happened in my joints. I mean, we don't really fully understand it, but I couldn't fully bend my legs. I was exhausted.

Demetri Kofinas: 00:57:17 It wasn't a neurological thing.

Brian Koffman: 00:57:20 It's not fully understood, but it's probably more of an arthritic thing, but it's not fully understood. I could walk a couple steps, but I was wobbly. I didn't have my balance. On top of this, I was also quite anemic because when you have all this inflammation, there's collateral damage. So, my hemoglobin was really low. My neutrophils that fight off, infections were low. Everything was low at that time. I didn't need transfusions, but I was borderline. So, as we like a newborn, but to walk around, they had to put a belt around my waist and have the physical therapist or my wife pulled me so I wouldn't lose my balance. I used a walker and I had to go home with a wheelchair. When I went back to the hotel, I say home, I mean the hotel, when I back to the hotel, I had to get the elevated toilet seat and a shower chair because I couldn't stand-

Demetri Kofinas: 00:58:10 How long was this process for?

Brian Koffman: 00:58:12 That took a couple of weeks for that to get better. It took a long time. Eventually I went down to walking with walking sticks and

gradually got better and went through physical therapy and trained myself.

Demetri Kofinas: 00:58:23 So basically your body went through hell. It went through a war after these T-cells were injected, these modified T-cells were injected in you.

Brian Koffman: 00:58:31 There was all kinds of collateral damage. Most people don't go through this as bad as I did and they didn't know what was going on. There's a little bit with CAR-T therapy, is they're building the airplane as they're flying it. It's new stuff. But I got to get to the good part of this. So, I went and I had this massive expansion of the T-cells and they restage me. That means they retest to see where I'm at. I'd had these massively enlarged lymph nodes and all of them had shrunk except one, and normal is 1.5 sonometers, 1.6 sonometers. That's called a partial emission because it didn't get a 1.5 but a year later it was still 1.6 and I think it was just scar tissue and never went back down.

Brian Koffman: 00:59:10 But the most impressive thing is they looked in my bone marrow, which had been heavily involved with CLL and they could find no trace of CLL down a one in 100,000 or one in a million cells.

Demetri Kofinas: 00:59:21 It just wiped it out.

Brian Koffman: 00:59:22 It wiped it out. It also wiped out a lot of my normal cells and other things. But all of those grew back. But 18 months later, when I was rechecked in my peripheral blood, there was no evidence of CLL.

Demetri Kofinas: 00:59:34 How soon after the dosage was administered, how long after that did you get the initial check that gave you-

Brian Koffman: 00:59:43 One month.

Demetri Kofinas: 00:59:43 One month. What was that like? What was it like seeing that? So, I assume you were also seeing this as a doctor, you were seeing these results. You were looking at the numbers, you were looking at the images in some cases, I imagine.

Brian Koffman: 00:59:55 Oh, yeah.

Demetri Kofinas: 00:59:55 What was that like for you?

Brian Koffman:	00:59:58	There's two parts here. Anxiously waiting like any patient and it was an unbelievable celebration. You just can't believe. It's like for the first time in, I've had the disease for 14 years, so this would be about 12 and a half years into it.
Demetri Kofinas:	01:00:15	And we skipped the Ibrutinib.
Brian Koffman:	01:00:16	Yeah, and I want to get to that too.
Demetri Kofinas:	01:00:18	We'll get that too. This, which we did before that, which was also extremely helpful.
Brian Koffman:	01:00:21	Yeah. For the first time in 12 and a half years, I had no detectable CLL. I could've gone, I couldn't have gone because I had other things. But if you tested me now, if I lied on an insurance physical, there would be no evidence that I have leukemia. There's no evidence at all. It's gone. It was an unbelievable celebration for us. We were restricted in terms of what we could do to celebrate. But we went out and had a nice dinner.
Demetri Kofinas:	01:00:48	What was that like? What was the town like?
Brian Koffman:	01:00:48	And it was like-
Demetri Kofinas:	01:00:49	All of you, the six of you?
Brian Koffman:	01:00:50	Well, this is up in Seattle. It was my wife and I at that point.
Demetri Kofinas:	01:00:54	Where did you go to dinner?
Brian Koffman:	01:00:54	We were just unbelievably happy. We went out. So, I'm vegan, but I ate some vegetables.
Demetri Kofinas:	01:00:59	Have you always been vegan.
Brian Koffman:	01:01:00	No, since my diagnosis 14 years ago. I figured out I got cancer, I don't need heart disease and other stuff.
Demetri Kofinas:	01:01:04	And it helps with the inflammation for sure.
Brian Koffman:	01:01:07	Yeah, absolutely. But we went out in Seattle. So, we went out for some incredible salmon, fresh salmon. It was just great. Then we did something that I was nervous about, but we took one of these scenic tours on a sea plane over Seattle. You know the pontoon planes that land on the Lake and take off and tour the Seattle area? We did that, which was incredible.

Demetri Kofinas: 01:01:29 Does this mean that when you got tested, also your other levels began to become more normal, like your platelets?

Brian Koffman: 01:01:36 Yeah. Eventually maybe-

Demetri Kofinas: 01:01:36 So to normalize as well?

Brian Koffman: 01:01:38 Yeah, they took a while to come back up, but they came back up and if you look at my blood count now, I'm not anemic. My platelets are in the normal range. My other white blood cells are in the normal range. My lymphocytes are ironically low rather than high because I have no B-cells and B-cells make up the majority because we don't have a marker that's pure enough at this point to only attack the CLL. So, it also attacks my normal B-cells. So, I make no antibiotics. Like I say, I don't get a flu shot because a flu shot won't work for me because I don't make any antibodies. I have no-

Demetri Kofinas: 01:02:10 They were the collateral damage.

Brian Koffman: 01:02:11 They were the collateral. So, I have to get an intravenous immune globulin. I'm dependent on the kindness of strangers. I get this pooled blood product every six, seven weeks to keep my immune system intact.

Demetri Kofinas: 01:02:23 What was that phone call like your kids since your kids weren't in Seattle?

Brian Koffman: 01:02:26 Right, yeah. It was an amazing, and we set up a Skype, a Zoom call and everybody-

Demetri Kofinas: 01:02:32 So exciting the anticipation to tell them the good news.

Brian Koffman: 01:02:33 Oh God. It was unbelievably great because that's why we went up there. I recognize that I'm lucky, not everybody can walk away and move to Seattle for two months. It's a major commitment. Though it's a clinical trial and things get paid for, and I have good health insurance, you're still living in a hotel room for a couple months because we got what we came for. we came up, there was no guarantee. I mean, the trial data was good, but it wasn't like 100% of people were getting this into complete remissions. So, we were unbelievably thrilled and we were on a high, and I'm still on that high 18 months later.

Demetri Kofinas: 01:03:07 So this is a year ago?

Brian Koffman: 01:03:07 18 months ago.

Demetri Kofinas: 01:03:08 18 months ago.

Brian Koffman: 01:03:09 18 months ago. When I've talked to the researchers, life doesn't have guarantees, but generally the higher the expansion of the T-cells, like we talked about, and the deeper the remission you get, most people don't relapse. Have I hit it out of the park? It's just the home run. Is this like Leonard Cohen says, the card that is so high and wild, I'll never have to deal another? I don't know that it's that, but I'm hoping. I mean, is this potentially curative? It's way too early to say. There are only a handful of patients that are more than five or six years out, but there are a handful of patients that are five or six years out of, had no relapse of their CLL.

Demetri Kofinas: 01:03:48 Well, this brings us to something else, which is that statistics are almost useless in these types of situations. I mean, you could look at what the general prognosis is, but that could be totally irrelevant in your case.

Brian Koffman: 01:04:04 So when you look at statistics, you have to make sure you're comparing apples to apples. When you're looking at a group of people, and if you're a 65-year-old and the group that they're comparing is an 80-year-old, those statistics may not apply to you. Or if they have certain prognostic markers and you have different ones, you have to make sure that. And of course, statistics can predict with great certainty what's going to happen to a group of individuals with great certainty, but it's a complete mystery what's going to happen to any individual in that group.

Demetri Kofinas: 01:04:33 But it is also backwards looking, right?

Brian Koffman: 01:04:34 Right. It's complete mystery what will happen to any individual because you can't tell who in the group. There's some in the good groups, some of the bad group will do well and all statistics like you say are looking backwards. One of the things I say to patients, never a good time to have CLL but there's never been a better time to have CLL because the treatments are so much better except for tomorrow and the treatments will leave me better tomorrow because it keeps getting better all the time. So, people who got those kinds of deep permissions tend not to relapse. That's what I'm hoping, I'm hoping in that group. But don't know.

Demetri Kofinas: 01:05:06 Well, you can't. I mean, you can't sit and worry about that. Right?

Brian Koffman: 01:05:09 Right.

Demetri Kofinas: 01:05:10 I mean, that's the most important.

Brian Koffman: 01:05:10 But I still get a blood draw. And again, I worry until that comes back.

Demetri Kofinas: 01:05:12 Sure, every time when you have to do that --

Brian Koffman: 01:05:15 Yeah. And every time I see the doc and he checks for my lymph nodes and all that stuff. But I'm getting used to being, having normal results. I'm getting used to expecting having a low lymphocyte now.

Demetri Kofinas: 01:05:25 Brings us back to that thing that you said, which is this, you put yourself in a place that you'll tell the patients that you work with, which is to underreact. And now you're getting to a place where you want to be more normal in your reaction now so that you can begin to live a more normal life. And that's the challenge.

Brian Koffman: 01:05:44 Right. I only get each day once and I tried to live it in the more normal way. I mean, it's not like I'm, even though I have a depressed immune system, I still get on a subway in New York. I still get on an airplane. You have to live your life. You have to take some risks and do what you have to do to complete the things that are important to you.

Demetri Kofinas: 01:06:06 So I want to make the best use of our time. I want to touch on the targeted therapies and then try and extract the most important things from this. And also touch on the advocacy work you're doing, which I think is very important generally speaking and also specifically for those people that might be able to benefit from it. So, let's talk a little bit about what you did before CAR-T cell therapy, which was Ibrutinib, which is one of these targeted therapies.

Brian Koffman: 01:06:31 We left out a window there between failing the transplant and getting to CAR-T. And it's all about timing because if I'd been diagnosed with CLL five years earlier, there wouldn't have been any options. I wouldn't be here for this interview. That's absolutely true. And if I diagnosed five years later, I probably never would have had a transplant. I want to just jumped to Ibrutinib. So, after I was relapsing, there was great controversy about what to do and how to treat the CLL and every center had its own approach. And when every doctor has a different opinion, that means that there's no good way to treat it. There's

no diversity of opinion about how to treat a hernia. Everybody does hernia surgery. It's not like there's a controversy about it or how to treat a strep throat. Everybody gets penicillin if they're not allergic.

Brian Koffman: 01:07:15 But in CLL there was all this controversy and suddenly at one of the major meetings in American Society of Hematology, there was this buzz about this new drug that didn't even have a name. It just had letters, PCI-32756 and it was a small molecule. Small molecules mean not broken down by the GI tract, so you can take it orally and it was a target-

Demetri Kofinas: 01:07:34 That's a big deal also.

Brian Koffman: 01:07:34 That is a big deal for patients. It's a targeted therapy. And again, like any new drug, it was used on the worst of the worst patients. Again, these patients with two legs in the grave, were getting this drug.

Demetri Kofinas: 01:07:47 That's also really important in terms of the conversation we had earlier about statistics. Because so many of the patients that are getting these experimental therapies are the worst of the worst.

Brian Koffman: 01:07:57 Right. That's where all these drugs start, is with the worst of the worst. With people who don't have other good options.

Demetri Kofinas: 01:08:02 The implication being that if they're working for those patients, imagine how well they'll work for other people at an earlier stage? And their immune systems may not be as compromised, et cetera, et cetera.

Brian Koffman: 01:08:10 Right. And to be able to move them up, that's more difficult. That gets us to a whole other issue that maybe we'll have time to talk about, which is equanimity and trials and how do you do that? But what happened here is there was this buzz. All of a sudden, the doctors at Mayo and the doctors at UCSD and the doctors at Ohio State and the doctors at Dana Farber and MD Anderson were all in agreement. There was something new happening in the CLL space. And this never happened before.

Brian Koffman: 01:08:36 They were all agreeing. They're all talking about a couple of new molecules. There was this one and another one called CAR 101, which later become idelalisib, and they were changing the way CLL would be treated. And I said, I've got to get me some of that because I relapsed after transplant. Things didn't look good. I was chemo refractory. So, I walked in the hall at the American Society of Hematology meeting and introduced myself to John

Bird who was a researcher doing one of these therapies and I got him to pencil me in for his trial in Ohio State and I fought to get the insurance to cover it because I was going out of state, but there was no trial in California and I jumped into a phase one trial. I'm an early adopter, like I said, a phase one trial of this drug and I picked right.

Brian Koffman: 01:09:20 This drug works in a very interesting way. The whole raison d'être, the whole purpose in life for a B-cell is to communicate with other cells and say, Oh, I need to form an antibody. You need me, I need to reproduce and make more antibodies. And it does this through the B-cell receptor or a BCR. It's like an antenna on top of the cell and it gets all these signals from other cells saying, stay alive, proliferate, help us. Well, the problem in CLL is it's chronically turned on, it's very promiscuous, it couples with anybody and everything and it's always getting this message that you're important, stay alive, it never dies and it keeps having babies.

Demetri Kofinas: 01:09:59 That's the malignant component.

Brian Koffman: 01:09:59 That's the malignant component.

Demetri Kofinas: 01:10:02 That's cellular mitosis component.

Brian Koffman: 01:10:03 Right. So, what the BTK or bruton's tyrosine kinase inhibitor did was downstream from this B-cell receptor on its way to send a message to the nucleus to stay alive, make more DNA, keep reproduce, make more antibodies. It blocked that, it snipped that off and the B-cell lost its purpose in life. It didn't get any messages to stay alive and it lost its homing mechanism that say, stay in the protective niches where your homeys in the bone marrow and the lymph nodes can protect you and where you can reproduce. It floated out into the bloodstream, which is easier to kill, like shooting fish in a barrel. They eventually died of loneliness. It wasn't like a rapid kill, but he just died off because they had no reason to stay alive. So, they just eventually died. The PCI-32765 which later became my Ibrutinib and other drugs like it worked very slowly and gently. And what was ironic, and this is an important piece, is when you first take them, your white blood cell count goes up, which people thought, oh my God, the disease is progressing.

Brian Koffman: 01:11:11 But the cancer is leaving the lymph nodes, leaving the bone marrow going into the blood. It's changing the compartment-

Demetri Kofinas: 01:11:17 It's disproportionally represented in the bloodstream.

Brian Koffman: 01:11:19 Right. So, it looks like the cancer is progressing but eventually comes down. That eventually can take two, three years to come down.

Demetri Kofinas: 01:11:26 Now, how visible is the transformation for the lymph nodes?

Brian Koffman: 01:11:30 I'll tell you a personal story on that. So, I started Ibrutinib. Two days later, I'm in the shower, and when you're a cancer patient your always [inaudible]. And I'm feeling, is it possible after two days my lymph nodes are getting softer and smaller? And it was two days later.

Demetri Kofinas: 01:11:45 Because they're dumping these B-cells.

Brian Koffman: 01:11:47 Yeah, it's dramatic.

Demetri Kofinas: 01:11:48 How soon after this did you get to shave your beard?

Brian Koffman: 01:11:50 Pretty quick. I kept a little trim here for a while in case I needed it. So, when you see that, there's a portrait of me on the website, I kept that little bit of a thin beard there, but I eventually got rid of it. I had grown attached to it, but I didn't have to do the big Santa Claus.

Demetri Kofinas: 01:12:05 You didn't need it though.

Brian Koffman: 01:12:05 I didn't need it.

Demetri Kofinas: 01:12:06 Long after you didn't need it.

Brian Koffman: 01:12:07 Yeah. So, I was able to do that. But the most important thing was I went into this deep, deep remission, but my cancer is mutagenic. It tends to mutate around things.

Demetri Kofinas: 01:12:18 That's generally true, isn't it?

Brian Koffman: 01:12:20 Well, some cancers are slower growing than others, but that's why you want orthogonal or right angle treatment so you kill cancer this way and you kill it that way. So, if it mutates around this problem, it cannot mutate around a different kind of problem. That's what they're looking at in combination therapies. That's why we use drug cocktails and stuff. But this non-chemo therapy approach that I was this early adopter of, is now becoming the standard of care in CLL. In the American Society of Hematology meeting last year, it was compared to the gold standard chemotherapies for people under 65 over 65. In almost every circumstance, it was superior to chemotherapy.

I was lucky in that I chose the right drug. But it's the prepared mind that gets lucky.

Brian Koffman: 01:13:08 I had done my research and I said, this looks exciting, but I got five or six years out of it. And that was long enough, just long enough to where the phase one trials of CAR-T therapy were starting. When I jumped into the CAR-T trial, I was patient 36. I wasn't one or two where they were figuring out the dose. I was patient 36 and only one patient had died at that point. They figured out the cytokine release, they knew how to control it.

Demetri Kofinas: 01:13:39 The CRS.

Brian Koffman: 01:13:40 Yeah, the CRS. Yeah.

Demetri Kofinas: 01:13:41 So this is like 2012 you started this therapy around then?

Brian Koffman: 01:13:44 No, so Ibrutinib would have been about 2012.

Demetri Kofinas: 01:13:48 Yeah.

Brian Koffman: 01:13:49 Yeah.

Demetri Kofinas: 01:13:50 That must've been very exciting.

Brian Koffman: 01:13:51 It was incredibly exciting. I was thrilled. Again, there was a thought that for some patients who got Ibrutinib front line is their first therapy and hadn't been beaten up like I'd been beaten up with a transplant before. Some of these patients are still on the Ibrutinib seven or eight years later and have not progressed.

Demetri Kofinas: 01:14:11 The progression happens because the cancer mutates to work around this pathway shutdown.

Brian Koffman: 01:14:15 We don't understand all the reasons that cancer progresses, but we do understand a couple of the most common ones with Ibrutinib. So Ibrutinib irreversibly bonds to the BTK and there's a pocket it bonds into. The cancer cells mutate so it can no longer bond, so it loses its efficacy. That's the most common way. Then when I got, which is less common, which is downstream, there's a gain of function. So, I turned a gene on that normally is only turned on if the BTK triggers like dominoes, but my gene learned to turn itself on, so it was a gain of function mutation that I had that turned on the BTK pathway again.

Demetri Kofinas: 01:14:54 There are so many things, we have a limited amount of time and I want to make the best use of it. I want to, before we get into the advocacy component and some other things, I don't know if I mentioned it, but one of the things I've also learned in researching this is that because blood cancers can be easily biopsied, all you need to do is draw the blood. This is in some ways the frontier of some of these targeted or immunotherapies because you can more readily test them. What is the prospect for these types of therapies for other cancers?

Brian Koffman: 01:15:27 Important question. The reality is that blood cancers are the poster child for targeted therapy. So, the first targeted therapy was Imatinib in CML. So, Dr. Mukherjee won a Pulitzer prize for writing about the emperor of all Maladies about that kind of thing. And the reason is that if you have breast cancer, we can biopsy it and we can save the specimens, but we can't biopsy it again a month later or three months later. But with blood cancers, I can get blood drawn and a week later I have another blood drawn and a month later I have another blood, and we can see how things are going. We can look at certain genes, are genes being upregulated, down regulated, under expressed, over expressed? What's happening? Is the cancer mutating, is there a second strain, is there a subclone? That all can be done. So, we can trial these drugs first. And it turns out that there's a limited repertoire on what the cancers can do in a lot of these anticancer drugs and anticancer antibodies also work for solid tumors and other things like that.

Brian Koffman: 01:16:23 The blood cancers are often on the front edge of how we're learning to advance cancer. So, it wasn't without reason, the American Society of Clinical Oncology, I think it was in 2015 named CLL the cancer of the year, it's almost like being dictator of the year. I mean would have been, but what they're saying is cancer advance of the year. Then last year they named CAR-T therapy is the cancer treatment advance of the year. So, there's a reason because it's easy to do this stuff. It's noninvasive or relatively noninvasive to monitor this and get good data. And every time I get blood drawn, I get an extra six tubes drawn because they're being sent to the Hutch or they're being sent to UCSD or they're being cryo-preserved so that somebody can say, Hey, I want to see somebody who's at this stage of their cancer with this and this. Can I measure this enzyme level? I got a hunch here that there's some going on. That's what all of us cancer patients do. You can't do that in other cancers to the same extent.

Demetri Kofinas: 01:17:19 So during this entire process, how did your CLL society come about, which is your nonprofit organization?

Brian Koffman: 01:17:28 When I was stepping away from being a family doc, because I was going for a bone marrow transplant, I was writing emails and stuff and my kid said to me, "Dad, that's so old school. Nobody reads emails anymore. You need a blog." So, I started blogging and I think Dr. Koffman's Amazing Cancer Journey, I can't even remember now. I was blogging, the blog got really popular for this orphan disease where the average age is 72 years old. There're 22,000 new cases a year. So, it's unlike breast cancer where there's more than a quarter million cases or more. It's entirely different kind of numbers.

Brian Koffman: 01:18:05 I started tele blog, 20,000, 30,000 people were reading the blog at a time and following my story. Then when I went into the Ibrutinib trial, the PCI-32765, it became even more wildly popular. I was leveraging my background as a family doctor to get interviews with docs and I was going to all the major conferences and stuff and I was telling my story. But it became clear after a while that I was telling it in this chronological order. And there were people who were newbies who were jumping in who didn't know what a B-cell was, didn't know what the spleen did, and it's somewhere in my blog, but you might have to go back eight months to find when I posted about that. So, it seemed like instead of working vertically, had to work horizontally.

Brian Koffman: 01:18:48 I set up a website for a nonprofit, went through the IRS approvals to get a 501(C)3 not for profit, and we set up this website that looked at things in a horizontal. We have a basic section for people who don't know the beginning of what CLL, what is CLL, how's it diagnosed, what's a complete blood count? We have spreadsheets for people to follow their lab results. We have a glossary of terms. We explain all the acronyms. We have a list of CLL doctors, but we also have an advanced section where people can learn the latest on CAR-T therapy or other things like that. We go to all the major hematology conferences and report from them on the latest research. You're not going to be able to follow that unless you've gone through the basic and other stuff, but it's all there.

Brian Koffman: 01:19:33 It's more searchable, it's more accessible. But we also know that some people don't learn on the web. So, we have 30 different support groups across the country in the US and two in Canada. And that peer-to-peer relation is nothing more powerful than sitting across the table from another CLL patient who's had the disease for 15 years, has been through three clinical trials, and it

looks great and it's doing well. What he can tell you is much more powerful than what another doctor can tell you about the survivorship. So, we have a whole program that we facilitate and help people with that.

Demetri Kofinas: 01:20:09 That's incredibly important.

Brian Koffman: 01:20:11 It's unbelievably important support groups.

Demetri Kofinas: 01:20:13 That's incredibly important.

Brian Koffman: 01:20:14 Yeah, we're really big on that, but we have standards for them. We have all kinds of rules for how to engage with that because we can't give medical advice. We have to respect confidentiality. But it's been a wonderful thing and we're constantly growing and training new people for new support groups across the country. We also do 12 educational forums a year at places like the National Institutes of Health or Dana Farber or Ohio State or Mayo Clinic or Cleveland Clinic. If it's a CLL place, MD Anderson, Swedish Hospital, if it's a CLL place, we're training people, we're teaching people about CLL. And unlike other conferences, half our conferences are patients and caregivers talking about their journey and the other half is hematologists talking about the latest research in CLL. We do half day conferences, but we also do research. We've presented papers for three over the last four years at American Society of Hematology.

Brian Koffman: 01:21:07 Done the largest survey ever of CLL patients. We're publishing peer review journals. And this is all with this old non-for-profit with four people. I also want to point out a program that I'm incredibly excited about, which I think is potentially disruptive to medical care if we can get enough support and resources for this. We're actually publishing research on this, ASH, the American Society of Hematology. We had a paper that was accepted there and we know that there's a survival advantage to having an expert on your team if you have CLL. This is so true in rare cancers because the doctors don't have experience treating it. So, Mayo did a clinic and showed that there's about a two-year survival advantage just having a CLL expert on your team. But not everybody can do that because they don't have the insurance, they don't have the dollars in the bank.

Demetri Kofinas: 01:21:52 The cost is enormous.

Brian Koffman: 01:21:54 Right.

Demetri Kofinas: 01:21:54 I've looked at some of the costs, especially of course we do CAR-T cell.

Brian Koffman: 01:21:57 Right, but even not doing therapy, just getting a second opinion. I won't mention the name, but I called a very famous cancer center and I said, "I'd like to get a second opinion there." And they said, "There's a $20,000 down payment to get the second opinion." This was not to get any therapies, to get the bone marrow CAT scan, BAD scan, all this stuff that they do, lab stuff, 20,000 bucks to walk in the door for them to make a suggestion as to what therapy would be done. Because-

Demetri Kofinas: 01:22:24 Why is it so expensive.

Brian Koffman: 01:22:25 Well, first they all want to do their own stuff. They don't trust where you had a CAT scan done.

Demetri Kofinas: 01:22:29 So that brings us also into a question of litigation and liability and the litigious healthcare system that we have, which may be too big of a conversation to have. I mentioned it, I know this very well because everyone in my family is a physician. I've endured many rants from my father and my uncle and my cousin or my aunt about this, that or the other thing. There're so many well-intentioned regulations that ultimately have very bad unintended consequences as a result.

Brian Koffman: 01:22:59 So we recognize that there was this problem or some people just geographically or they have insurance, they have Veteran's insurance and there's not a CLL expert or they have Kaiser insurance or whatnot. Nothing wrong with those docs there, but they couldn't get to a CLL expert. So, we offer, it's underwritten by pharmaceutical, free consult online, HIPAA compliance, so it's completely confidential. We consolidate their medical records, we go through their electronic medical records. We provide a synopsis to a CLL expert at places like Harvard or Ohio State or UCSD or city of hope. Top, top centers in the patients get to spend a half an hour of face time with a doctor asking their two or three most important questions after the doctors review their medical records.

Brian Koffman: 01:23:48 We write up a synopsis and that synopsis goes to their doctor in rural Texas or in Nebraska where they don't have a CLL expert. Then that doctor has the benefit of a consult from Harvard. So, the expensive program-

Demetri Kofinas: 01:24:00 So these physicians are participating pro bono?

Brian Koffman: 01:24:03 No, we pay the physicians and we pay the platform that does this, but it's based on a grant that we put together. It's underwritten by pharma and the donations we get. So, it's free to the patients. It's not free to us. It's by far, our most expensive program. But we're presenting data on 105 patients that we did this for, but the data is embargoed right now, so I can't share it with you. But let me just say this, that we made differences. We saved lives. We got tremendous gratitude, not just from the patients, but from the community hematologists who said, "Oh my God, I didn't realize I learned something here. This is the first patient I ever did this for." We are changing lives with this technology, so that's another one of our many programs that we do.

Demetri Kofinas: 01:24:47 So this is a moment here where I think we can offer some really important practical advice, which is how to navigate that line between being an informed patient and being a burden or disliked by your physician because you're spending a lot of time on Google coming in and presenting him or her with information that may or may not be accurate. It also brings up the challenge of, again, you said something earlier, it had to do with the fact that if you Google online it can be very dangerous because forget even what information you're going to learn and you're going to give your doctor. You could get incredibly depressed when in fact you shouldn't be at all. Because what you're looking at is again, historical data that has no relevance to your outcomes whatsoever.

Demetri Kofinas: 01:25:35 How do you navigate that? What do you tell patients? What do you tell people, because I guess also people are coming to you after they've already learned about it, but how would you suggest that people proceed to be their own advocate first and walk that line in order to get the help they need in order to make the best decisions possible knowing again that plenty of physicians don't necessarily know what the latest science is?

Brian Koffman: 01:26:03 Becoming your own advocate, I think is critically important. And I have a bias. When doctors give talks, we have given disclosure since I got this money from this pharmaceutical or that money and my disclosures are my biases, which my bias is towards novel therapies. My bias is towards clinical trials. My bias is towards shared decision making and my biases is to expert physicians taking care of you. These are my biases that I bring to the table. So how do we get patients to be aware of these kinds of things and advocate for themselves? For some patients, they can become quite an expert themselves and we have a ton of stuff to educate and you have to be sophisticated on the web. But there are sites like our cllsociety.org, cllsociety.org and

other sites like the Leukemia Lymphoma Society or Lymphoma Research Foundation that have very well curated sites that are position reviewed and they can get really good quality information on.

Brian Koffman: 01:27:04 But for some patients, they don't want to do that. So, can they outsource that? And the answer is yes, they can outsource that, but they need to outsource it to someone who knows CLL. Is there a doctor out there who's going to say, I'm inadequate to treat? Well, there's a few, but most of them, this may come as a big surprise, but some doctors have ego issues and they feel like they could treat anything and they don't know what they don't know. So how do you-

Demetri Kofinas: 01:27:27 They don't want to say that they can't treat you also, that's another thing.

Brian Koffman: 01:27:29 Right.

Demetri Kofinas: 01:27:30 Even in some cases where they might be familiar with other therapies, they may not tell you about them or send you there because again, ego and there are all sorts of reasons.

Brian Koffman: 01:27:39 There's all kinds of reasons, some of which are more nefarious. Yes.

Demetri Kofinas: 01:27:42 Yeah, they're hard to believe actually, but it's unfortunate, but continue please.

Brian Koffman: 01:27:46 So how do you pick a CLL doctor? It's tricky because this is an issue that we have. How do we list people to CLL doctors? So, we asked a bunch of CLL docs how they recognize a CLL doctor. What essentially, they all did was look in the mirror and say, oh a CLL doctor, and they describe themselves. But what is that description? That description is someone who mostly sees CLL patients. Like more than half their practice is CLL patients. So, they're not seeing a lot of breast and colon, they're just seeing CLL. Maybe they see some other blood cancers, but mostly it's CLL. And if it's not CLL, it's a related B-cell lymphoma that's similar and they're doing research in CLL. Most but not all are at academic centers. That's what you need to do, is have one of those people on your team. And if he can't do that, then we can provide that access through our expert access program.

Demetri Kofinas: 01:28:32 Can we just really emphasize how important that is? I don't know that people really understand how big of a difference it is if you have a physician on your team who actually spends time

with this particular illness. And this is true across the board, not just for CLL, it's for anything.

Brian Koffman: 01:28:48 If you have appendicitis, you don't want your surgeon to have done one appendectomy in the last year. You want somebody who's doing them all the time and you don't want them to do an appendectomy like he did them 30 years ago when he went through medical school and his residency. You want somebody who's up to date and doing things latest way.

Demetri Kofinas: 01:29:07 The science curve shifted tremendously from what this person is aware of.

Brian Koffman: 01:29:11 Right. So, you want somebody who's got experience, who knows the nuances, and there are so many tragedies out there that we see. The low hanging fruit for us in the CLL world is we have these fabulous treatments that are available now, but so many of the patients aren't getting them.

Demetri Kofinas: 01:29:30 They're not aware of them.

Brian Koffman: 01:29:31 They're not aware because they don't know and their doctor doesn't know or they don't know how to use them or they're frightened by them. And there's different buckets of CLL and there are these, we talked a little bit about the prognostic and predictive markers. Well, they're not absolute, they can be extraordinarily helpful. But we know from real world data that about four to 10 patients is not getting the appropriate testing at times that they need them. So, people are getting therapies without being tested to see whether they're appropriate. And even when they're tested and there's markers that say, chemo isn't going to work for you, we know a significant percentage of patients are still getting chemotherapy.

Brian Koffman: 01:30:14 This is the low hanging fruit. These are lives that we can save and we have saved them through our expert access program where a patient was going to go one way, we gave them this opinion, they took her to their doc, the doc said, "Good idea, let's do that testing first. Oh, thank God we did the testing. I'm going to treat you a different way because I didn't know that. Because what I planned wasn't going to work." So, we've done that but I want to reach everybody, that's what we try to do. There's four people in our little not-for-profit. I listed some, not all the things that we do. We're looking for resources and support to grow what we're doing so we can reach out to more people and make more people aware. That's the low hanging fruit for us, is to get the people the best care that's available now because that's excellent for a lot of people.

Brian Koffman:	01:31:05	Our other big mission is a curative therapy and we don't really have that yet. We're getting close, but we're almost a victim of our own success, Demetri. Because we have drugs that are so good that people are backing away saying, well, I'm going to go after another cancer where the prognosis-
Demetri Kofinas:	01:31:21	I mean, researchers.
Brian Koffman:	01:31:22	Researchers, if you're a young hematologist or oncologist and want to make a name for yourself, you're not going to go into CLL because you're not going to make a big name for yourself because it's done and dusted. It's not-
Demetri Kofinas:	01:31:35	You're not going to get federal funding.
Brian Koffman:	01:31:37	It's much harder to get funding from people. It's much harder to advance your career and the pharmaceutical companies are saying, when I've got a drug that has a 90% response rate and I've got to beat it, it's going to be hard for me to get my drug to the market.
Demetri Kofinas:	01:31:50	What about the fact that this is again, the poster child for some of these advanced therapies? Isn't there a case that he made that this is the best place to experiment?
Brian Koffman:	01:32:01	The case to be made is that blood cancers are the best place to experiment.
Demetri Kofinas:	01:32:04	Exactly.
Brian Koffman:	01:32:07	But it may not be CLL. It might be a different blood cancer where the prognosis is worse.
Demetri Kofinas:	01:32:10	I see what you're saying.
Brian Koffman:	01:32:10	There's still a lot going on and there's still stuff going on in CLL but there's less. So, that's our second goal. That's a much bigger goal, is we want to encourage young hematologists to dedicate their career. So, we have the people that brought us all these breakthroughs made their career in CLL, but we want to make sure there's a new generation.
Demetri Kofinas:	01:32:32	How do you do that?
Brian Koffman:	01:32:34	You support their research, you fund their research. So, you give them a dedicated day or two a week in their postdoc time to say, I want you to research. You get competitions together and

say give us four or five research proposals and we'll fund you for three years of research and you get outside people to judge, which is the best research. This is not happening so much in CLL.

Demetri Kofinas: 01:32:56 So there's a grant writing arm to your organization. So, a very big part of this is about raising funds?

Brian Koffman: 01:33:02 You bet. It's not just for me, it's for any not-for-profit and any 501(C)3 because there's so much more we can be doing. Like I said, the low hanging fruit is getting everybody the best possible care, but the other thing is to find a curative care and the research money is starting to dry up in CLL and we want to be able to fund that. But that's a big budget item to fund a research. But we have a really strong medical advisory board and our thought is the best bang for our buck is going to be getting young fellows, young researchers, giving them a grant, try to get their institutions to match that grant, give them three years, pick what we hope are going to be winner projects to move forward on this so we can develop stuff. That's the kind of thing that we think we can do within our reach with just a little more grant funding.

Demetri Kofinas: 01:33:50 So how do people get involved to help? How can people donate to your organization? How can they participate in this process to try and tackle that second component, which is finding a permanent cure for CLL?

Brian Koffman: 01:34:05 Well, thanks for asking that question, Demetri, I appreciate that. So, the easiest way is to go to cllsociety.org and we have a donate button right there and there's all different kinds of ways and people want to, they can actually reach out to me. I'm very accessible. I'm all over the web, B for Brian Koffman, K-O-F-F-M-A-N@cllsociety.org, bkoffman@cllsociety.org. They can email me, I can have a discussion with them, I can help them with that. But we're pretty accessible. We're pretty out there in the community, but that would be the best way to reach out.

Brian Koffman: 01:34:37 Well, just go to the website or if they have particular questions or want to look at us in different ways or have a conversation with me, it would be great if they could just email me, bkoffman@cLLsociety.org. That would be another way to do this because we're leaving patients behind that aren't getting the care that they need and it's getting harder and harder to do more and more of the research we need. I'm not saying we're the one of the national institutes of health and other people are still doing it and we need to push for more of these therapies. More with the CAR-T, more of the things we need to find ways

to get these things paid for, because there are a lot of issues that we're involved with.

Demetri Kofinas: 01:35:17 Well, the person that put us in touch, he knows another individual whose father apparently you saved. I can't say enough about this low hanging fruit that you call it the low hanging fruit. I think it's hard for people to understand just how big of a deal it is to be educated because I think people have this expectation that somehow there's this uniform medical establishment and that the information is just there. I know from my own personal experience, having gone through a brain tumor diagnosis and seeing literally doctors within walking distance in some cases of one another at Columbia, at Mount Sinai, at Cornell, and getting completely different diagnoses to the point where the outcomes would have been totally orthogonal. In one specific case, in the case of Colombia, this physician I think was very well aware of what was happening down in Cornell, but for whatever reason didn't bring it to our attention.

Demetri Kofinas: 01:36:22 That is a remarkable thing. So, I want to say there's reason for hope. There's so much reason for hope, not just generally speaking in terms of what's happening in the advances that I'm aware of that you're so much more aware of than I am, but just in education. And I think overcoming the fear and engaging with the material, I think you guys have really made that much easier with your organization on the website. I did some of that just preparing for this conversation and I know that if you're a patient, it's scary. It's daunting to engage with that. But I think if you are a patient or if you're anyone that if you've got loved ones that are going through something like this, it's so important to engage with the material and I think that fear begins to melt as you confront it.

Brian Koffman: 01:37:07 So let me respond to that a couple of ways. The first is your experience, which I think is a very common experience in CLL. One of my mottos that I say to patients, I have different commandments that I teach patients in dealing with this is one, that you're going to have to make life changing decisions with incomplete knowledge and conflicting advice. Life changing decisions with incomplete knowledge and conflicting advice. There is absolutely no question because if it's easy to treat, then it's easy to treat and everybody does the same thing. But it's not that way with a lot of brain tumors and it's not that way in CLL. That's one thing I want to say. The other I would say is there's a lot of patients who come to their very first session in one of our support groups and have that deer in the headlights look and

you're using language and they don't know what a lymphocyte is and people are saying-

Demetri Kofinas: 01:37:58 And even those words are super scary. Some of those words are scary.

Brian Koffman: 01:38:00 Right, and there's all this medical leaves and there's the experienced patients who are doing this. I will tell you, it washes over you and you can get better with that, but you can also outsource this. You can outsource this to an adult child. You can outsource this to a spouse or you can outsource it to a CLL expert. If you have an expert who's doing this, you don't have to be a world expert yourself. A lot of people don't want to be and that's okay. But if you're not the expert, then you better have an expert on your team. You've got to do that because that's where the survival advantage is. I think you need to be engaged with your own therapy and there's ways to do that. We do a little teaching around that too. You want to be, the most precious commodity for all of us is time. And especially for docs, they don't have time.

Demetri Kofinas: 01:38:46 That's another tough thing. That's a very difficult thing because as a patient you want all the time in the world with your doctor and not just because you want to learn more, but because you want that emotional assurance that they care. It's hard to deal with this. And of course, the physician has to have some healthy emotional distance from the patient.

Brian Koffman: 01:39:03 Right, so when you present, one of the things that bugs me as a family doc is people will bring up the most important thing last.

Demetri Kofinas: 01:39:10 They're afraid.

Brian Koffman: 01:39:11 Yeah. I spend all this time on looking at their toenail and as I'm walking out the door, they say, "That crushing pain I get in the center of my chest when I climb the stairs, that's nothing. Is it doc?2

Demetri Kofinas: 01:39:19 They know it's important. They just, they're afraid to say it.

Brian Koffman: 01:39:21 Yeah, they're afraid to. Don't do that if you're a cancer patient, bring up the most important thing. It's unlikely the doctor is going to get to all five of your questions. So, make sure you ask your one and two first, that you get those in. Be concise, be factual. These are kinds of things you can do. And don't be afraid to be assertive if something's important to you. I also recommend bringing a recorder, bring your phone and turn it

on record. If your doctor doesn't want to be recorded, get a different doctor. Because my wife and I have walked out of consults and had completely different opinions of what's going on. Have some-

Demetri Kofinas: 01:39:53 Different recollections of what was said I imagine.

Brian Koffman: 01:39:54 Yeah, absolutely.

Demetri Kofinas: 01:39:57 Because you want it to hear a certain thing. Your cognitive bias is so strong when you're going into a meeting with a physician in such circumstances.

Brian Koffman: 01:40:04 So record it, bring your significant other with you to these meetings. Like I say, this is a family journey. I couldn't have done this without my wife and she listens and hears things that I don't hear and I'm listening differently because I'm a doc. So, it's critical. These are all practical tips in terms of what you can do to get the most out of those doctor's appointments. But becoming educated, our motto is, Smart Patients Get Smart Care. That's our motto. That's what we try to promote.

Demetri Kofinas: 01:40:34 I want to emphasize something you said about you making life changing decisions with incomplete knowledge. I think for many people it's a shocking experience because particularly for risk averse people, I think it's interesting you say you're an early adopter. I think that's to your advantage in these types of situations because you really are thrust into a circumstance that for many people it's completely undesirable. I mean, certainly the cancer itself is undesirable, but a circumstance of making these types of life changing decisions with incomplete information, and it's something that you really have to embrace. I think in my own experience, what helped me through this was embracing it and finding value in the journey, realizing that there is value in courage and there's something to that. This also, you said you're Jewish, you're a practicing Jew?

Brian Koffman: 01:41:27 Yeah.

Demetri Kofinas: 01:41:27 So you're religious in some sense. And I think that it helps to have some engagement with the mystery and not just seeing yourself as a sack of cells or whatever else. Dr. Koffman, there's so much more we could talk about. This is probably the longest episode I've ever done.

Brian Koffman: 01:41:47 Oh my gosh. Yeah.

Demetri Kofinas: 01:41:49 So we have to wrap it up. I appreciate you coming on. I mean, I want to give you the floor to end it with whatever you want to say. We gave the website out, what else would you like to say to our listeners?

Brian Koffman: 01:42:02 Well, first I want to thank you for the opportunity to do this. I think what we do is a model for what can be done in other disease states, other cancers, and we're anxious to grow and be able to reach the people that we're not reaching now. We're anxious to get the next generation of researchers out there and fund them. So, we are looking for help, people who are going to help us fundraise or people who can directly donate to us through the cllsociety.org. We're looking for that kind of help because what we do is going to make a difference.

Brian Koffman: 01:42:39 Some of the research in CLL is already starting to look like it's going to be helpful in lung cancer, breast cancer or other things like that. We know that we can make a huge difference beyond what we're doing, but we're also modeling different ways of being. This is all been essentially done from our kitchen table with a couple people. Now we've expanded, we've got four people but we're looking to grow this and make it bigger, make it sustainable and we need outside help to do that. So, if there's ways people know to help us in terms of developing resources, fundraising or that they can write us a check, we'd be extraordinarily grateful for that.

Demetri Kofinas: 01:43:18 You gave a lecture at some event in Ireland long ago.

Brian Koffman: 01:43:23 Yeah.

Demetri Kofinas: 01:43:23 Great lecture, I recommend for anyone that's either dealing with CLL specifically or looking for a really hopeful presentation, an honest but hopeful presentation and also a moving presentation because that's the one where your wife narrated this beautiful comic that your son put together. Again, cllsociety.org, is that the...

Brian Koffman: 01:43:46 That's right, cllsociety.org. All one word, CLLSociety.org.

Demetri Kofinas: 01:43:47 Cllsociety.org, and if they want to donate they can do that on the homepage. There's a donate button there?

Brian Koffman: 01:43:51 Right, at the top of the page.

Demetri Kofinas: 01:43:52 And I've put a link to that website in the description to this week's episode. I've let you all know that there is no overtime

to this week's episode because I wanted to give as much of this information out as possible. There is of course, a transcript available to subscribers as well as the rundown and an afterthought segment that I'm going to do after Dr. Koffman leaves today in place of the overtime.

Demetri Kofinas: 01:44:16 You can find all of that at patreon.com/hidden forces. There's a link to the Patreon in this description. But if it's an issue and you can't afford the subscription for whatever reason, given the nature of this material, email me. I don't know when I can get back to you because I get a lot of emails and I hope not to miss it. But if I see the email and if I don't see it, email me again and I'll get you a transcript and a copy of the rundown so you don't have to pay for it. Again, Dr. Koffman, thank you so much for coming on the program.

Brian Koffman: 01:44:47 Thank you for having me. It's been great talking with you.

Demetri Kofinas: 01:44:51 Today's episode of Hidden Forces was recorded at Creative Media Design Studio in New York city. For more information about this week's episode, or if you want easy access to related programming, visit our website at hiddenforces.io and subscribe to our free email list. If you want access to overtime segments, episode transcripts, and show rundowns full of links and detailed information related to each and every episode, check out our premium subscription available through the Hidden Forces website or through our Patreon page at patreon.com/hiddenforces.

Demetri Kofinas: 01:45:30 Today's episode was produced by me and edited by Stylianos Nicolaou. For more episodes, you can check out our website at hiddenforces.io. Join the conversation at Facebook, Twitter, and Instagram @hiddenforcespod, or send me an email. As always, thanks for listening. We'll see you next week.