Professor Elizabeth Helen Blackburn, AC, FRS, FRSN is an American biological researcher at the University of California, San Francisco, who studies the telomere, a structure at the end of chromosomes that protects the chromosome for which she won the Nobel Prize in 2009.

Lynn Hershman Leeson interview with Dr. Elizabeth Blackburn
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LH: How did you discover the telomere?

EB: The telomere was known just at the level of looking at microscopic pictures- not at very high resolution. It was known that it behaved as a predictadent chromosomes- instead of an unpredictadent- and so there was nothing known about the molecular nature of it. When the molecular technology started coming in the very early 1970's then I decided I really wanted to see what the molecular nature of the telomere was. By having the good fortune to be in a lab where somebody was looking at very small very abundant chromosomes- I could technically look at this. So the process was using emerging techniques for analyzing DNA. The question was- well, what are they like? Nobody knew what the end of a chromosome would be like- in terms of its DNA. That was a very interesting question to me, initially.

LH: So it was basically intuitive?

EB: It was an intuitive sense. I thought- this is going to be interesting. Every time you ask a question you're going to be surprised. This was one of these

things where you just want to know what it's going to be like- an explorative feeling- and you don't know what the answer is. You haven't come in with what's right or wrong initially- you want to look and find out. Then it becomes more creative in a sense and you start having ideas about what this means, how it might be the way it is, and what more you can learn. Then you have to start really thinking about how you can find out if this idea you have is working- if it's true. You have to have this kind of creative mix of what you can do and what the question is. Anybody can ask a question in Biology- unlike in Physics- there are so many possibilities that any fool can come up with a possibility. But it doesn't do any good if it's not grounded and rooted in what biology is all about- which is a history of how life developed.

It doesn't have rules that you think would be the way they are- you don't know what they are so you have to look at what has been done in biology and you learn from that. Then you say well you know a certain amount but you don't know a whole lot. You have to ask- is this a good way to ask a question that is worth asking. Its this continuous interaction between making a leap of thinking and also being totally grounded in reality because a fancy idea that has no reality is worth nothing in biology- because the goal is you're trying to understand the nature of this very complex, natural phenomenon that is biology. It's really complex.

Physics emphasizes finding the rules, and on some level- its much more predictable. In biology basically the predictions usually turn out to be things that were grounded in some real biology already. So if you don't know what the biology is then you have to step out of that and try to figure out what that is-always making sure that what you've discovered is actually going on and isn't just a figment of your imagination.

LH: Were you surprised by what you found?

EB: Very surprised! It was so fun. It was very visual – the sort of science we were doing then- you separated out DNA that had been radio actively labeled by tiny traces of radioactivity and you separated it out in a 2-dimensional array of products (which came from a chemical analysis of the DNA). There was a certain expectation. What you do is develop an x-ray

film- you're literally in a dark room developing an x-ray film- the film is opaque to begin with and as it develops- it becomes clear. When you hold it up to the red light to see what's there – there is this one very dramatic spot in a ray of spots- and it was like- what is this? It was very striking, and then there was a lot of science I had to do in trying to figure out what did that mean. Basically what it meant was that there was a DNA sequence- a little building block sequence that happened over and over again and the reason this spot got so strong was that it repeated fifty times at the end of every DNA molecule- so there were 50 copies of that sequence which added up to a very strong spot.

LH: What did finding fifty mean?

EB: We had no idea what that meant. Except that it was nothing that had ever been seen because nobody had ever seen the end of a chromosome. People had seen repeated sequences of a different kind, but this was so different that we didn't know what it meant. Then we noticed that it started changing- after I had found this sequence and analyzed its nature- then we found that it could really change. That really broke the rules- the bottom line was that it looked like there would be an enzyme that was making more of this that would add on these little building blocks. So that was the discovery of telomerase. It was looking at the DNA, seeing how it behaved in living cells, and letting the cells tell you that something is going on- then you try to work out what that was.

The crazy idea was that there was going to be this enzyme that exists and I said, well I know ideas are cheap. So then the hard work was to say I know there's such an enzyme that will add DNA to the end in little repeated sequences lets look for it in a biochemical way. That was what I did. My graduate student, Carol Greider, joined me and we both succeeded in finding that there was indeed this enzyme activity.

LH: What does that mean?

EB: What it meant was, first of all it was answering a big riddle in Biology and the riddle had gone like this- so you think back to DNA and the famous

double helix and every time a cell divides than the helix has to get replicated- its all compacted into chromosomes. There is a yard of DNA in each of your cells right- but each one of the DNA is really compacted so it looks like a little sausage.

So the enzymes that copy DNA are really good at copying the bulk of DNA but the way they're built they cant copy the extreme end. So when you replicate one DNA molecule and get two- actually one of them is a little shorter than the parents so you can see this is clearly a recipe for disaster if life is going to continue- this is not a very tenable situation. And yet that was what people knew in the early 70's about how DNA was replicated.

Then suddenly to have this enzyme that replenished the ends- just adding a sort of stuffer DNA on the ends- is basically all that was needed. It doesn't code for proteins or anything intelligent- its just filler DNA so that now when the DNA doesn't get copied all the way to the end, it's just some of those repeats that don't get copied. And this enzyme telomerase, as we named it, then that can add extra repeats and now if it's balanced out then they will never be shortening. It meant that it answered this riddle in biology.

LH: What will it mean to humans?

EB: Yes, so we are here and we have telomerase in our germ cells- we have telomerase in lots of our cells of our body. Then the question got really interesting much later and more recently. That was- we die when were elderly of diseases, and there are diseases of aging- does any of this reflect that if you didn't have enough telomerase than the cells would run down their telomereic DNA as they self produce. As the cell dies and reproduces- it has to have a telomeres to top off the end- what if it's not enough. What we're finding is it looks like in humans it can be limiting, as we get older. So does that have any impact on diseases that kill you?

Now there's this epidemiology-sort-of analysis that when you look at who is getting heart disease and who's telomeres are shorter, because if the telomerase cant finish the ends off- then the telomeres will get shorter and shorter. What we're finding is that this enzyme for who knows what

biological reason- it's just the way we are- its very limiting, we have a limited amount of it. It gets us through all of our growing up and reproduction- all that evolution for the species was supposed to have selected for.

Then the theory is that there's not so much selection for the elderly- although there's actually Iceland gnome studies that suggest that there's selection for grandmothers. There's this lovely genetic study that actually implies that grandmothers have been selected for this- and you can immediately think of all the reasons why that could be the case- why helping more successfully bring up the young, etc. It was a theory that there wouldn't be that much selection after people had reproduced and brought up their next generation.

So now telomerase most of us we get older and older and we care about whether or not were getting cardiovascular disease and things like that. And so what we're finding is that if you don't have good telomerase activity and proper maintenance of telomeres- that actually puts people at risk of cardiovascular disease. We would never have thought of that at the beginning but we looked and started finding and other people started finding as well these relationships and it says this is something that matters. So then the question is how can you get more of this. Now were looking at intervention studies. What we've learned was that its not just genes although that will of course play a roll- it turns out that in a really interesting study I did with collaborators here at UCSF, in particularly a clinical psychologist whose name is Elissa Epel, in the psychiatry department, she was studying individuals who had chronic life stress. The two groups we've got the most immediate data on are care-giver groups- one of which is mothers whose biological child is chronically ill with autism, bowel disease, etc. The mother is the caregiver and she's under stress for not just a short time but years.

We found that the worse the stress was and the worse the person perceived it by quantitative measures, (and you can do that), and the longer she had been in situation, the worse was the wearing down of her telomeres and her risks for developing cardiovascular disease. And so that tied in this telomere shortening thing because it said that the chronic stress that comes in here to the brain was sending all this through the body physiology, which the brain

is well known to do. One of the measures we can extract out of this is that the telomeres are running down. We were just delighted by this. The organism in this case- the people- were telling us something that we didn't have any particular prediction that this would necessarily have to happen. Although people get pretty haggard when thy get under this stress, so there was this possibility that they were literally aging faster. But there cells- their telomeres- are running down faster and the telomeres are down by this stress.

LH: Why did you come up with the name?

EB: Telomerase, well we thought about this for a while. Telomeres are the ends of the chromosomes and at that stage were focusing on the DNA part of it, the protein actors that shoot a sheath around this DNA. So that's telomeres and here is this enzyme that is making more telomeres right, and so we we're trying to think of precedence. There's DNA polymerase - which is this enzyme that does the regular copying of DNA- that replicates the chromosomes of all DNAs. So we thought there's polymerase that make a polymer- in one case a RNA- so we thought well why not have telomerase- instead of having telomere polymerase- we'd call it telomerase. So that's how- Clair Wyman, who was a graduate student in the lab, came up with that name.

LH: It seems like we are genetic mutations in a sense-. One can find these things when the technology exists. Do you believe that in a sense were in a culture of sampling, of remixing these kinds of mutations?

EB: Yes, do you mean mutations as sort of how humans act?

LH: And evolve.

EB: Absolutely, it's so interesting how we just adapt. When something new comes out, we just immediately embrace it and say how can we use it for something that were interested in. So in my little world of biology research- the technologies that are available completely change how you think about a problem. So I will give you one example- it was a gene. We have thousands,

tens of thousands of genes in our total genetic material. If you could get your hands on the gene- with the older technology- then you just study this gene to death, you just focused on that.

Now there's a whole genomes' worth of genetic information. So getting a gene, meaning getting its DNA sequence- that's just a given- it's just by the computer with a click and it's all there. So, now suddenly that's not the issue anymore, now it frees you to think about- what are we learning? Now we're not laboring away just trying to get the sequence of the gene, but how do we think about the whole picture? So we embrace that, and think of this idea and we think we've counted up the genes that code for proteins and they come up with this rough idea of thirty thousand and a whole lot of variations on each of those, which turns out that thirty thousand is not really just thirty thousand, because you could have one gene and it could actually be cut and spliced in different ways. So you can arrange it, and make thirty-something different genes, so we actually have a lot of genes because the variations add up to huge numbers.

You could alternatively use the same constitutes to create new things so the genome is used in that way with cells and genomes in humans, very extensively. So that was good- people said great, we've got protein genes etc.- but they thought just about proteins. Now, there's another part of things between DNA and proteins and that's RNA, (DNAs copied into working copies and that's called RNAs), people always thought that's what RNAs are for- for working copies for proteins, but in fact that's not true. Telomeres is actually really interesting its made of an RNA plus a protein.

The RNA has a little portion that's copied into that DNA repeat sequence that I told you that's added to the end. People always say the template, and its not just a template, its a big folded RNA fitted into the enzyme its totally bound into the protein. So this is a rival nuclear protein and an enzyme- it's made of RNA its made of protein- this is an enzyme where both are important. People had discovered RNA could even be an enzyme by itself. Now they're discovering all sorts of RNAs- all in between the genes in what was called the junk DNA in between the protein genes and the gnome. And now they're made into all sorts of RNAs- they could be doing all sorts of

things. The technology allowed that to show up and now we embrace this idea.

There's a ton of information that was under the surface. The protein genes were the tips of the iceberg- there's all this other sort of things that is this playground just waiting to be understood. These RNAs often regulate the proteins, but you see the RNAs in Telomerase do something actually quite active- so who knows what other things the RNAs may be doing.

Your question is very interesting- there's initially a skepticism about new ideas- so you have to make sure they're not cranks- right. But once it's verified then your universe just shifts it in and we now embrace this whole idea. The genome is now filled with this subterranean information that because of historical accidents we hadn't really appreciated it- we meaning people who were studying biology in various ways. So it's endlessly interesting you just unlock secret after secret after secret and you just adapt to it. I'm always amazed about how adaptable we actually are- we just embrace this whole new thing- these things would have been total heresy ten years ago.

LH: Can you say something about the Dr. Jekyll & Mr. Hyde?

EB: So telomerase, if you think about what's its doing for humans- which is what we generally care about, I mean I care about the science but people will relate to the question of what good is this. Because it was prominent in cancer cells, that for a while in the 1990's sort of dominated the thinking on telomerase in human cells. If you look at a cancer cell and a tumor cell and say, what is the activity of telomerase- its very active in 80% - 90% of human tumors, including very active ones. That made total sense because cancer cells are famous for just keeping on and multiplying. The telomerase doesn't let them have the malignant properties but it lets them keep on replicating so they don't have to worry about maintaining their chromosome ends. They have a ton of telomeres and they just keep filling out the ends of chromosomes so the ends don't get too short. The telomerase, I like to say, gives them permission to keep multiplying. This is definitely a dark side of the enzyme, a sort of Mr. Hyde side, because this enzyme is promoting the

malignant properties of cancer, which is clearly not something you want to see being promoted. So the enzyme is enabling this behavior of the cancer cells. The cancer cells have a lot of other changes too- genetic changes and non-genetic changes. They're deft to all signals to cease multiplying- they don't obey any rules about where they should be- breast cancer cells will go off into bones and lungs- and it has no business being there.

Normal cells would know their place and they wouldn't be migrating all over the place and finding homes in the wrong places- so it wouldn't be a problem. The cancer cells have all of these things wrong with them. Telomeres mostly just lets them multiply, but we've just found recently it also has other functions- it has night and day jobs- so we knew the day job- but it also moon lights and it promotes some of these malignant properties themselves.

That suddenly made sense- now why is telomerase so active in cancer cells- because- hey you don't need that much telomeres to maintain your telomeres. You realize that this job- that we don't fully understand is going on too. Its definitely an enzyme that in the context of cancer cells is a very dangerous thing to have, right- and yet in the context of totally normal cells we were talking about and saying these are maintaining the good telomeres and maintaining self renewing of the good in our body and organs- and telomerase helps that- through the decades of adult life. So that's' definitely the Dr. Jeckel aspect. The same enzyme but in totally different contexts it has totally opposite ramifications of what's good and bad.

LH: I've read that people are predicting that this is the aging gene and that this is going to help us live longer- understanding that the Dr. Jeckel qualities will help us live longer. What will the ramifications of an aging population be?

EB: The thing that seems like telomerase is most helpful for in normal cells isn't- turning them into Methuselahs. It seems to be more like what we know- that it's important for the aspect of aging, which is the part that's all about susceptibility to the diseases of aging, like cardiovascular disease, diabetes and cancer.

Telomerase seems to be if they're in good amounts in normal cells- protective against those. So there's this new term that I think is not bad, instead of life span its health span, so I don't think its going to make you live more than 100 years or whatever the normal expectancy is stretching out is supposed to be. When people are healthy, (and centenarians- they can live to be a hundred years- they clearly have some genetic advantages).

The thing is, for most people living healthfully until they die- is the most important thing. Interestingly that's what the connection with telomerase seems to be about. Now it is true that centenarians seem to have good, healthy, long-looking telomeres, (so that's good), and they're very free of things like cardiovascular disease, diabetes, and cancer, things that kill most elderly. What we're finding is that the risk for those things is related to having less telomerase. So in other words, if there were more telomerase-active just in the normal cells (not in the cancer cells)- that would get you to be more like a centenarian- its not going to turn you into a 200 year old. That's a whole other different set of things going on. But I find that interesting, that's what affects the vast majority of the people. Centenarians are people who live to a hundred- were very fascinated by them- but there's a tiny fraction of the total population- and even though there's more and more of them- still there not most of us.

They have a confluence of lucky genetic situations– it's not really what happens to the majority of us. But I find it interesting to think about well what happens to what most of us, and this is what having limiting telomerase is all about. So the question is can you make more telomerase? You can have a magic pill and everything will be all right- we all know magic pills right- they're great up to a point and then you discover a downside to them. It turns out there's a downside to these otherwise good pills. So the question I am really fascinated by is could you use the fact that we know chronic stress dampens down telomerase- so what about the opposite? So were doing studies with people doing very deliberate stress reduction programs- and were looking to see does that actually measurably help things- or not. Preliminarily it does- so that's interesting but this is just in the ongoing stage right now so we don't have all the information. This is what it looks like so

far, and that to me is more realistic- and it sort of starts to speak to the whole person in a much more medically- probably important way. Its all very tempting to pop a pill- and I'm all for popping a pill when they work right, but if we don't know how to do that then what do we know how to do. And there are certain things that suggest you can do certain things to try to do. Just like the family doctor said- relieve your stress, exercise and eat well all those things.

We're at this kind of cusp of understanding how this is going on- and we don't know it all we can do is look at the numbers come out and say we know these numbers relate to risk factors for cardiovascular disease and other diseases of aging. So that's good- if we can see how the numbers are working in the right direction its showing progress- its informative.

LH: Can you tell me something about why you said that you related to the Conceiving Ada film? What was it about the film that you understood?

EB: Yes- well I loved it in lots of ways. The character Ada- there were times when she was talking about yearning- she expressing in this film a sort of yearning to be doing what she was doing. She wanted that time and space and freedom and that sort of feeling she was projecting- I think scientists really relate to that.

LH: Obsession

EB: Obsession sounds really unhealthy, no- its what you're driven to. You just feel you have to do it, and you don't want anyone interfering- and you may be ruthless about making sure that they're not going to interfere.

LH: But Ada's problem, when she was alive, had to do with how women were perceived and other than her mother, (who was a mathematician), who was training her in the sciences- she was really restricted. And when she was able to eat one satious thing.

EB: Yes- and we are still so restricted in current society- there's so much push back about women feeling that they can say- I really want to do this.

There's so many things saying you should be doing this that and the other. Its really hard with family- you're always the tension is really strong- well I'm driven to do this and I'm pulled to do this- and you want to do them both. I don't think it's gone away at all- and I think it's why it was so powerful- it really spoke to something that is just as real now in some ways. I think there are a lot of expectations about how you are supposed to be- if you're a woman. Even in the world of science- there is this norm that is imposed on people- and I didn't think there is necessarily going to be this kind of freedom giving way that's really what you need- to do science. You can do all the manipulations of science- with the entire tool and all the stuff like that, so people can just churn out stuff. And I don't think that's really the creative side of science, because you need that kind of freedom to do that. I think that science and other creative endeavors are akin at a sort of creative edge. You can sit there and pot around and you can be doing science- you can be doing endless experiments, there's no shortage of ability, and tools and things that you can do. But actually really trying to think about what it all means- what is the nature of Biology as opposed to manipulating certain things.

It is something where you need peace and quiet. I try to protect my mornings. My assistant says, "you have quiet week", and then I say "I have a real week"- if I don't have appointments in it- then it's actually a productive week, as opposed to a week that's just frittered away. There's so much and women are expected to be doing lots of tasks- managing this that and the other feeling- that really detracts from having creative time.

LH: And make unexpected leaps

EB: Yes, you need that thinking time to let the ideas sort of well up and happen.

LH: Did you experience any kind of oppression- and how did you over come that?

EB: When I was a student and a post doc, those are sort of heavenly times for scientists because you are unfettedly doing just science and research you

have no responsibilities other than doing that. We all know in our careers that time is a wonderful thing. Then there's a sort of progression, as you go into a research position and you have some responsibilities. I was teaching, I was at Berkeley for 12 years. They protected my first year and then you were expected to be a faculty member and interact and to do your duty like that. And it's harder for women I'd say, to say no to that, (its sort of a cliché but it's true). It was important to be in a department where people did understood that their time should be protected and really are more creative and you're doing your job more if you aren't burdened with lots of things. So I was in a fairly good department in that way. And then I had a little fierceness about it too. I really did feel a little fierce that I wasn't going to let these things impinge on me too much. I was a good citizen up to a point and in teaching but there was up to a point where that was understood- that if I were burdened with huge amounts of teaching then that would inevitably impact my research. And it wasn't just me- that was the culture of the department. I know you had to have to have this constant- being ready to push it back- and just sort of fix in your mind- and say if this is something that impacts on it that was sort of helpful to think about- if it was impacting on my research. And very early on I got some advise- early on starting as an assistant professor- I got some advise from a women's group they had on a Saturday morning and the department administrative head said- you had to go to this. And she dragged me to it and they said hey- you're going to be judged for your research so just make sure that anything you say you do that its going to be making an impact. And that was interesting that something I had been feeling- and then somebody said it- I was like okay- good. So you have to have a fierce protection of it. And then it gets really hard when I had my mother, and it was hard when Ben was young. And so how did I protect myself? We had a great person who she still works for us but she came in everyday- and she was his nanny but also more than that- she was like a third parent. I would leave home and I forgot I was a mother- until 8 or 9 hours later. So that was a real freedom- being able to have the privilege of trusting someone else with your child. If something happened then I would swing back into mother mode, but you really just had to be free to be in this other world.

LH: It's true because the generosity- in a way- is like the cancer cells you're talking about. It can get out of control.

EB: Yes, giving yourself out to all these things- and you know you can contribute to all these things. You have to have this sense that your work is really going to make- you have to have this sense that your work is something that's important. Especially that you have to have this sense that your work is something that's important- and that's the perspective you have. Others could say well maybe it's not- but that's the perspective you feel that you say now this is what's important, what I'm about and going to put my real serious energies into. Then as you go on and on and the lab gets larger- and I always try to keep things limited because I didn't want to be having a huge big show. Just a lab where there's creative people- doing things, but not this sort of show. Again, you've got more freedom to operate. I think in answer to your question, you said what were the things I used- I think that it was a sense that I really do kind of guard my freedom in a way- and if I feel someone impinging on it- I get somewhat fierce- at least inside- I don't necessarily show it. I immediately go into- I'm going make sure that this is not frittering my time away- I guess that's my biggest fear. You can have such a frittering day- and it looks very busy- but it's not.

LH: What's Carol Girder doing now?

EB: She has a lab in Hopkins- and the work she's focusing on- she uses mouse models- but very much the same kind of thing. Like me, she chaired at a department. I chaired at a department for a number of years, on a rotating basis- but again it was like frittering. And so she's doing really interesting projects where you can look at the mouse models and manipulate what happens genetically- telomeres and telomerase- and really honing in on studying what goes on. So in humans you don't know if they're going to be the same as they are in mice. Mice are going to die after two years- and they don't die of old age- they die of other reasons. Humans we die with a life expect antsy of eighty years, so it's a whole different thing. Just because it's true in model system doesn't necessarily mean that's it true in real life- that's where I said that I really want to know what's true in humans.

LH: Can you say a little about what your finding- what you were saying the enzyme proteins were merged? And maybe use the term “genetic remixing”.

EB: Well, I’m not sure exactly what your term means- you will have to tell me more of what you mean.

LH: Things that are reused and resampled- and re-combine in different ways.

EB: Yes, so telomerase are made of both RNA and a protein and they both come together. Either doesn’t do anything- the two have to come together- they fold into each other very intimately and that becomes a whole new entity. Which is called a ribonuclear enzyme- instead of a ribonuclear acetic enzyme or a protein enzyme it’s now an enzyme made up of two different kinds of entities- and each is important. It was thought that only the proteins were important but again there were more and more hints that RNA is actually quite important. Now it is becoming more and more acceptable that yes, this sort of thing is becoming a truly by-partide kind of thing- that’s its not just two things- its all bound in together.

LH: It’s a recombination of elements that you’re finding out?

EB: It’s a recombining in space of the elements- now the proteins can have other partner’s too- we don’t know if the RNA has other partners. But in tis particular partnership there is this enzyme telomerase- raising all these questions- of how did that happen? Was RNA the ancestral form? Did it acquire a protein? Was the ancestral form acquiring RNA? It’s very hard to figure out what happened billions of year’s ago- but again it’s a fascinating thing.

LH: Do you think the combination of these things in our combining helps in our evolutionary process?

EB: Its one more way of taking the elements and making something new out of it. Bacteria don’t have any telomeres- but all organisms with a nucleus ranging from fungi to plants and animals- they all have telomeres. There are a few exceptions. And they have tricks to get by with out telomeres. So it is

something that evolved- right at the dawn of when the eucarriats emerged, (that's the interpretation). The how and why is just kind of lost in time. The enzyme telomerase- I have to tell you this great thing it does. Everybody said that DNA could never be copied from RNA. But the telomere- the little repeated sequence- they're copied from a short sequence of the RNA, (the RNA that's part of telomerase). The only place where people had seen this, (its called reversed transcriptase- it's like reversing the rules), people had only seen this in things like retro viruses like HIV, so it had always thought to be an abnormality- that normal cells wouldn't have this thing. But here it was- it was a normal part of what we have- it was essential. In fact, HIV and telomerase- they have a rooted similarity. So I wonder if these kinds of viruses- the reverse transcriptase of viruses- didn't evolve from their cellular counterpart- telomerase, because telomerase cells have been around longer than viruses most of the time. So it's this fascinating- that here the closest comparison to telomerase is the protein part was the HIV, (reversed transcriptase). But it doesn't have the RNA built in- it just threads the RNA through and copies it. The RNA kind of interacts with the protein but not as much. Where as with telomerase- the RNA is embraced in the enzyme and then just a little portion of it is copied.

LH: Maybe you can make another comment about cancer- and your relationship with what you're doing with cancer, so could we just get one statement on that?

EB: Telomerase is very active in the great majority of human cancers- even in the common cancers- so even 80-90% of cells, human cells, its very active. That makes sense because Telomeres is maintaining the ends of the chromosomes, and those ends have top be maintained as the cells multiply- and that's what the cancer cells do they just multiply- out of control. They don't listen to any signals that say- stop multiplying, and telomerase gives them that ability to keep multiplying.

LH: Can you treat them to behave differently?

EB: One of the questions is- can you cut off the cancer cells telomerase action and see if that will suppress its ability to reproduce tumors, and the

answer is yes. There are no good drugs out there- so the ways we have been looking at it have been largely experimental in terms of looking at model cell systems. And some model pre clinical systems- not involving humans. So there is clearly an ability to cut off the growth of cancer cells, that we can see- it does happen. It's not clear yet if that's going to be the greatest drug in the world, but the biology is very sound. That's a long way to having a real useful drug.

It's certainly a target for cancer cells- because they're under such hyper drive for telomerase- they're actually quite vulnerable to having they're telomerase choked off. Even though normal cells have a lower level of telomeres that are needed- there's kind of an over-reliance of the cancer cells that we think is the best target for it. It's always never as you thought- you think well if you inhibit telomeres- you inhibit it in all cells-, which would be a bad idea. But the cancer cells have so warped everything that's inside them- they have become like addicts.

If you're a heroine addict and it's cut off then you have this terrible reaction because you're whole system has become reliant on it. So it's a little bit like that for cancer cells -they become reliant on this hyper drug- telomeres- so when its choked off they have a much worse reaction than a normal cell that says: well I've always been living without telomeres, I can do it still.

So the biology is a little different form what you'd expected, and yet this is a good way of attacking cancer cells. We try various sorts of ways in the lab- were not developing drugs- but the hope is, and we and lots of others have shown that this is a good way of doing it, shows it is. Then the question might be well is there a drug that actually might be useful. It's certainly reasonable- but it hasn't happened yet because these things don't just get developed really quickly.

LH: I want to know about your internal value of yourself and how you protect your ideas.

EB: Yes, I think you do have to have a kind of strong belief in yourself to do science, because everything about trying to sort of push the boundaries in

biology is there. And its very complicated in many ways to break new ground because you have to have a mix between being crazy and having an idea- and then being super disciplined to say I am going to take this through the most rigorous set of criteria because if its not verifiable and true than it's a waste of time.

So you have to be prepared to have an idea and then go out there and really have it fail. That means you have to have resilience to that- meaning you have this lovely idea, and you're just in love with it- but it could be proved wrong.

When I was at Berkeley, one of my students joked that we would have a theory of the month. So you have to have these and all the time you're out there trying out all these crazy ideas- up to a point- in your mind, and then you think- is there a way I can come up with how to test it? Should we be asking questions that haven't been asked before? Sometimes things that you observed prompt the questions. Then you have to have a leap and say there's something new in the textbook that's never been found before. And then you rigorously prove that what it was- is really true.

So one day Carol would come and say, - there is this total thing and undercut it all, and I would say- oh I can think of this- and the next day I would come and say- I can completely see how this as a total artifact, and she would say now I see this. So you had to be constantly doing this back and forth in your mind- because you can fall in love with your idea- and try and get all the evidence to support it.

In Biology you can screw you're way around a lot of evidence to make it look good. So that's the thing- you have to always be standing back to cut yourself off at the knees at the same time. I think you do have to have that sense that my ideas are going to be worth that much to endure all that pain. It's also that sort of ability to relinquish it- you have to have this sort of Pollyannaish- oh, isn't this great- that's what I learned instead. So that's what I have learned over the years to do- you look at the experiments and say- well this is such and such idea, forgetting that last week I was totally enthused about this other idea.

You do this within the lab- your not putting it out there in publications until you feel much firmer on your feet- and then you put it out as models. Unfortunately models get locked and become quickly dogma and so they're sort of human nature. We quickly grab something and say here it is- so it's very provisional. It's a really on going thing but I think you really have to have a sense that you can take it.

LH: I think you also have to believe in your instincts.

EB: That is so true. Barbara McClintock was very influential to me in that way because she's very famous as a geneticist who discovered genes that jump around which was so totally non cononical of these things in the 1930's and in the1940's. I would talk with her sometimes when I visited the lab. I remember there was this really memorable talk where she really felt she would understand the organism and really look at this and say always trust your instincts in your research. I remembered that. That had to come from having done enough of it to have a sense of it what was going on. You couldn't just trust your instinct the minute you walked in. There was a sense that after you got familiar with what you were doing and you sort of thought something odd's going on here – then don't dismiss, although its not in this sort of science rule book. So that was what she could really break out of that thinking and be very rigorous about her experiments. She would trust her instincts. People didn't know that DNA was the genetic material when she did a lot of her experiments looking under the microscope at chromosomes and they're behavior and she was deducing things- and you read some of these things- like as we now know how chromosomes replicate their own DNA. And she was just right on- she was like this brain that could visually take on how chromosomes were behaving under the microscope when you do certain genetic things to them.

LH: So you could say that Barbara McClintock was able to stay with her intuitive ideas?

EB Barbara Mcclintock really kept with her intuitive ideas. She was somebody who protected her freedom. People thought she was being

marginalized because she wasn't this professor and that, but actually she was really appreciated in the genetics research community. Luckily there were those people who realized what she was and why that was good to do.

LH: Hedy Lamarr, too, did you know she invented wireless technology? She learned all that science while she was 16 and married to Hitler's arms dealer. She considers herself a scientist- rather than an actress.

EB: Isn't that interesting- that's not how the world sees her.

LH: She made most of her money completely on her own through her inventions.

EB: How interesting- that's just the knee-jerk reaction is that she an actress.

LH: She invented her wireless system with Georges Antheil so the United States could win WWII. Kennedy discovered it-this during the Cuban missile crisis. Her patent was given to the U.S. but was in a file. Nobody took her seriously.

EB: I love it when people who are serious science and you don't expect it.

LH: Tilda's degree is in Political Science

EB: Now somehow that doesn't surprise me because she makes such thoughtful things.

LH: She's going to be thrilled with your interview because she has said that what you say also echoes her concerns.