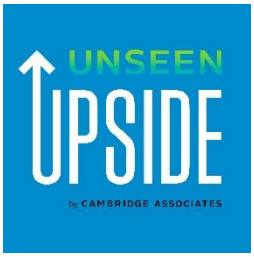


**Season Four: Episode Five**
**Unlocking the Dark Genome for Lupus and other Autoimmune Disease**
**Launch Date: Mar 2024**

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**Keri Mastrogiacomo**: It was January in New England, you know? She had a cold for a few weeks that she sort of just couldn't get rid of.

**Hillary Ribaudo:** Keri Mastrogiacomo lives in Braintree, Massachusetts, and has four children. And she's talking about her oldest daughter, Peyton.

**Keri:** I was at work one day and she texted me and said she wasn't feeling great. She was going to take a tub and hope that she could feel better. And then a few minutes later, I get another text from her that says, "this is really strange, but my Ankles are so swollen, I look like auntie Krista nine months pregnant." Peyton also has a little flair for the dramatic. So, I was like, okay, let's see. And she sent me a picture and my stomach dropped because I thought, “that's not okay.”

**Hillary:** Peyton is now a senior in college, but a few years ago, that cold she couldn't shake was one of the first signs of a life-changing diagnosis**.**

**Keri:** Peyton was 17 at the time. You know, we were told, "Oh, it's probably a virus or it could be what we're looking at is lupus." And we were still kind of just like, It's a virus. This is a virus. We're going to be home in half an hour. And you're going to be fine. And it wasn't. Her journey started and we were thrown into that journey of lupus and trying to find out not only what it was, but how to learn to live her life with a chronic illness.

**Hillary:** Systemic lupus erythematosus, or SLE, is the most common type of lupus. It's a chronic autoimmune disease where the immune system mistakenly attacks healthy tissues and organs in the body. And it often results in painful inflammation and damage to the skin, joints, kidneys, heart, lungs, and even the brain. It's estimated that more than five million people worldwide have some form of this disease. 9 out of 10 people diagnosed with lupus are women, and it is more likely to affect women of color.

**Rosana Kapeller:** When you start thinking from a personal standpoint, how debilitating autoimmune diseases can be, I feel very strongly that we don't have great medicines yet. I mean, we have made major strides. Don't get me wrong. But I think there is much more that needs to be done.

**Hillary:** Why some people get lupus, and some don't is something scientists are trying to figure out. And current treatment options are limited. But scientists may have discovered the key to better understanding lupus and other autoimmune diseases through something called the dark genome.

**Rosana:** We are unlocking the dark genome to develop breakthrough medicines for serious diseases like cancer, autoimmune diseases and neurodegenerative diseases.

**Cues:** Theme Mux

**Hillary**: I'm Hillary: Ribaudo and this is Unseen Upside by Cambridge Associates, where we explore investments beyond their returns. This season we're talking to leaders and investors behind healthcare innovations that could change how long-and how well-we live. And in this episode, we are diving into the enigmatic world of the dark genome.

**Cues:** End Mux

**Hillary:** Keri vividly recalls the overwhelming sense of uncertainty on that day you heard about earlier that completely changed Peyton's life.

**Keri:** I called her pediatrician, and she took a look at her, they ran some tests, did some urine cultures there and definitely saw that things were off. So, she said, "totally erring on the side of caution, go to the emergency room. They can do more tests than we can." And we were there for a week.

**Hillary:** And it was during this time that she got the diagnosis.

**Keri:** She has lupus nephritis. So, her kidneys were in kidney failure. At the time, they said that her kidneys were functioning at 20%.

**Hillary:** Peyton's story resonates with me. When I was a teenager, I was also diagnosed with lupus. And hearing Keri describe the first flare-up that Peyton had, reminds me so much of my own journey and those early days of being really sick and knowing something was terribly wrong, but having no idea of exactly what it was.

**Keri:** You know, there are 11 criteria to diagnose lupus and she actually didn't meet most of them. Everything came with, "but we don't know, but we're not sure." You know, you want to hear what's wrong and then you want to hear what we're going to do to fix it. And none of that was coming.

**Hillary:** Diagnosing lupus is challenging because it can present with a range of symptoms that can mimic those of other diseases. Since there isn't one definitive test for lupus, doctors usually have to use a combination of your medical history, physical exams, lab tests, and imaging tests that's what they use to make that diagnosis.

**Keri:** It quickly became very frustrating that it was like, well, it is or it isn't. Very scary, very uncertain, and incredibly vulnerable that you have no control over any of this.

**Hillary:** And beyond diagnosis, treating the disease is also a challenge. But scientists are now at a point where they are starting to fill in the gaps.

**Rosana:** I am driven by cutting-edge technology and cutting-edge biology.

**Hillary:** Rosana Kapeller is the founder and CEO of ROME Therapeutics. A biotech company based in Boston, Massachusetts**.**

**Rosana:** I am more of a generalist and I'm a therapeutic area agnostic, for me is more, are we in the right time? Do we have the right knowledge to be able to attack a certain problem?

**Hillary:** Rosana is an MD and holds a PhD in molecular and cellular physiology from Tufts University, and you could say she has a pioneering spirit embedded in her own DNA.

**Rosana:** I was 12 years old when I declared that I was going to be a doctor and that I was going to go and live outside of Brazil. I have many scientists in my family, and women scientists, which is amazing.

**Hillary:** Like her great aunt, Regine Kapeller-Adler, who made significant contributions towards the modern pregnancy test.

Today at ROME, Rosana and her team are harnessing the power of the dark genome to develop breakthrough medicines for serious diseases like lupus. But before we get into the nitty-gritty of the dark genome, let's make sure we understand the basics of genomics.

**Rosana:** So, the genome is the complete set of DNA carried by each cell in your body. Each one of our cells carry this code, if you will.

**Cues:** Mux

**Hillary:** Picture the genome as a massive instruction manual for your body. It's composed of DNA, which acts like a language that cells use to know what to do. In humans, this manual is divided into 23 pairs of chromosomes - think of them as the book chapters -

nestled inside the cell's main hub, the nucleus. Genes are specific sections of DNA, and everything your body needs to function, and grow is detailed in this manual.

**Rosana:** the DNA governs how our cells behave, and by doing so, influences everything from our eye color to our propensity for certain diseases. So, people can have heart diseases based on their genes. However, almost all research in the genome has been focused on just 2 percent of our genome. And that is the part that code for what we call the traditional protein. So, the proteins that today we see as drug targets.

**Hillary:** Over two decades ago, an international team of researchers completed The Human Genome Project. This project -that took about 13 years- stands out as one of the most significant biomedical achievements of the 20th century. The goal was ambitious: to decipher the chemical makeup of the entire human genetic code and develop tools that would allow scientists to identify genes involved in rare and common diseases.

At that time, there was a widespread belief that the human genome primarily contained instructions for producing proteins, crucial for cell functions, and believed to play a key role in our evolution and cognitive abilities**.** But surprisingly, it turned out that less than 2% of the three billion letters in the human genome are actually about proteins**.** So, what about that remaining 98%?

**Steve Kafka:** The rest is dark. [Laughs] So that's at the basic level what we're talking about.

**Hillary:** Steve Kafka is a general partner at S32, a venture capital firm investing at the frontiers of technology and healthcare**.**

**Steve:** There's a set of genes that drive human development, including disease development, and then a huge majority of the human genome is basically quiescent.

**Cues:** space

**Hillary:** Around the time of the race to sequence the human genome, Steve was also beginning his career in biotech. By then, he had already completed a PhD in Political Economy and Government at Harvard University. And spent several years as a strategy consultant to the bio-pharma industry

**Steve:** I was very fortunate to land a first job at Millennium Pharmaceuticals, which is one of the real success stories in the Boston biotech community. And interesting fun fact about Millennium is that out of the group of folks who worked at Millennium, at the latest count there's something like 75 folks who have gone on to be CEOs of biotech companies.

**Hillary:** One of those former Millennium employees-turned-biotech-CEOs is Rosana. Although Rosana and Steve didn't work together directly back then, their career paths did cross, and the connection remained.

**Rosana:** I was at Millennium for 9 years, that's where I got my first view into what drug discovery and development looked like, and we were really exposed to a lot of innovative thinking.

**Hillary:** Rosana says that around the time of the Human Genome Project in the early 2000s, there were references in the scientific literature to that unknown 98% Some geneticists thought these were the remains of damaged genes that were no longer useful, basically, the leftovers of human evolution. So, they started using the name -Junk DNA.

**Rosana:** We couldn't really understand the information that contained. So, we basically just junked it.

**Hillary:** Rosana explains that eventually with the advances in technology, it became obvious that this DNA was not junk.

**Rosana:** I mean, that we even called it junk is a little bit short-sighted, because, why 98 percent of our genome would be junk? Would make no sense, so they must be doing other things.

**Rosana:** So, think about the dark matter of space, you know, we can't see it, we can't measure it. Same idea here, we can't map it, we can't measure it. So, it started being referred as dark matter of the genome.

**Hillary:** And at some point, the community renamed it the dark genome.

**Rosana:** Because it was a mystery.

**Hillary:** Today, Rosana says that more than a mystery, the dark genome is like a puzzle. But with a million pieces with no edges and no picture to follow! We are still figuring out exactly what all the parts of the dark genome do which is so important for understanding disease like Lupus to  So, but research has given us some clues, like how it plays a role in regulating genes, and how it helps to shape the genome's structure.

**Rosana:** For instance, the middles and ends of each chromosome are repeating DNA structures. So, they basically work to keep the chromosomes in place. So, most of the dark genome is made up of repetitive elements, or repeats.

**Hillary:** Remember that we said that the genome is like a book, where the chromosomes are the chapters? Well, that DNA -that language that we talked about- that makes up the genome has its own alphabet. It’s made out of these “letters,” and they are called nucleotides.

**Hillary:** Imagine DNA as this twisted ladder, with these building blocks holding the two sides together. Just like certain letters go together in words, with DNA, under normal circumstances, A - Adenine pairs with T - Thymine (thigh-mean), and C - Cytosine pairs with G - Guanine (guanine). These are called DNA base pairs.

**Steve:** And repeating sequences of those letter combinations have been introduced into the human genome over time, largely by viruses. COVID is a recent example of this, but there have been millions of viruses over time that have left their mark in the human DNA, and they're just sitting there.

**Hillary:** Rosana says these repeats can be thought of like parasites or pathogens.

**Rosana:** And we have hundreds of thousands of copies of this ancient virus or repetitive elements in our DNA today. They're remnants of viruses that incorporated themselves into our genome over many millions of years. But they have retained their virus-like ability to replicate and quote-unquote infect cells. And then they also, what they can do is that they can copy and paste itself into the genome. So, they are called jumping genes. You know, they can go from one chromosome to the other chromosome. And 54% of the total genome is comprised of these repetitive elements.

**Hillary:** And these jumping genes are what Rosana and her team at ROME Therapeutics are interested in.

**Rosana:** Even as we go in everyday business, we have all these genes jumping in our genome. And also, we have found that there is a very strong ties of some of these jumping genes with several diseases. So, ROME was founded to basically understand that. How do you tie those genomic parasites, if you will, to the initiation and progression of certain diseases?

**Hillary:** The majority of the dark genome is made up of these genomic repeats. And there are several types. You can think of them like different families.

**Rosana:** This is going to be absolutely mind-boggling. The first one is called LINE-1, or *Long Interspersed Nuclear Element 1*. And that comprises 20% of our genome. Most of it are little pieces, because when it jumps, you know, and reintegrates into the genome, a lot of times it reintegrates only little pieces of it. But many times, it can integrate all of it.  it can reinsert itself into the genome as a DNA molecule. It's crazy. It's like a virus. It's exactly like a virus. We have about a hundred-plus copies of functional or active LINE-1s. And what you have to understand about it, it's different from genes.

So genes that are present in 2% of a genome, usually, you have two copies of each gene, one in each chromosome. In the case of LINE-1, is a hundred copies of LINE-1, and they are all over the place and all the different chromosomes, so why are they there? What is the importance of LINE-1? It's playing a very key role. And that's what we're trying to understand.

**Hillary:** But don't forget there are other elements of the dark genome**.**

**Rosana:** you have HERPS, which stands for Human Endogenous Retroviruses. That's about 8% of our genome. Then you have Alus and SINEs, and satellite repeats, so you can see that there is a whole variety of repeats.

**Hillary:** And they have played a crucial role in shaping who we are.

**Rosana:** These are not classical genes, but some of them become genes. So, for example, you know, for mammals to have placenta. They had to co-opt one of the proteins encoded by one of these viruses. So, there is a protein called syncytin, which was originally an envelope protein of one of these viruses, and that protein is responsible for placenta formation. So if we had not co-opted it and made it into a gene, we would not have placenta, and mammals would not exist. So, this whole process plays a very important role in evolution.

**Hillary**: That's right – part of the dark genome is the reason why the placenta even exists! None of us would be here without these repeats. They're not junk at all! And they've even given us clues as to why some people develop certain diseases.

**Rosana:** The other interesting thing about repeats, is that they're extremely well controlled in the adult organism, meaning that they are dormant. Most of the time, they're not expressed. They only get expressed when cells are sick, or they're exposed to some kind of environmental stress. You know, it is like, they're exposed to sun, they're exposed to irradiation, they're exposed to smoking. So, we believe that when these repeats get expressed, and they're behaving like a parasite or a virus, they activate our host defense mechanism.

So that's all well and good when it's transient. It's like having a cold, it goes away. But if that mechanism is not turned off, then it's like having a chronic viral infection. And that leads to a lot of diseases like autoimmune disease and neurodegeneration and may also play a role in cancer.

**Hillary:** Understanding LINE-1 repeats,  is especially important in the identification of new targets for drug development

**Steve:** Human biology is just beautifully complex.

**Hillary:** Here's Steve Kafka again.

**Steve:** And I think in this darkness, we're just at the very beginning of being able to find some points of light that will give us new ways of treating disease.

**Cues:** Seg B - Lupus, one of many autoimmune diseases, is one of the first targets where DG research could make a difference.

**Hillary:** It's been 17 years since I was first diagnosed with Lupus. And in many cases, Lupus is not like other diseases where you can simply take a pill every day and you'll be fine. Treatment for lupus is really a combination of things and involves a lot of trial and error to see how your version of the disease reacts.

**Keri:** When you have no control over a situation, you do your best to control it.

**Hillary:** here is Keri Mastrogiacomo again.

**Keri:** So, the doctors would laugh at me when we would show up at the appointment because I had a binder and I had everything, that was my way of being in charge and controlling it.

**Hillary:** After Peyton's diagnosis, there was a point where she was taking 8 different medications.

**Keri:** It was difficult because as you know, with medications come side effects. It's like, well, this medication is going to make you feel better for this, but it's going to also make you feel like that.

**Hillary:** Were there any really difficult side effects that made her not want to take the medication, or just made the treatment options that she was given especially difficult?

**Keri:** Prednisone. Even hearing the word just gives me such a pit in my stomach because of just the horrible side effects to that. And that was the one that she was on most. The prednisone made her feel good and healthy again on the inside. But one of the worst side effects for Prednisone is weight gain and they call it Moon Face, you know, she's a 17-year-old girl.

**Hillary:** Moon face is one of the more common side effects of taking Prednisone, and it occurs when fluid builds up under your skin and causes your face to look really puffy or swollen.

**Keri:** She hates looking at pictures of her junior prom because she was at the peak of it. And she'll say that she looks at that picture and just felt so sad inside because so much was stolen from her.

**Hillary:** It's a miracle drug, but when you are a teenage girl, you do not want to have moon face and water retention. I had the exact same thing. Looking back at those pictures, obviously you look and you're like, I hate how I look, but also, It's just a reminder of how sick you were at that time.

**Hillary:** And for patients like Peyton, drugs are very important to control this disease.

**Keri:** With every flare-up comes more damage that you will do to your kidneys that will eventually become irreparable.

**Hillary:** As scientists dive deeper into the dark genome, they're discovering new areas for target selection, and this is vital in the initial phases of developing new and better therapies. Improved drug options could truly change the lives of those struggling with Lupus and other complex chronic illnesses.

**Rosana:** One of the key things for almost anything we do in the biopharma industry is target selection. And before we select the target, we have to discover targets, and we have

to validate those targets. Is the first key step of making a drug, which is to choose which target your drug will act on.

A target is oftentimes a protein, but may also be, for instance, a strand of RNA. Or it can be a cell or something else. Because relatively little has been known about the dark genome, ROME's target discovery is filling those blanks to find novel targets in the dark genome.

**Steve:** ROME's first foray here is with LINE-1 reverse transcriptase, sometimes called LINE-1 RT in lupus, which is a super important disease area because the therapies here are antiquated and really not terribly effective in a reliable way.

**Hillary:** This is S32's Steve Kafka, and we'll get to reverse transcriptase in a minute.

**Steve**: And so we need new ways to treat and maintain patients with lupus. And that's going to require us understanding the biology and actually what's going on. And that's where the potential of the dark genome comes in.

**Hillary:** Rosana says up until recently, we simply didn't have the technology to uncover what we now know about LINE-1.

**Rosana:** So even if we suspected that LINE-1 was a driver of autoimmune diseases, LINE-1 would not be a target 10 years ago, but today it is

**Hillary:** She attributes the progression we've seen over the last decade to three advances.

**Rosana:** Number 1 is next-gen sequencing.

**Hillary:** Next-generation sequencing, also known as NSG, refers to a set of technologies introduced in 2005, that revolutionized genomics by allowing for rapid and cost-effective sequencing of large amounts of DNA or RNA. Number 2…

**Rosana:** Long-reach sequencing, very important as well, because repetitive sequences, you need to have long-read sequences.

**Hillary:** Long-read sequencing is another innovation in DNA sequencing technology that makes it possible to measure gene network interactions across chromosomes.

**Rosana:** The third piece also is machine learning, or artificial intelligence is playing a major role here. Because we now have the bioinformatic tools to put the different pieces together. Imagine that you have a million-piece puzzle, and every single piece looks exactly the same. How are you going to put it together? They have slight imperfections that may tell you that piece one goes before piece two, but it's very hard for us to see it. So now with the computational power that we have in our fingertips, that is possible.

**Steve:** Over the past five years there's been a huge breakthrough in our ability to sort of learn in software. And so one of the things that's super exciting about the dark genome is that it's a vast source of data. And being able to tap into these repeat elements, create the

map of them, and then have the tools with DNA sequencing and RNA sequencing, and, large and increasing troves of clinical data, as well, to create associations between all these different data elements, using generative AI kinds of models, and then layer that on top of processing power and large data storage, which are also required to do all this. And that's all getting more accessible and cheaper over time. You put all those elements together and our ability to get beyond the tip of the iceberg with the dark genome, I think is incredibly exciting.

**Rosana:** It's so important in science that we're able to see, map, and that we're able to measure, quantify. Without these two things, we can't really understand the biology, we cannot really understand how to modulate it, the impact in diseases, and now we can do that.

**Hillary:** Rosana is deeply invested in finding better treatments for autoimmune diseases, but this is also personal for her.

**Rosana:** There are a lot of different types of autoimmune diseases, and there is one particular class of autoimmune diseases that are called type one interferonopathies. And what that means is that they are caused by high levels of a specific type of interferon.

**Hillary:** Interferon is a natural substance that helps the body's immune system fight infection and disease.

**Rosana:** So, lupus is caused by that, psoriasis is caused by that, dermatomyositis is caused by that, etc., etc. So I have psoriasis. I have both plaque psoriasis and psoriatic arthritis, which is a different manifestation than someone that have lupus, but in a way is a spectrum because all these diseases have one thing in common, which is high levels of interferon.

**Hillary:** This is where LINE-1 comes in

**Rosana:** And LINE-1, when we block LINE-1, we block the production of interferon.

**Hillary:** On November 16, 2023, ROME announced groundbreaking data confirming the significance of something called reverse transcriptase (RT) in LINE-1 as a novel target for drug discovery in autoimmune diseases.

Reverse transcriptase is a vital enzyme that links RNA and DNA, acting as a copy machine in our bodies by converting RNA into DNA. This process is essential for cellular functions like protein synthesis and gene expression. And ROME's breakthrough is huge because the data reveal therapeutic potential of their first-in-class LINE-1 RT inhibitors, which offer a promising approach to halt disease-triggering inflammation.

**Rosana:** So, reverse transcriptase, very similar to what is encoded by the human immunodeficiency virus. So, if you remember the ‘80s, you know, when we started understanding HIV, people were dying. Then we developed reverse transcriptase inhibitors and other drugs. They have to take the drugs for the rest of their lives, but disease is well

controlled, and people actually live pretty healthy lives. The surprise here is we found out that both LINE-1 and the human endogenous retroviruses encode reverse transcriptase. So, what is the role of that reverse transcriptase? Is to convert RNA into DNA into the cytosol and activate our host defense mechanism. And then when this mechanism is activated, basically your body behaves as if you have an infection.

And if you think about autoimmune diseases, what is autoimmune diseases? It's just sterile inflammation. Basically, the lack of tolerance to your own body. So, what we want to do is to block this initiation signal that we believe is derived by these parasites that we have living inside us.

**Hillary:** The idea is to turn off -or inhibit, or block- LINE-1 repeats so that they cannot be expressed.

ROME is in preclinical development today, which means that the team is gathering and analyzing data from both animal studies and human cells to decide if their drug is ready for human trials. The plan is to start their clinical stage - so testing therapies on real people—very soon.

**Rosana:** Every time that you get into the clinic with a drug you first have to test for safety. So, we have to do all that work before we get to patients. But hopefully we're going to start seeing it in patients in the next couple of years.

**Cues:** Seg C - Investments and the future

**Katherine Cavanagh:** I think many of us, myself included, have a personal connection to autoimmune disease, and yet autoimmune disease as a whole is an extremely under-resourced area despite a massive patient population.

**Hillary**: Katherine Cavanaugh is an associate investment director at Cambridge Associates, and she says ROME Therapeutics presents a compelling investment opportunity for several reasons.

**Katherine:** For us is exciting that there is not only a big unmet need paired with an old and not highly effective standard of care for diseases like lupus, dermatomyositis, other indications that they're going after. But this not only creates an opportunity for exciting impact and innovation, but for a strong investment through them being first movers in this area.

**Hillary:** Katherine and her team manage portfolios for large family offices and institutions. Lately Katherine's been focusing her research on private investments specifically in venture and growth equities across various sectors like life-sciences, climate tech, Ag-Tech, B2B SaaS and Ai. But Katherine's career actually started far from investment and close to genetics.

**Katherine:** One of my first work experiences was as an intern at a diagnostic genome sequencing startup. Definitely inspired both my excitement and the patience that I realize is needed for innovation broadly, but especially in life sciences. I think the progress and growth in early-stage companies is definitely not linear, but it's extremely exciting for those who have the patience to stick around through the ups and downs.

**Hillary:** Like Rosana and Steve, Katherine has seen the space grow and mature.

**Katherine:** This means in practice that this ecosystem needs a lot of different types of capital to allow these companies to move through their life cycle and succeed. We definitely are spending a lot of time on early-stage biotech investing but have been taking a look at more creative opportunities that have come out as a result of the space maturing. So that could be drug royalties, or crossover, or investing in a different inflection point, or more structured deals.

**Steve:** Science is really hard. And it takes a team to make it happen and to sort of bring it all the way to patient impact.

**Hillary:** Steve Kafka has been at S32 since 2019, and he's focused on technology and life science applications of technology**.**

**Steve:** And so along the way we have to collect sort of believers who are going to bring intellectual capital, financial capital, capabilities, a willingness to change policy or sort of influence policy where required in certain disease areas or in certain application areas.

**Hillary**: Section 32 was founded in 2017 by American entrepreneur and venture capitalist Bill Maris**.**

**Steve:** Bill had been the founder and initial CEO at what was called then Google Ventures, now called GV, the venture investing arm of Google.

**Hillary:** S32 invests broadly across technology. They have investments in artificial intelligence, enterprise software, cyber security, quantum...

**Steve:** also, in applications in health technology, in computational biology, and in precision medicine. We have about 2 billion under management today. We just closed our fifth fund earlier in 2023. And so, we're actively investing out of that fund right now.

**Hillary:** S32 is a relatively small team. But they pack a lot of experience**.**

**Steve:** We're just four managing partners or general partners. All of us have had long careers in some combination of operating, company building roles, and or investing kinds of roles.

**Hillary:** since my conversation with Steve, S32 Added its fifth general partner former google executive Andy Conrad, and Andy founded and served as the CEO of verily life

sciences which was Google's moonshot effort at the intersection of healthcare and Data science.

**Hillary:** Steve says that at Section 32, each partner has their own network of advisors and trusted thought leaders.

**Steve:** In my world, I have a set of folks that I can call and when there's a new area of biology or an area of disease that maybe is evolving rapidly, and I want to understand better, you know, a lot of this is, I guess I would call it, primary research and having a group of folks that we can each tap into to help us really form our views.

**Hillary:** For Steve, there's both a science and an art to investing**.**

**Steve:** There are repeated key considerations about the veracity and the robustness of a given technology. Does it really work?

Having folks who have the sort of the wherewithal and the fortitude and the passion to run through walls metaphorically speaking, and have had track records of success in doing just that is really critical to us.

**Hillary:** People like Rosana Kapeller at ROME Therapeutics.

**Steve:** She's just a great example of how important that kind of experience is in our investment decision.

**Cues:** Mux

**Hillary**: ROME Therapeutics's name is meaningful on a couple of levels.

**Rosana:** is an abbreviated form of the word repeatome, R-ome,

**Hillary:** Repeatome refers to all of those families of repetitive DNA, or repeats**.**

**Rosana:** which is that part of the dark genome we're focused on here at ROME and also reflects a spirit of exploration and innovation that in ancient ROME changed the course of history.

We hope that our spirit of brave exploration at ROME today will also create a brighter future for those to come. And of course, we cannot escape ROME was not built in a day, but all roads lead to ROME.

**Hillary:** Rosana says the idea for the company grew out of her time as entrepreneur in residence at GV.

**Rosana:** I was the very first entrepreneur in residence at GV, formerly known as Google Ventures. Now I'm a fellow with the life sciences practice there, where I became familiar

with the research of our scientific founders, David Ting and Ben Greenbaum, showing some really remarkable connections between the dark genome and disease.

Together we founded ROME and incubated it at GV. And we launched the company back in 2020. With a series A from G. V., Arch, and M. G. B. And that was our 50 million series A. And then Section 32 led our series B.

**Steve:** When we invested a couple of years ago now, you know, they were building the technology to be able to map the dark genome and build that data set, which is today a really valuable I think proprietary resource to the company.

**Hillary**: Steve Kafka again.

**Steve:** And then really building a drug hunting and drug development team, you know, has been essential to building out a pipeline, you know, the tip of the spear here is the LINE-1 RT. But, beyond that, there's a bunch of really interesting potential programs in the pipeline.

And that's been the result of Rosanna recruiting and bringing on board a really terrific and experienced group of chemists and biologists and translational medicine folks to build out that capability.

ROME is not the only one working in this area. I think they're a real thought leader in the area.

**Hillary:** For 2 years, ROME has co-hosted the Dark Genome Symposium, convening thinkers from other companies and across academia. And together they are building momentum.

**Steve:** New therapeutic drug development, that's a really important area because our health care spending and our health care outcomes are a huge part of our economic growth and success as a company and as a globe, honestly. And so, our ability to invest in new innovations that ultimately are going to help people be healthier and live longer and be more productive in society, if we do our work right to actually help these companies bring new medicines, to market in this case. We will also be creating return for our investors.

**Katherine:** It's definitely very different than software investing or investing in old economy. Our team and colleagues have spent a lot of time working really hard to get to know the key players and map out the landscape.

**Hillary:** Katherine says the combination of unmet need, disruptive innovation, and lowering development costs means more investors will be attracted to investing in dark genome research. And that research can happen at both for-profit and not-for-profit institutions.

**Katherine:** And so, I think it is very cool and exciting that CA is in this seat to engage with both sides of it. So, we're advising healthcare institutions, advising these academic institutions, and also evaluating for-profit investments like ROME that have these deep academic roots as well.

Innovation is definitely really long-term and takes many years to come to fruition, but that timeline lines up pretty perfectly with the purpose of our endowments and their ability to seek out long-term positive outcomes, grow their capital base, support their own research and innovation, and that flywheel is really not only financially beneficial but also mission-oriented, which is really exciting.

**Hillary:** In the meantime, patients like myself and Peyton continue to live with the uncertainties of Lupus.

**Keri:** She's 22. You know, her doctor would stress constantly you cannot get pregnant on this medication, there will be severe birth defects. You know, when she comes to that point in her life is supposed to be such a, a fun, happy time. And I feel like it's already overshadowed by, you have to get off this medication and you have to be off it for a certain amount of time. We have to find a different one that is going to work. And the frustration of that is her reality.

**Hillary:** I remember my rheumatologist insisting on prescribing me birth control for that reason and I'm like, “Relax.” He's like, “you can't get pregnant.”
“I'm like, I am 16, like, I am not getting pregnant,” but it's the same thing because it's so dangerous. Um, but I had one healthy pregnancy. I'm pregnant again. So, it can be done and it can be fine. They monitor you very closely, but I've been 100 percent fine.

**Keri:** That was one of the things, you know, always trying to find the good and the bad. Um, that was one of the things that Peyton had said to me before, like what happens when the time comes that I do want to have a baby? And I said, oh, you're going to be monitored so closely. You know, so there are things like that, that, you know, bring hope that it's like, okay, this is still a possibility.

**Hillary:** And they know so much more, it's interesting, my son is two, already with the second pregnancy, they know more than they did two years ago. So they're already doing things differently, which just tells you how much is being studied, and how much they're paying attention. So yes, lots of extra ultrasounds.

**Hillary:** And so, the promise of new treatments gives hope to patients like Peyton and her mom**.**

**Keri:** One of the things Peyton always says is that she doesn't want lupus to define her, she doesn't want it to be the first thing that people think about her or feel bad for her. I wish that I knew in the beginning that there may be some bad days. But there are going to be lots of good days.

**Hillary:** I love that

**Hillary:** If you want to learn more, please visit us www.cambridgeassociates.com/unseenupside/ or check out the show notes. If you like what you're hearing, leave us a review and tell your friends and colleagues.

At Cambridge Associates, our podcast team includes Michelle Phan, and me, Hillary: Ribaudo. And a special thank you to Megan Morrissey, Robert Scherzer, Krista Matthews, and Deirdre Nectow. And I also want to say Thank you to Peyton Mastrogiacomo for allowing us to share her story.

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Next time on Unseen Upside join us we explore the convergence of AI & Healthcare and the promising new innovations that are emerging as a result…

*"Thinking about Ai is an opportunity more than a threat, we need to get more efficient at our single biggest expense which is healthcare, and I remind my tech-friends who Kinda view healthcare investing is a kind of curiosity that healthcare part of the economy is bigger than tech."*

Before you go, one of our colleagues has an important message about the contents of this podcast.



-THE END-